Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Sartor O, de Bono, J, Chi KN, et al. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med. DOI: 10.1056/NEJMoa2107322

This supplement contains the following items:

1. Original protocol (pages 2–88), final protocol (pages 89–183), summary of changes (pages 95–96).
2. Original statistical analysis plan (pages 184–240), final statistical analysis plan (pages 241–307), summary of changes (pages 308–319)

ENDOCYTE

PROTOCOL NO. PSMA-617-01:

VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF ^{177}LU-PSMA-617 IN THE TREATMENT OF PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)

Clinical Protocol No.:	PSMA-617-01
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IND No.:	133,661 (^{177}Lu-PSMA-617)
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Phase of Study:	Phase 3
Investigational Products:	^{177}Lu-PSMA-617
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Approval:

[signed electronically in MasterControl]

Medical Officer Signature *Date*

Site Principal Investigator Signature

The investigator signature page is provided in Appendix 3 along with a link to form FDA 1572 or equivalent if the site is outside of the United States.

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Revision History

Version No.	Date	Summary of Changes
1.0	22 March 2018	Not applicable; initial clinical trial protocol.

Clinical Trial Summary

Protocol title:	VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)
Clinical phase:	Phase 3
Objectives:	The primary objective of this study is to compare overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ^{177}Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/best standard of care alone. Key secondary objectives are an arm-to-arm comparison of the following: • Radiographic progression-free survival (rPFS) • Response Evaluation Criteria in Solid Tumors (RECIST) response • Time to a first symptomatic skeletal event (SSE) Additional Secondary Objectives: • Safety and tolerability of ^{177}Lu-PSMA-617 • Health-related quality of life (HRQoL; EQ-5D-5L, FACT-P and Brief Pain Inventory – Short Form (BPI-SF)) • Health economics • Progression-free survival (PFS) (radiographic, clinical, or prostate-specific antigen [PSA] progression-free survival) • Biochemical response as measured by PSA. Alkaline phosphatase [ALP] levels and lactate dehydrogenase [LDH] levels will also be measured.
Study design:	Patients with PSMA positive scans will be randomized in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 plus best supportive/best standard of care or to receive best supportive/best standard of care only. Best supportive/best standard of care will be determined by the treating physician/investigator but will exclude investigational agents, cytotoxic chemotherapy, other systemic radioisotopes, and hemi-body radiotherapy. Novel androgen axis drugs [NAADs] (such as abiraterone or enzalutamide) are allowed. The study is open-label and patients will be monitored throughout the 6 to 10-month treatment period for survival, disease progression, and adverse events. A long-term follow-up period will include the collection of survival and treatment updates, adverse events assessment, as well as blood for hematology and chemistry testing. During follow-up, patients will be contacted every 3 months (±1 month) via phone, email, or letter for 24 months or until the the overall censoring rate for survival reduces to a level identified in the SAP. An End of Treatment visit should occur once a patient is to enter the long term follow up. This visit should occur approximately 30 days from the last dose of ^{177}Lu-PSMA-617 or best supportive/best standard of care, but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study. The planned enrollment for this study is 750 patients.
Study population:	The study population includes patients with progressive PSMA-positive mCRPC who received at least one novel androgen axis drug [NAAD] (such as enzalutamide or abiraterone) and were previously treated with 1 to 2 taxane regimens. Patients treated with only 1 prior taxane regimen are eligible if the patient is unwilling or the patient's physician deems the patient unsuitable to receive a second regimen.

Investigational product:	Patients randomized to receive the investigational product will receive 7.4 GBq (±10%) ^{177}Lu-PSMA-617 intravenously every 6 weeks (±1 week) for a maximum of 6 cycles. After 4 cycles, patients will be assessed for (1) evidence of response, (2) residual disease, and (3) tolerance to ^{177}Lu-PSMA-617. If the patient meets the criteria above, and agrees to continue with additional treatment of ^{177}Lu-PSMA-617 radioligand therapy, the investigator may administer 2 additional cycles. A maximum of 6 cycles of radioligand therapy is allowed. After the last cycle of ^{177}Lu-PSMA-617, patients can continue best supportive/best standard of care alone. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu-PSMA-617 treatment, then no additional doses of ^{177}Lu-PSMA-617 will be administered after Cycle 4. These patients can continue on best supportive/best standard of care alone after Cycle 4.
Assessment schedule:	Radiographic imaging will be done every 8 weeks (±4 days) during the first 24 weeks of treatment and every 12 weeks (± 4 days) thereafter, regardless of treatment delays, through the End of Treatment visit. The previous 2 PSA values will be noted before randomization. Serum testosterone and PSA levels will be measured within 3 days prior to Day 1 of each cycle. Hematology and chemistry will be done weekly during Cycle 1 (within 3 days prior to each time point) and within 3 days prior to Days 1, 15, and 29 in Cycles 2 to 6 (i.e. every two weeks). After Cycle 6, hematology and chemistry will be done every 8 weeks (±1 week) until the patient starts long term follow up. Patients will complete the BPI-SF, EQ-5D-5L and FACT-P questionnaires about their pain level and HRQoL during screening and prior to treatment on Day 1 of each cycle and through the End of Treatment visit. Patients will be monitored throughout the study for SSEs.
Statistical methodology:	There will be 2 interim analyses to evaluate if the trial should be stopped early for efficacy. This trial has 90% overall power and an overall Type I error rate of 0.025 1-sided.
Duration of Study:	Total duration of the study will be approximately 38 months.

List of Abbreviations and Definitions

Abbreviation	Term/Definition
ANC	Absolute neutrophil count
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
BPI-SF	Brief Pain Inventory – Short Form
CFR	United States Code of Federal Regulations
CR	Complete response
CRF	Case Report Form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease control rate
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EQ-5D-5L	European Quality of Life (EuroQol) – 5 Domain 5 Level scale
EudraCT	European Union Drug Regulating Authorities Clinical Trial
FACT-P	Functional Assessment of Cancer Therapy - Prostate
GCSF	Granulocyte colony-stimulating factors
FDA	Food and Drug Administration
FAS	Full Analysis Set
^{68}Ga	Gallium-68
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board

Abbreviation	Term/Definition
IV	Intravenous
LDH	Lactate dehydrogenase
^{177}Lu	Lutetium-177
mCRPC	Metastatic castration-resistant prostate cancer
NAAD	Novel androgen axis drug (such as abiraterone or enzalutamide)
ORR	Overall response rate
OS	Overall survival
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SSE	Symptomatic Skeletal Event
TEAE	Treatment-emergent adverse event
SOD	Sum of the diameter
ULN	Upper limit of normal
US	United States
WBC	White blood cell
^{90}Y	Yttrium-90

The following clinical protocol describes the scientific rationale, objectives, design, statistical considerations, and organization of the planned trial including the plan to assure the safety and health of the trial participants. Additional details for conducting the clinical trial are provided in documents referenced in the protocol, such as an Investigator's Brochure (IB), the Pharmacy Manual, or in the Appendices.

The format and content of this clinical trial protocol complies with the Guideline for Good Clinical Practice (GCP) [E6(R2)] issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

The term subject, participant, and patient are used interchangeably throughout this protocol and are used to denote an individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1. INTRODUCTION

1.1 Background information

Prostate cancer and unmet medical need

An estimated 1.1 million men worldwide were diagnosed and 307,000 died due to prostate cancer in 2012. Almost 70% of the cases are diagnosed in more developed regions due to the use of prostate-specific antigen (PSA) testing, but there is only modest variation in mortality rates globally which is driven by metastatic, and often castration-resistant disease (Ferlay et al 2013, Bray et al 2012).

There is an urgent need for more effective treatments to improve outcomes for patients with metastatic castration-resistant prostate cancer (mCRPC). Prostate cancer is the third leading cause of cancer mortality in United States (US) men (Siegel et al 2017), driven by prostate cancer patients who no longer respond to hormonal therapy. Once patients reach the mCRPC stage, their expected overall survival is low as was seen in the randomized phase 3 study of cabozantinib vs prednisone in men with mCRPC who had received prior docetaxel and abiraterone acetate and/or enzalutamide; the median overall survival of the prednisone control arm was 9.8 months (Smith et al 2016). Post-docetaxel mCRPC patients have an annual death rate of 73% (Scher et al 2015).

The median age at diagnosis of mCRPC is 70 years (Flaig et al 2016). Metastatic prostate cancer has a predilection for bone. As a result, approximately 90% of mCRPC patients develop bone metastases (Kirby et al 2011), and 49% of them will develop a serious skeletal event within 2 years (Saad et al 2004). Common presentations include bone pain, bone marrow failure, fatigue, or complications such as fractures and cord compression. These presentations typically require radiation or bone surgery, which can significantly impair physical, emotional, and functional well-being (Weinfurt et al 2005). These patients, many of whom are elderly, can be extremely symptomatic and at risk of serious oncological complications. They can be a considerable challenge in the clinic due to the symptoms of metastatic soft tissue and visceral disease, general frailty, bone marrow impairment, and because they have exhausted approved

agents. In mCRPC patients facing advanced illness with little hope for a cure, the focus of treatment shifts from active anti-cancer treatment to palliative care for relief of physical symptoms, maintaining function, and attempting to improve their health-related quality of life (Cella et al 2009). Therefore, in addition to tracking essential clinical outcomes, it is also important to assess and evaluate changes in HRQoL of such fragile patients as they receive treatment.

Several agents have been approved for the treatment of mCRPC, and NCCN, ASCO, ESMO, and APCCC guidelines provide some consensus and guidance for their use. Regardless, none of these therapies are proven to prolong survival after enzalutamide or abiraterone. In practice, abiraterone acetate or enzalutamide are often used in the first-line mCRPC setting; Sipuleucel-T is best used in mildly asymptomatic small volume disease; and ^{223}Radium is used to treat men with bone-only disease. Taxane-based chemotherapy is most often used today after abiraterone or enzalutamide and for symptomatic patients, particularly with visceral disease. Docetaxel is used more commonly that cabazitaxel. Because both agents have a typical chemotherapy side effect profile, they are often not considered for patients due to comorbidity, poor hematological reserve, or patient refusal (Zielinski et al 2014).

Six small published series with a total of 499 patients have examined the efficacy of either abiraterone or enzalutamide in men previously exposed to a taxane and either abiraterone or enzalutamide. These modern hormonal agents produced only modest activity, including PSA decline >50% in 3% to 22% of patients, a median PFS of 2.7 to 4.6 months and a median OS of 7.2 to 12.2 months (Azad et al 2015, Cheng et al 2015, Badrising et al 2014, Brasso et al 2015, Loriot et al 2013, Noonan et al 2013). It's important to note that this is in contrast with the level of anti-tumor activity demonstrated in the pivotal clinical trials for these agents that led to approval. In that setting, patients had only received prior docetaxel and had not been exposed to prior therapy with either abiraterone or enzalutamide. As these modern hormonal agents have been used in earlier lines of therapy, the use of a second agent following docetaxel has resulted in diminished efficacy, likely due to cross resistance.

Therefore, there are limited options available to patients who fail or refuse taxane-based chemotherapy, particularly if alternative agents currently approved in this setting (abiraterone and enzalutamide) have been used earlier in the disease.

Prostate-specific membrane antigen

Prostate-specific membrane antigen (PSMA) is a transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II. PSMA is highly overexpressed in nearly all prostate cancers, but has restricted, and several hundred-fold lower, expression in some normal tissues such as the duodenal mucosa, proximal renal tubules, and salivary glands (Bostwick et al 1998, Ghosh and Heston 2004, Mannweiler et al 2009). Additionally, PSMA overexpression also correlates with advanced, high-grade, metastatic, androgen-independent disease (Ross et al 2003). The differential expression of PSMA from tumor to non-tumor tissue has resulted in numerous targeted strategies involving both disease localization using radioactive imaging as well as therapeutic intervention, and therefore may be an attractive target for men with mCRPC.

In addition to the expression pattern, the functionality of PSMA plays an equally important role in its value as a tumor-specific targeting mechanism. Specifically, the binding of a high affinity ligand to PSMA, such as the targeting moiety in ^{177}Lu-PSMA-617, leads to internalization through endocytosis and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003). This functional feature of PSMA allows for the development of low-molecular-weight targeted radiopharmaceuticals with favorable pharmacokinetic and tumor penetration properties, rather than being restricted to antibody-based targeting strategies (Haberkorn et al 2016).

The result of both selective expression and ligand-based uptake using PSMA as a target is a reduction in background uptake and off-target toxicities as well as an increase in the amount of radioactivity that localizes at the tumor site.

^{177}Lu-PSMA-617 mechanism of action

The novel PSMA-targeted radioligand therapy ^{177}Lu-PSMA-617 consists of the PSMA-binding ligand [redacted], ^{177}Lu-PSMA-617 exhibits high PSMA binding affinity and internalization, prolonged tumor retention, and rapid kidney clearance (Benešová et al 2015). PSMA-617 was uniquely developed for both imaging and radioligand therapy of prostate cancer, and can be radiolabeled with gallium-68 (^{68}Ga), lutetium-177 (^{177}Lu), indium-111, copper-64, scandium-44, actinium-225, or yttrium-90 (^{90}Y).

^{177}Lu, the radioactive cargo being delivered by PSMA-617, has physical properties that make it an ideal radionuclide for the treatment of mCRPC. ^{177}Lu is a medium-energy β-emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2 mm. The shorter β-range of ^{177}Lu provides better irradiation of small tumors, in contrast to the longer β-range of ^{90}Y (Emmett et al 2017). The shorter path length also acts to direct the energy within the tumor rather than in the surrounding normal tissues, while the path length is still sufficient to create bystander and crossfire effects within the tumor lesion. ^{177}Lu has a relatively long physical half-life of 6.6 days that combines with the intratumoral retention of ^{177}Lu-PSMA-617 to reduce the necessary dosing frequency. It is these physical properties, and the benefit of PSMA-targeting, that allow for the delivery of effective activities of ^{177}Lu to prostate cancer cells.

^{177}Lu-PSMA-617 for metastatic castration-resistant prostate cancer

The novel therapeutic drug ^{177}Lu-PSMA-617 was developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ) in collaboration with University Hospital Heidelberg for the treatment of patients with metastatic prostate cancer (Kratochwil et al 2015, Hillier et al 2009). Based on preclinical data that demonstrated high PSMA binding affinity and compound internalization, prolonged tumor uptake, rapid kidney clearance, and high tumor-to-background ratio, ^{177}Lu-PSMA-617 proceeded into clinical development at investigative sites in Germany.

Data evaluations based on compassionate use according to the German Medicinal Product Act, AMG §13 2b, Clinical Trial Notification (Australia) regulations, and other countries where expanded access programs are in place per local regulations, reported a favorable safety profile

and promising results for PSA response rates of systemic radioligand therapy with ^{177}Lu-PSMA-617 in patients with mCRPC.

Dosimetry data suggest that ^{177}Lu-PSMA-617 is targeted to PSMA-expressing tissue, which may include the salivary glands, kidneys, and small and large bowel. The highest exposure is to salivary glands, however in compassionate use studies xerostomia appears low grade and occurs at a rate of approximately 8% in treated patients. Clearance of ^{177}Lu PSMA-617 from the kidney occurs rapidly. To date nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. The exposure to normal bone marrow tissue is predictably low as it does not express PSMA, and corresponds with normal plasma clearance. There was some evidence of reversible hematological toxicity that occurred following ^{177}Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 70% respectively.

The first published clinical series of ^{177}Lu-PSMA-617 consisted of 10 patients (Ahmadzadehfar et al 2015) treated between November 2013 and January 2014, with 5.6 GBq/150mCi (4.1–6.1 GBq/110–165 mCi). PSA decline >50% occurred in 50% of subjects, which increased to 60% after 2 cycles of 6 GBq/160 mCi (4.1–7.1 GBq/110–190 mCi). The level of PSA decline >50% (most commonly used to assess tumor response in these studies) has remained remarkably consistent across several clinical series when 2 or more doses of ≥6 GBq/160 mCi are given.

Hofman (2017) presented the first prospective open-label, single-arm, non-randomized Phase 2 study of ^{177}Lu-PSMA-617 in 30 metastatic castration-resistant prostate cancer patients dosed with up to 4 cycles of 4–8 GBq/110–220 mCi administered every 6 weeks (Hofman et al 2017). The primary endpoints of this study were to evaluate both safety and efficacy, as measured by PSA response, bone pain score, quality of life measurements, imaging response and survival.

Of the screened patients, 85% were identified as PSMA-positive via PET imaging and eligible for treatment. Most subjects had been exposed to at least 1 taxane chemotherapy and either abiraterone or enzalutamide in the mCRPC setting. In this heavily pre-treated patient population with few therapeutic alternatives, 57% of patients on ^{177}Lu-PSMA-617 showed a PSA response defined by a reduction in PSA of at least 50%, and 43% had a reduction of PSA of 80% or more. In 17 patients with measurable disease, the overall response rate as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was 71% (complete response [CR] and partial response [PR]). Median overall survival was 12.7 months. These safety and efficacy data also translated into significantly improved quality of life scores in 37% and reduction in pain scores in 43% of subjects.

In summary, over 20 compassionate use publications and prospective Phase 2 clinical trial data describe the use of ^{177}Lu-PSMA-617 in patients who have been exposed to approved agents. In the post-taxane, post-androgen axis inhibitor setting ^{177}Lu-PSMA-617 has demonstrated a well-established, predictable, well tolerated safety profile. Clinical series have confirmed 8% incidence of Grade 1 to 2 xerostomia, less than 10% asymptomatic hematological of Grade 3 to 4 toxicity and no significant renal toxicity. Efficacy has been demonstrated on multiple clinically

significant endpoints, including PSA response, soft tissue lesion response measured by RECIST, PFS, OS, pain and quality of life. No standard dose and schedule have been developed.

The preliminary clinical evidence indicates ^{177}Lu-PSMA-617 may demonstrate clinical benefit in patients with mCRPC in a setting where patients had been exposed to chemotherapy and NAADs and there is no recommended standard of care.

This Phase 3 study will assess the efficacy of ^{177}Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC by measuring overall survival in a randomized, prospective, open-label trial.

1.2 Summary of nonclinical studies with clinical significance

***In vitro* PSMA affinity and internalization studies**

According to Benešová et al, the results of the binding assay of PSMA-617 in PSMA-positive LNCaP cells demonstrated a very high binding affinity, with an equilibrium dissociation constant (K_i) value of 2.34 ± 2.94 nM. The internalization of PSMA-617 is highly effective with an internalized fraction of 17.51 ± 3.99 percent of the added activity/10^6 LNCaP cells (n = 3) at 37°C (Benešová et al 2015).

Organ distribution in mice bearing PSMA-positive LNCaP tumors

The organ distribution with ^{177}Lu-PSMA-617 in mice showed a high specific uptake in LNCaP tumors and in the murine kidneys, as expected. Importantly, the high initial kidney uptake is almost completely cleared within 24 hours whereas the tumor uptake remained high or even tended to slightly increase during that time frame. Other organs such as the liver, lung and spleen demonstrated low uptake at 24 hours after injection (Benešová et al 2015).

Biodistribution in Wistar rats

Pharmacokinetic evaluation of ^{177}Lu-PSMA-617 in normal healthy male Wistar rats exhibited major renal clearance with no significant uptake in any of the major organ/tissue (Das et al 2016). More than 80% of the injected activity was excreted within 3 hours post-injection. Retention of residual activity was observed in intestine, liver, kidneys and skeleton at 24 hours post-administration. However, uptake in these organs, except skeleton, was observed to gradually decrease with the time.

Repeat-dose toxicity in Wistar rats

The toxicity of non-radioactive PSMA-617 administered once weekly by intravenous (IV) administration to male Wistar rats over 22 days was tested in a toxicology study. The animals were treated with 40, 160, or 400 µg PSMA-617/kg b.w. by IV bolus injection on test days 1, 8, 15, and 22. The control group was treated with physiological saline. The no-observed-adverse-effect-level was found to be above 400 µg PSMA-617/kg body weight administered once weekly by IV bolus injection (Leuschner 2016). The estimated mass of the PSMA-617 precursor which is applied per treatment cycle is likely to be approximately 150 to 250 µg. Using the NOAEL for repeat dosing of PSMA-617 of 400 µg/kg in rats, this accounts for a safety margin of approximately 16-27 fold, assuming that the average patient has a body surface are of 1.7 m^2. However, considering that a more intensive dosing schedule was tested in rats, relative to the

proposed, and well-studied, clinical regimen of once every 6 to 8 weeks, this safety margin may be a conservative estimate.

1.3 Summary of known and potential risks and benefits

Preclinical work, dosimetry studies, and clinical experience with ^{177}Lu-PSMA-617 since 2013, suggest positive response rates and a favorable safety profile in patients with mCRPC (Kratochwil et al 2016, Rahbar et al 2017, Kulkarni et al 2016, Haug et al 2016, Rathke et al 2017, Soydal et al 2016, Rathore et al 2016, Rahbar et al 2016a, Ahmadzadehfar et al 2016, Ferdinandus et al 2017, Rahbar et al 2016b, Yadav et al 2017).

Dosimetry studies have confirmed that ^{177}Lu PSMA-617 is targeted and normal tissues that express PSMA are exposed to radiation (Delker et al 2016). These tissues are salivary glands, renal, and small and large bowel. Renal absorbed dose is cleared rapidly and exposure appears similar to that seen with ^{177}Lu-DOTATATE. The exposure to normal bone marrow tissue should be low and correspond with normal plasma clearance.

Nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. There was some evidence of reversible hematological toxicity that occurred following ^{177}Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 70% respectively. Rahbar (2017) reported ^{177}Lu-PSMA-617 was associated with asymptomatic Grade 3 or 4 leukopenia, anemia, thrombocytopenia in 3%, 10%, 4%, respectively. Mild reversible xerostomia occurred in 8% of subjects. No significant diarrhea or renal impairment were reported from a retrospective review of doctor reports (Rahbar et al 2017).

Dr. Hofman recently presented results from the first prospective clinical trial with ^{177}Lu-PSMA-617 (Hofman et al 2017). In the trial, 30 mCRPC patients were dosed with up to 4 cycles of 4–8 GBq. Prospective common toxicity criteria for adverse events (CTCAE) v4 safety data was defined. He found his regimen to be well-tolerated. The incidence of drug related Grade 3 or 4 neutropenia, anemia and thrombocytopenia were 7%, 7% and 13% respectively. The only other Grade 3 or 4 drug related toxicity were Grade 3 fatigue and bone pain in 3% of patients.

Potential risks of ^{177}Lu-PSMA-617 include the effects of radiological toxicity, namely xerostomia, fatigue, myelosuppression and mild nausea and vomiting.

Additional details of the nonclinical and clinical experience with ^{177}Lu-PSMA-617 are provided in the IB.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 Trial objectives

2.1.1 Primary objective

The primary objective of this study is to compare overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ^{177}Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone.

2.1.2 Key secondary objectives

Key secondary objectives are an arm-to-arm comparison of the following:

1. Radiographic progression-free survival (rPFS)
2. RECIST response to include:
    a. Overall Response Rate (ORR) as measured by RECIST v1.1 criteria
    b. Disease control rate (DCR) as measured by RECIST v1.1 criteria
3. Time to a first symptomatic skeletal event (SSE)

2.1.3 Additional secondary objectives

1. Safety and tolerability of ^{177}Lu-PSMA-617
2. Periodic assessment of health-related quality of life to evaluate impact of intervention on patient well-being (HRQoL; EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF])
3. Health Economics
4. Progression-free survival (PFS) (radiographic, clinical, or PSA progression-free survival)
5. Biochemical response as measured by PSA. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

2.2 Trial endpoints

2.2.1 Primary endpoint

The primary endpoint is OS and is defined as the time from randomization to the date of death from any cause.

2.2.2 Key Secondary endpoints

The key secondary endpoints include the following:

1. Radiographic progression-free survival (rPFS) defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate

Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause.

2. RECIST response to include:

    a. Objective response rate (ORR) (CR + PR) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions. Duration of Response (DOR) will also be measured in patients with a CR or PR from date of first response to the date of RECIST progression or death.

    b. Disease Control Rate (DCR) (CR + PR + stable disease [SD]) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions.

3. The time to a first SSE defined as 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, whichever occurs first.

2.2.3 Additional Secondary endpoints

1. To evaluate the safety and tolerability of ^{177}Lu-PSMA-617
2. Aspects of HRQoL will be reported using the EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF]
3. Health economics
4. Progression-free survival is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.

    a. Radiographic progression is defined as the date of radiographic disease progression as outlined in the Prostate Cancer Working Group 3 (PCWG3) Guidelines.

    b. Unequivocal clinical progression. Unequivocal evidence of clinical progression is defined as:

        - Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
        - Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression even in the absence of radiological progression
        - Marked deterioration in ECOG performance status to ≥ Grade 3 and/or in the opinion of the investigator ECOG deterioration indicates clinical progression
        - In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

c. PSA progression is defined as the date that a ≥ 25% increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance). Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.

5. Biochemical response endpoints:

   a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a ≥50% decrease from baseline that is confirmed by a second PSA measurement ≥4 weeks.

   b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

3. TRIAL DESIGN

3.1 Overview of the clinical trial design

This is a Phase 3, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in addition to best supportive/best standard of care as compared to best supportive/best standard of care alone (Figure 1).

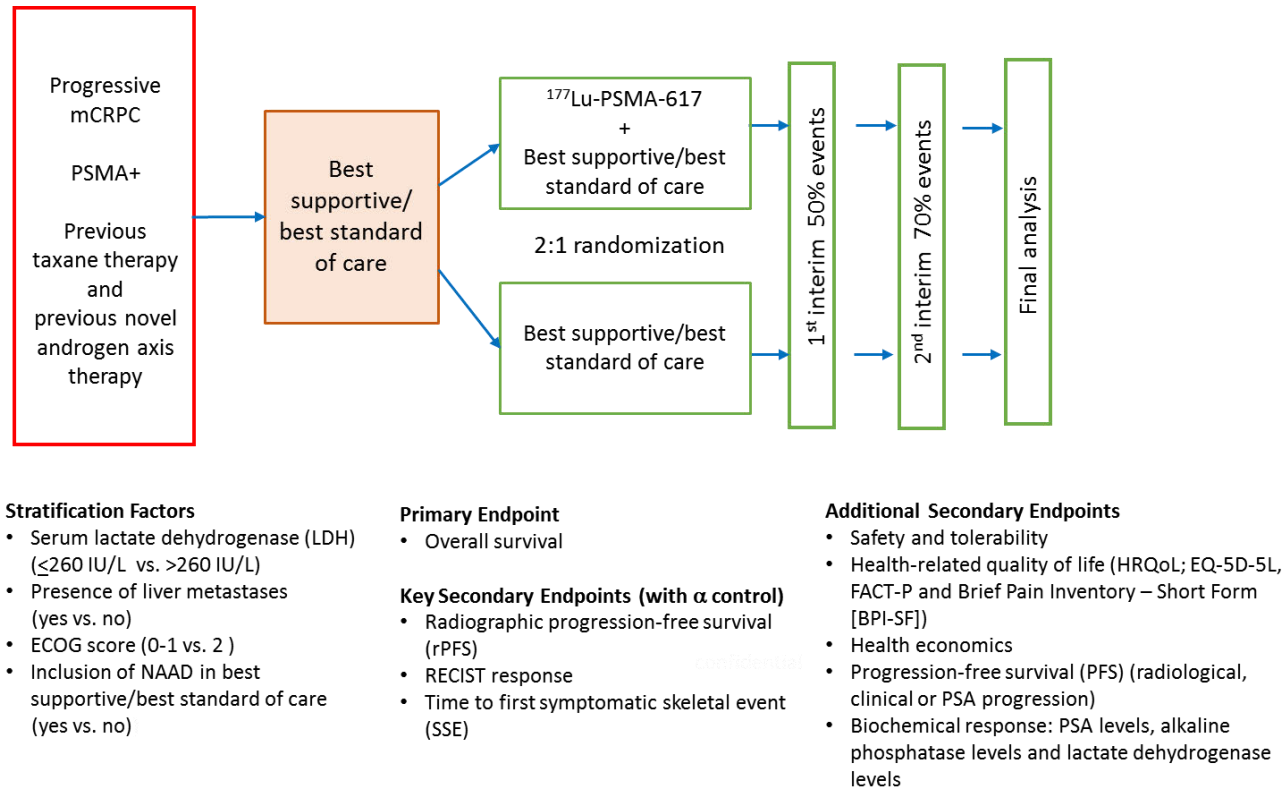


Figure 1 Diagram of trial design

ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

Best supportive/best standard of care includes available care for the eligible patient according to best institutional practice and at the discretion of the investigator. Novel androgen axis drugs [NAADs] (i.e., enzalutamide or abiraterone) are allowed.

Investigational agents, cytotoxic chemotherapy, other systemic radio isotopes (e.g. radium-223) or hemi-body radiotherapy treatment may not be administered on study.

At screening, potential subjects will be assessed for eligibility and will undergo a ^{68}Ga-PSMA-11 PET/computed tomography (CT) scan to evaluate PSMA positivity. Only patients with PSMA-positive cancer will be randomized in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 plus best supportive/best standard of care (investigational arm) or to receive best supportive/best standard of care alone (BS/BSC-only arm). Randomization will be stratified by 4 factors (Section 3.4.3).

Patients randomized to the investigational arm must begin ^{177}Lu-PSMA-617 dosing within 28 days after randomization. These patients will receive best supportive/best standard of care and 7.4 GBq (±10%) ^{177}Lu-PSMA-617 once every 6 weeks (±1 week) for a maximum of 6 cycles.

After the Cycle 4 dose of ^{177}Lu-PSMA and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- Has shown good tolerance to the ^{177}Lu-PSMA-617 treatment.

If the patient meets all of the criteria above, and agrees to continue with additional treatment of ^{177}Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet any of the criteria or does not agree to additional ^{177}Lu-PSMA-617 treatment, then no additional doses of ^{177}Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ^{177}Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

Best supportive/best standard of care for each patient will be selected at the discretion of the patient's physician, prior to randomization and will be administered per the physician's orders and continued until the patient comes off the treatment part of the study and enters the long-term follow-up stage.

A patient may choose to discontinue the treatment part of the study at any time. If a patient withdraws consent for the treatment part of the study, the patient will continue to be followed for long term follow up unless they specifically withdraw for the long term follow up of the study.

An End of Treatment (EOT) visit should occur once a patient is to enter the long-term follow-up part of the study. This visit should occur approximately 30 days from the last dose of ^{177}Lu-PSMA-617 or best supportive/best standard of care, but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

After the EOT visit, patients will enter the long-term follow-up period. The long-term follow-up period will include the collection of survival and treatment updates, adverse events assessment, as well as blood for hematology and chemistry testing. During follow-up, patients will be contacted every 3 months (±1 month) via phone, email, or letter for 24 months or until the the overall censoring rate for survival reduces to a level identified in the statistical analysis plan (SAP).

This study will enroll approximately 750 patients involving about 80 sites worldwide.

3.2 Rationale for the study design

The primary objective of this study is to compare overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ^{177}Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone. Secondary endpoints have been defined by PCWG3 as well as FDA and EMEA guidance. In view of the highly symptomatic nature of advanced mCRPC both validated pain (BPI-SF) and HRQoL (EQ-5D-5L and FACT-P) measurements will be collected using various questionnaires.

3.3 Measures taken to minimize/avoid bias

Patients will be randomized to 1 of 2 treatment arms. Randomization will be stratified to avoid bias in treatment selection (Section 3.4.3). Treatment will be open-label.

Reading of the baseline ^{68}Ga-PSMA-11 PET/CT scan will be done by central readers for consistency.

3.4 Description of the clinical trial

3.4.1 Description of investigational medicinal product

The ^{177}Lu-PSMA-617 solution for injection consists of a sterile solution in glass vials containing 7.4 (±0.74) GBq of ^{177}Lu-PSMA-617 at time of injection.

Refer to the ^{177}Lu-PSMA-617 IB for additional details of the investigational medicinal product including the pharmacological class and action, the dosage form including excipients, and any available packaging and labelling.

3.4.2 Dosage and rationale for dose selection

In the investigational arm, patients will receive best supportive/best standard of care regimen and IV 7.4 GBq (±10%) ^{177}Lu-PSMA-617 once every 6 weeks (±1 week) for a maximum of 6 cycles. After 4 cycles patients will be reassessed to determine if a further 2 cycles can be given for a maximum of 6 cycles (Section 3.1).

The basic principle of ^{177}Lu-PSMA-617 radioligand therapy is to systemically deliver low dose rate radiation specifically to multiple PSMA positive prostate cancer lesions, while sparing normal tissues. To date, 11 dosimetry studies have been conducted and published in over 100 patients. The results are consistent across the studies, and demonstrate exposure that correlates well with the expected rapid clearance of a small molecule, and the limited distribution pattern of a PSMA-targeted radionuclide. The primary sites of non-tumor uptake were the salivary glands, lacrimal glands, and kidneys, with excretory mechanisms contributing to exposure in the kidneys where approximately 50% of the injected dose is cleared within 48 hours (Kratochwil et al 2016). PSMA-negative tissues like the bone marrow, are exposed transiently to ^{177}Lu-PSMA-617 while in circulation, however this exposure is minimized due to its rapid elimination.

^{177}Lu-PSMA-617 is well tolerated according to the clinical experience that has been documented in 24 publications, summarizing the safety and or efficacy information from over 500 subjects. Across these studies doses have ranged from 2.0-9.3 GBq, and schedules have typically followed an administration schedule of once every 4 to 12 weeks, for 1-8 cycles. The majority of these publications have used a regimen of 4 cycles of 6 GBq every 8 weeks, as published by the German Radiopharmaceutical Society in 2015. However efficacy and safety information from the prospective phase 2 study suggested that dosing of 6-8 GBq every 6 weeks for 4 cycles was well tolerated and efficacious (Hofman et al 2017).

Clinical series now show reports of more than 4 cycles of ^{177}Lu PSMA-617 being administered safely as a means to maximize the benefit to the patient (Rahbar et al 2018). In addition, a recent review suggests optimal dosing of 6 cycles of ^{177}Lu-PSMA-617 administered every 6 weeks in a

decreasing scale reaching a total cumulative absorbed dose of 44 GBq (Emmett et al 2017). Six fractions of 7.4 GBq, delivers a similar total dose of 44.4 GBq.

In the ANZUP1603 study in 200 Australian patients (NCT03392428), which is comparing ^{177}Lu-PSMA-617 with cabazitaxel, the dose starts at 8.5 GBq ^{177}Lu-PSMA-617 and reduces by 0.5 GBq per cycle, i.e. 8.5, 8, 7.5, 7, 6.5, 6 (cycle #6). A maximum of 6 cycles given every 6 weeks is what is being evaluated, which equates to a cumulative dose that is similar to that for this proposed study.

The clinical safety review and detailed analyses of the radiation exposure support the intended dose and frequency of ^{177}Lu-PSMA-617 administration in this clinical trial.

3.4.3 Subject allocation to treatment

Patients will be randomized by an interactive response system in a 2:1 ratio to the investigational treatment arm or the best supportive/best standard of care-only arm using a permuted block scheme. Randomization will be stratified by the following factors:

- LDH (≤ 260 IU/L vs. > 260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0 or 1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care (yes vs no)

3.4.4 End of treatment visit

An EOT visit should occur once a patient is to enter the long term follow up part of the study. This visit should occur approximately 30 days from the last dose of ^{177}Lu-PSMA-617 or best supportive/best standard of care, but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

3.4.5 Duration of Subject Participation

Patients may continue treatment until radiographic progressive disease, withdrawal of consent, the occurrence of unacceptable toxicity, or a determination by the investigator the patient is not clinically benefiting. As per the patient's physician, when the participant requires care that is not allowed on study, the participant will discontinue treatment and enter the long-term follow-up period.

Total duration of the trial for randomized patients is expected to be 19 to 23 months, including a 1-month screening period, 6 to 10-month treatment period and a long-term follow-up period lasting 24 months or at least until the overall censoring rate for survival reduces to a level identified in the SAP.

Total duration of the study, from first date of randomization to last follow-up, will be approximately 38 months.

3.5 End of trial definition

The trial and long-term follow-up procedures are expected to continue for approximately 38 months or until the overall censoring rate for survival reduces to a level identified in the SAP.

For timing of the 2 formal interim analyses and any rules for early statistical curtailment, refer to Section 8.7 and Section 8.8.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

Written informed consent must be obtained prior to any study-related procedures. The Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the participant's financial responsibility. Participants must also be notified that they are free to discontinue from the study at any time. The participant will be given the opportunity to ask questions and allowed time to consider the information provided. A copy of the signed written informed consent form (ICF) will be given to the participant for their review and signature.

4.1 Inclusion criteria

To qualify for enrollment, patients must meet the following criteria:

1. Patients must have the ability to understand and sign an approved ICF.
2. Patients must have the ability to understand and comply with all protocol requirements.
3. Patients must be ≥18 years of age.
4. Patients must have an ECOG performance status of 0 to 2.
5. Patients must have a life expectancy >6 months.
6. Patients must have histological, pathological, and/or cytological confirmation of prostate cancer.
7. Patients must have a positive ^{68}Ga-PSMA-11 PET/CT scan, as determined by the sponsor's central reader.
8. Patients must have prior orchiectomy and/or ongoing androgen-deprivation therapy and a castrate level of serum testosterone (<50 ng/dL or <1.7 nmol/L).
9. Patients must have received at least one NAAD (such as enzalutamide and/or abiraterone).
10. Patients must have been previously treated with at least 1, but no more than 2 previous taxane regimens. A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane. If a patient has received only 1 taxane regimen, the patient is eligible if:
    a. The patient is not willing to receive a second taxane regimen, or

b. The patient's physician deems him unsuitable to receive a second taxane regimen (e.g. frailty assessed by geriatric or health status evaluation or intolerance).

11. Patients must have progressive mCRPC. Documented progressive mCRPC will be based on at least 1 of the following criteria:

    a. Serum PSA progression defined as 2 consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL.

    b. Soft-tissue progression defined as an increase ≥20% in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions.

    c. Progression of bone disease: evaluable disease or new bone lesions(s) by bone scan (2+2 PCWG3 criteria, Scher et al 2016).

12. Patients must have ≥1 metastatic lesion that is present on baseline CT, MRI, or bone scan imaging obtained ≤28 days prior to beginning study therapy.

13. Patients must have recovered to ≤ Grade 2 from all clinically significant toxicities related to prior therapies (i.e. prior chemotherapy, radiation, immunotherapy, etc.).

14. Patients must have adequate organ function:

    a. Bone marrow reserve:

    - White blood cell (WBC) count $\geq 2.5 \times 10^9$/L (2.5×10^9/L is equivalent to 2.5×10^3/μL and 2.5 × K/μL and 2.5×10^3/cumm and 2500/μL) OR absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L (1.5×10^9/L is equivalent to 1.5×10^3/μL and 1.5 × K/μL and 1.5×10^3/cumm and 1500/μL)
    - Platelets $\geq 100 \times 10^9$/L (100×10^9/L is equivalent to 100×10^3/μL and 100 × K/μL and 100×10^3/cumm and 100,000/μL)
    - Hemoglobin ≥9 g/dL (9 g/dL is equivalent to 90 g/L and 5.59 mmol/L)

    b. Hepatic:

    - Total bilirubin ≤1.5 x the institutional upper limit of normal (ULN). For patients with known Gilbert's Syndrome ≤3 × ULN is permitted
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤3.0 × ULN OR ≤5.0 × ULN for patients with liver metastases

    c. Renal:

    - Serum creatinine ≤1.5 x ULN or creatinine clearance ≥50 mL/min

15. Albumin >3.0 g/dL (3.0 g/dL is equivalent to 30 g/L)

16. Patients on a stable bisphosphonate or denosumab regimen for ≥30 days prior to randomization are eligible.
17. HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial.

For patients who have partners of childbearing potential:

18. Partner and/or patient must use a method of birth control with adequate barrier protection, deemed acceptable by the principle investigator during the study and for 3 months after last study drug administration.

4.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Previous treatment with Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223 or hemi-body irradiation within 6 months prior to randomization. Previous PSMA-targeted radioligand therapy is not allowed.
2. Any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy [including monoclonal antibodies]) within 28 days prior to day of randomization.
3. Any investigational agents within 28 days prior to day of randomization.
4. Known hypersensitivity to the components of the study therapy or its analogs.
5. Other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy.
6. Transfusion within 30 days of randomization.
7. Patients with a history of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired. For patients with parenchymal CNS metastasis (or a history of CNS metastasis), baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast).
8. A superscan as seen in the baseline bone scan.
9. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.
10. Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, active

hepatitis B or C, or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.

11. Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. Patients with adequately treated non-melanoma skin cancer, superficial bladder cancer and patients with prior history of malignancy who have been disease free for more than 3 years are eligible.

4.3 Subject withdrawal of consent for study or treatment

A patient may choose to withdraw his consent for participation in the study at any time. If a patient only withdraws consent for the treatment part of the study, the patient will continue to be followed for long-term follow-up unless he also specifically withdraws from the long-term follow-up period.

This trial design is intent to treat so that all subjects will be followed for approximately 24 months or until the overall censoring rate for survival reduces to a level identified in the SAP.

5. TREATMENT OF SUBJECTS

5.1 Treatment with the investigational medicinal product

5.1.1 Administration of ^{177}Lu-PSMA-617

Once every 6-weeks (± 1 week), 7.4 GBq (±10%) ^{177}Lu-PSMA-617 will be administered. A 7.4 GBq dose is equivalent to 200 mCi or 7400 MBq.

Treatment with ^{177}Lu-PSMA-617 must be performed in accordance with national and/or local radiation and safety requirements.

A saline flush with ≥10 mL of normal saline must be administered to ensure patency of the intravenous line before administering with ^{177}Lu-PSMA-617 administration.

^{177}Lu-PSMA-617 will be administered slowly by the intravenous route through an indwelling catheter and followed by a saline flush. The time of administration must be recorded. The total activity administered must be measured (GBq).

Vital signs will be collected 15 minutes before and at 30 and 60 minutes following injection.

Patients should also be monitored for any evidence of pain or burning sensation during the injection. Patients should be encouraged to maintain a good fluid intake on the day of treatment and following therapy.

A decision to order ^{177}Lu-PSMA-617 should be communicated to the sponsor or designee no later than 15 business days prior to the planned administration for each cycle.

5.1.2 Toxicity risk reduction and supportive care for ^{177}Lu-PSMA-617 injections

Supportive care should be provided as deemed necessary by the treating physician.

Oral hygiene
Patients should be advised to use sodium bicarbonate mouthwash during the first 3 days of each cycle.

Nausea and vomiting
Mild nausea and vomiting may occur without prophylactic therapy and antiemetic treatment is recommended. Oral or IV ondansetron (or equivalent) and/or dexamethasone or equivalent institutional anti-emetic regimen should be administered on the day of ^{177}Lu-PSMA-617 administration. If oral administration is given, it should occur at least 30 minutes before dosing and, if by injection, at least 15 minutes prior to infusing ^{177}Lu-PSMA-617.

Additionally, dexamethasone and domperidone/metoclopramide or institutional anti-emetic regimen may be administered on Days 2 and 3 of each cycle if required at the discretion of the investigator.

Other anti-emetics should be used as required as per standard clinical practice.

Additional suggested treatment guidelines
A listing of additional suggested treatment guidelines can be found in Appendix 2. These are to be used at the discretion of the investigator.

5.1.3 Management of toxicity adverse events: dosing delays and modification

Within the first few days of treatment the most common adverse events (AEs) are general fatigue and an increase in bone pain. Symptomatic hematologic toxicity may occur but is not common.

Every effort should be made to keep the treatment cycle of 6 weeks (±1 week) at the prescribed doses. At the discretion of the investigator, a dose of ^{177}Lu-PSMA-617 may be delayed or reduced. Table 1 provides dose modification recommendations. Only one reduction in administered activity is permitted. If a patient has further toxicity that would require an additional reduction in administered activity, treatment with ^{177}Lu-PSMA-617 must be discontinued. Once a dose is reduced, treatment with ^{177}Lu-PSMA-617 should not be re-escalated.

- If a treatment delay persists for >4 weeks, treatment with ^{177}Lu-PSMA-617 must be discontinued. If treatment with ^{177}Lu-PSMA-617 is discontinued due to an AE, abnormal laboratory value, or toxicity, treatment with best supportive/best standard of care may continue at the discretion of the investigator if the patient has not radiographically progressed as measured by PCWG3 criteria.

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Anemia, leukopenia, or neutropenia: • Hemoglobin <10 g/dL • WBC count <3.0 × 10^9/L • ANC <1.5 × 10^9/L	≥ Grade 2	Hold ^{177}Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Manage as deemed appropriate by investigator. The use of growth factors is permitted but should be discontinued once the AE resolves to Grade 1 or baseline. Checking hematinic levels (iron, B12, and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated for anemia.
Thrombocytopenia (platelet count of < 75 x 10^9/L)	≥ Grade 2	Hold ^{177}Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle. Transfusions may be given as clinically indicated for thrombocytopenia.
Non-platelet hematological toxicity (except lymphocytopenia that responds to medical intervention)	Grade 3 or Grade 4	Reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle
Serum creatinine increased ≥40% from baseline AND calculated creatinine clearance decreased >40% from baseline		Reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle
Salivary gland toxicity	≥ Grade 2	Reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle
Non-hematological, clinically significant toxicity not otherwise stated	≥ Grade 2	Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Electrolyte or metabolic abnormalities that are correctable within a 48 hr period without sequela	≥ Grade 2	Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Gastrointestinal toxicity	≥ Grade 3	Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Fatigue	≥ Grade 3	Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Pain	≥ Grade 3	Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Spinal cord compression		Hold ^{177}Lu-PSMA-617 administration until the compression has been adequately treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
Fracture in weight bearing bones		Hold ^{177}Lu-PSMA-617 administration until fracture is adequately stabilized/treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
AST or ALT >5 × ULN in the absence of liver metastases		Discontinue ^{177}Lu-PSMA-617
Renal toxicity	≥ Grade 3	Discontinue ^{177}Lu-PSMA-617
Any serious AE that requires drug discontinuation or treatment delay of >4 weeks		Discontinue ^{177}Lu-PSMA-617
Any unacceptable toxicity		Discontinue ^{177}Lu-PSMA-617

Note: Hematologic parameters (i.e., CBC with differential analysis) will be monitored every week in Cycle 1 only. Cycles 2 to 6, it will be monitored every 2 weeks. After Cycle 6, it will be monitored every 8 weeks.
AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; Lu = Lutetium; PSMA = prostate-specific membrane antigen; ULN = upper limit of normal; WBC = white blood cell

5.2 Best supportive/best standard of care

The best supportive/best standard of care for the patient in either arm will be administered as per physician's orders and protocol at the institution. Novel androgen axis drugs [NAADs] (i.e., enzalutamide or abiraterone) are allowed.

5.3 Concomitant medications/ supportive care

5.3.1 Permitted concomitant medications/ supportive care

The best supportive/best standard of care for the patient in either arm will be administered as per physician's orders and protocol at the institution. Patients will continue to be treated with best supportive/best standard of care until they require a treatment regimen not allowed on this study or have radiographic progressive disease as measured by PCWG3 criteria.

Patients receiving bisphosphonates, denosumab, zoledronic acid or similar therapy prior to randomization may be maintained on this therapy during the study. Bisphosphonates can be stopped or started at the discretion of the investigator throughout the study.

Patients must remain castrate and receive a luteinizing hormone-releasing hormone analogue (agonist or antagonist) or polyestradiol phosphate throughout the study.

Other treatments for prostate cancer, not specifically excluded as part of the study, should be used in accordance with the routine clinical practice and at the discretion of the investigator. These may include: corticosteroids, antiandrogens, or ketoconazole.

Local external beam radiotherapy, including palliative external radiation is allowed.

Supportive care should be provided as deemed necessary by the treating physician.

Medications for myelosuppression
Blood transfusion or erythropoietin stimulation agents are allowed throughout the study after randomization. Routine prophylaxis with GCSF/granulocyte-macrophage colony-stimulating factor and erythropoietin is not recommended. Nevertheless, use is permitted at the investigator's discretion.

Refer to Section 5.1.3 for guidance on the management of toxicity.

5.3.2 Prohibited concomitant medications

Investigational agents, cytotoxic chemotherapy, other systemic radio isotopes (e.g. radium-223), or hemi-body radiotherapy treatment may not be administered on study.

5.4 Monitoring treatment compliance

The investigational medicinal product will be administered only at the investigational site under the direction of the investigator. Compliance with ^{177}Lu-PSMA-617 therapy will be monitored and ensured.

5.5 Treatment discontinuation

Patients may discontinue the treatment part of the study for any of the following reasons:

- Evidence of tumor progression by radiological assessment as measured by PCWG3 criteria
- Unacceptable toxicity
- Patient non-compliance or voluntary withdrawal
- Required use of a prohibited treatment
- Evidence that the patient is no longer clinically benefiting
- At the sponsor's or investigator's discretion

Patients that discontinue treatment due to unacceptable toxicity should return to the clinic for the End of Treatment visit. Participants who discontinue ^{177}Lu-PSMA-617 due to unacceptable toxicity may continue to receive best supportive/best standard of care alone during the treatment part of the study until they discontinue the treatment part of the study and enter long term follow up.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1 Screening procedures and baseline assessments

Screening procedures and baseline assessments will be performed within 4 weeks of randomization except for baseline imaging. Baseline medical imaging (CT with contrast/ MRI, and bone scan) is to be performed within 28 days of start of treatment. Any medical imaging

done within this time frame may be accepted as the baseline imaging. The screening procedures are detailed in Table 2.

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Informed consent	As per local/central IRB/IEC/REB timing requirements but prior to the performance of any study specific procedures.
Inclusion/exclusion criteria	Refer to Section 4.1 and Section 4.2 for additional details.
Medical history	Collect medical history, including the following details about prior prostate cancer treatment(s): • Date of initial diagnosis • Approximate start and stop date of each therapy • Date and type of progression (e.g. PSA, radiological, bone, or no clinical benefit) • Site of progression (new lesions, existing lesions, or both) when available
Prior/concomitant medication review	
Full physical examination	Should be performed by a qualified medical practitioner.
Height	
Weight	
ECOG performance score	Refer to Appendix 4 for the ECOG performance score scale.
Vital signs	Includes: blood pressure, pulse, and respiratory rate
CT with contrast/MRI	CT with contrast /MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations The radiological technique used for measurement of the baseline images should also be the radiological technique used for each reassessment.
^{99m}Tc diphosphonate bone scan	Baseline and follow up radiological disease assessments must include bone scans performed with technetium-99m labeled diphosphonates as per the local standard of care for patients with prostate cancer. Use the PCCTC bone scan assessment tool to document lesions (included in Appendix 11).
Histology	Pathology report of the most recent biopsy required at enrollment.
Disease pattern	Bone, visceral, soft tissue, and lymph nodes
12-lead ECG	
Hematology	Refer to Section 6.3.1 for list of tests
Chemistry	Refer to Section 6.3.1 for list of tests

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Urinalysis, macroscopic (microscopic when indicated)	Refer to Section 6.3.1 for list of tests
Serum testosterone	
PSA	Includes PSA results and dates of 2 previous measurements. Prior measurements are needed to assess PSA velocity/doubling time.
BPI-SF, EQ-5D-5L and FACT-P	Baseline pain score assessment (BPI-SF) and HRQoL (EQ-5D-5L, FACT-P) assessments. HRQoL assessments may be either self-completed by the subject, or administered via face-to-face interview and completed by a caretaker/clinician.
Best supportive/best standard of care determination	To be decided prior to randomization, as part of screening.
PSMA PET/CT scan	To be done once all other eligibility requirements are confirmed. The metastatic lesion requirement may be confirmed at the same time as the baseline ^{68}Ga-PSMA-11 PET/CT[a] scan. Baseline ^{68}Ga-PSMA-11 PET/CT[a] scan must be done within 4 weeks of start of treatment but not within the 6 days prior to start of treatment. PSMA eligibility will be determined by central readers.
Screening registration	Initial screening registration should take place after the patient has signed the Informed Consent Form. It should be completed once all screening assessments have been completed and results confirmed except for metastatic lesion requirement and PSMA positivity.
Study enrollment	Study enrollment should take place after screening registration is completed and once the metastatic lesion requirement is confirmed by the site and PSMA positivity has been confirmed by the central readers. Patients randomized to the investigational arm are to begin dosing with ^{177}Lu-PSMA-617 within 28 days after randomization.

[a] For background and additional details on ^{68}Ga-PSMA-11, refer to the ^{68}Ga-PSMA-11 Investigator's Brochure.

BPI-SF = Brief Pain Inventory – Short Form; CT= computed tomography; ECG = electrocardiography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; HRQoL = Health-related quality of life; IEC = Independent Ethics Committee; IRB = Institutional Review Board; MRI = magnetic resonance imaging; PCCTC = Prostate Cancer Clinical Trials Consortium; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; REB = Research Ethics Board; RECIST = Response Evaluation Criteria in Solid Tumors;

6.2 Efficacy assessments

For the timing of efficacy assessments, refer to the schedule of assessments provided in Appendix 1.

6.2.1 Radiographic imaging for tumor assessments

Radiologic assessment should follow PCWG3 guidelines. Periodic radiographic imaging will include both:

- CT with contrast/MRI imaging
- Bone scans with technetium-99m labeled diphosphonates

CT with contrast/MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis.

Disease progression by bone scan will be defined as at least 2 new bone lesions at the first post-treatment scan, with at least two additional lesions on the next (confirmatory) scan (2+2 PCWG3 criteria, Scher et al 2016). For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan (2+2 PCWG3 criteria). If the second scan confirms the metastases, then the date of progression is the date of the scan when the first 2 new metastases were documented.

6.2.2 RECIST criteria

The responses of soft tissue, lymph node, and visceral lesions to treatment will be characterized using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations (see Appendix 6 and Appendix 7).

6.2.3 Symptomatic skeletal events

The time to the first SSE will measure the time to the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain, whichever occurs first.

6.2.4 Pain score

Pain will be assessed using the Brief Pain Inventory – Short Form (BPI-SF).

The Brief Pain Inventory- Short Form will be used as part of this study to assess the severity of pain and the impact of pain on daily functions. Full details regarding the BPI-SF, its validation and clinical application are available in the Brief Pain Inventory User Guide (Cleeland 2009).

A copy of the BPI-SF questionnaire is provided in Appendix 8.

6.2.5 Health-related quality of life

The ECOG Performance Status scale will be used to assess patients' ability to perform daily living tasks and their range of basic physical ability. A copy of the ECOG scale is provided in Appendix 4.

The EQ-5D-5L questionnaire will also be administered as a part of this study to assess HRQoL. EQ-5D is an international, validated, standardized, generic questionnaire for describing and valuing HRQoL (Rabin 2001). EQ-5D was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQoL Group 1990).

This instrument generates a preference-based health-state utility score (EQ-5D utility index) and an overall health-state score based on a visual analogue scale (EQ-5D VAS).

EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics and face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. The most recent version of EQ-5D is the EQ-5D-5L, which was developed to improve the instrument's sensitivity and to reduce ceiling effects. The number of dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) has not changed, however the new version includes five levels of severity in each of the existing dimensions in place of three (EuroQoL Group 2015). Full details regarding the EQ-5D-5L questionnaire, including references, are available at the EQ-5D website: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about.

A copy of the EQ-5D-5L questionnaire is provided in Appendix 9

The FACT-P questionnaire will also be administered as part of this study to specifically assess the HRQoL of prostate cancer patients. The FACT-P is made up of 2 parts: the FACT-G (general) questionnaire with 27 questions, and the Prostate Cancer Subscale (PCS) with an additional 12 questions. The FACT-G (Functional Assessment of Cancer Therapy – General) questionnaire is one of the most widely used HRQoL instruments and measures HRQoL in four different domains: Physical well-being, Functional well-being, Emotional well-being, and Social/Family well-being (Cella et al 1993). The PCS is designed specifically to measure prostate cancer-specific quality of life. Each item in both the FACT-G and PCS is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as global quality of life score with higher scores representing better QoL. The FACT system has a number of advantages as a method of measuring QoL:

- Questionnaires have been developed to reflect patients' concerns
- Measurements are reliable, reproducible, and have been validated in numerous studies (Cella et al 1993, Esper et al 1997)
- Available in over 45 different languages
- Designed for patient self-administration, but can also be administered by interview format (Webster et al 2003)

Full details regarding the FACT-P questionnaire, including references, are available at the FACIT website: http://www.facit.org/FACITOrg/Questionnaires.

A copy of the questionnaire (FACT-P version 4) is provided in Appendix 10.

HRQoL will be periodically assessed at baseline, prior to administration of each cycle of ^{177}Lu-PSMA-617, and through the End of Treatment visit.

6.2.6 Health Economics

A health economics (HE) sub-study will be performed. Core health resource use information will be collected, using case report forms (CRFs) on days in hospital and any outpatient visits. Data collected on concomitant medication may also be used in the economic analysis.

For the economic modelling, costs will be imputed on the basis of representative country unit costs at the point of analysis using standard fee schedules. Health outcomes will be assessed in terms of quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios. Quality adjustments will be based on patients' responses to the EQ-5D health status measure which will be administered at baseline, before each cycle of therapy, and each point of follow-up as part of the QoL questionnaire.

6.2.7 Clinical progression

Clinical progression will be assessed by the investigator. The following criteria should be used to determine when a patient has met the standard for unequivocal evidence of clinical progression:

- Marked escalation in cancer-related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical, or radiological intervention for complications due to tumor progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status to ≥ Grade 3 and a finding of the investigator that the deterioration indicates clinical progression
- In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

6.2.8 PSA levels

Local labs will measure PSA levels. Increases and decreases will be tracked to assess PSA responses as per PCWG3 (Appendix 7).

6.3 Safety assessments

6.3.1 Clinical laboratory evaluations

Local labs will perform hematology, chemistry, serum testosterone, and urinalysis testing.

Chemistry, urinalysis, and hematology testing will include the following:

Chemistry	• sodium • potassium • total and direct bilirubin • ALP • AST • ALT	• LDH • blood urea nitrogen • creatinine • uric acid • phosphorus • chloride	• bicarbonate • calcium • glucose • total protein • albumin
Urinalysis	• urine pH • protein content • specific gravity • appearance and color	• glucose • ketones	
Hematology	• complete blood count (white blood cell count and differential) • red blood cell count • hemoglobin • hematocrit • platelet count		

6.3.2 Vital signs

Blood pressure, pulse and respiratory rate will be assessed.

6.3.3 Electrocardiograms

A 12-lead ECG will be done at screening.

6.4 End of treatment visit procedures

The assessments and procedures to be done at the EOT visit are defined in the Schedule of Assessments tables, provided in Appendix 1.

6.5 Long-term follow-up procedures

A long-term follow-up period will collect AE assessments, and survival and treatment updates from patients every 3 months (± 1 month) via phone, email, or letter. Hematology and chemistry blood work will also be collected. Patients who withdraw their consent to participate in the treatment portion of the study will be asked for permission to continue long-term status updates.

7. ADVERSE EVENTS

7.1 Adverse event definitions

The following definitions comply with the ICH E2A guidance, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and the safety definitions of the World Health Organization (WHO) International Drug Monitoring Center.

Term	Definitions[a]
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Adverse Drug Reaction	For an investigational medicinal product all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
Serious Adverse Event (SAE) or Adverse Drug Reaction	A serious adverse event or reaction is any untoward medical occurrence that at any dose: • results in death; • is life-threatening; • requires inpatient hospitalization or prolongation of existing hospitalization; • results in persistent or significant disability/incapacity; or • is a congenital anomaly/birth defect. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Unexpected Adverse Drug Reaction[b]	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., Investigator's Brochure for an unapproved investigational medicinal product).

[a] ICH E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.
[b] Also referred to as a Suspected Unexpected Serious Adverse Reaction (SUSAR).
AE = adverse event; SAE = serious adverse event

7.2 Evaluating and recording adverse events

All adverse events (AEs) will be graded according to CTCAE v5.0.

AE monitoring for treatment-emergent ^{68}Ga-PSMA-11 events will begin with the administration of ^{68}GA-PSMA-11 and continue for a period of at least 6 days and will continue up to the first dose of ^{177}Lu-PSMA-617 for the investigational arm and up to Cycle 1 Day 1 for the best supportive/best standard of care-only arm. AE monitoring for treatment-emergent ^{177}Lu-PSMA-617 events will commence with initial dosing of ^{177}Lu-PSMA-617 and continue up to and including 30 days after the last dose of ^{177}Lu-PSMA-617. AE monitoring for the best supportive/best standard of care-only arm will commence with Cycle 1 Day 1 and continue up to and including 30 days after the last dose of best supportive/best standard of care.

All AEs and abnormal test findings, regardless of suspected causal relationship to ^{68}Ga-PSMA-11 and/or ^{177}Lu-PSMA-617, will be recorded in the patients' case histories. For all AEs sufficient information will be obtained to permit an adequate determination of the outcome of the event and an assessment of the casual relationship between the AE and ^{68}Ga-PSMA-11 and/or ^{177}Lu-PSMA-617. AEs or abnormal test findings felt to be associated with ^{68}Ga-PSMA-11 and/or

^{177}Lu-PSMA-617 will be followed until the event or its sequelae or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

The investigator will promptly review AEs and abnormal test findings to determine if: 1) the abnormal test finding should be classified as an AE; 2) there is a reasonable possibility that the AE was caused by ^{68}Ga-PSMA-11 and/or ^{177}Lu-PSMA-617; and 3) the AE meets the criteria for a serious adverse event (SAE). If the final determination of causality is "unknown and of questionable relationship to the study drug" the adverse event will be classified as associated with the use of the study drug for reporting purposes. If the final determination of causality is "unknown but not related to the study drug" the determination and rationale will be documented in the patient's case history.

7.3 Immediate Adverse Event Reporting

Endocyte will ensure that all relevant safety information as required by local and/or national laws, directives and/or regulations are reported to the appropriate Competent Authorities as well as the Principal Investigator and/or IRBs/Ethics Committees.

7.3.1 Serious Adverse Events

SAEs require expeditious handling and MUST IMMEDIATELY be reported upon discovery so the sponsor may comply with regulatory requirements.

Any SAE, regardless of causal relationship, must be reported to the Sponsor Contact listed in the Sponsor Contact section (Section 7.3.3) immediately (no later than 24 hours after the investigator becomes aware of the SAE) by emailing or faxing a completed SAE form to the number/email indicated and then confirming by telephone that the email/fax was received. Compliance with this time requirement is essential so that the sponsor may comply with its regulatory obligations.

Follow-up information relating to an SAE must be reported to the Sponsor Contact in Section 7.3.3 within 24 hours of receipt by the investigator by emailing or by faxing a completed SAE form to the number indicated and confirming by telephone that the fax was received. The patient should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified.

SAEs which are: 1) associated with ^{68}Ga-PSMA-11 and/or ^{177}Lu-PSMA-617; 2) fatal or life-threatening; and 3) unexpected, will be reported to the principal investigator and/or IRBs/Ethics Committee/Research Ethics Boards (REBs) and the Regulatory Authorities within 7 days of awareness of the respective information. Other SAEs which are: 1) associated with the investigational drug or study treatment; 2) non-fatal or non-life-threatening; and 3) unexpected will be reported to the principal investigator and/or IRBs/Ethics Committee/REBs and Regulatory Authorities within 15 days of awareness of the respective information.

7.3.2 Serious adverse event subject follow-up

Follow-up information to a reported SAE will be submitted to the principal investigator and/or IRBs/Ethics Committees and Competent Authorities in accordance with local regulations and international guidelines. If the results of the follow-up investigation show that an SAE that was

initially determined to not require reporting does, in fact, meet the requirements for reporting, the investigator will report the SAE to the principal investigator and/or IRBs/Ethics Committees/REBs in accordance with local regulations and international guidelines.

7.3.3 Sponsor Contact Information for Immediate Reporting

Serious adverse events and follow-up information should be reported on a completed serious adverse event report form to [redacted] by fax at [redacted] or emailed to [redacted] If reported by fax, please confirm receipt of fax via phone call to [redacted] at [redacted].

8. STATISTICS

This section outlines the general study design, study endpoints, and statistical analysis strategy for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR). Post hoc exploratory analyses will be clearly identified in the CSR. Full details will be in the Statistical Analysis Plan (SAP). Any deviations from the statistical plan will be described and justified in a protocol amendment and/or in the CSR.

All statistical analyses will be carried out using SAS version 9.3 (or later). The SAP will be written and finalized prior to the first planned interim analysis and without knowledge of any by-treatment group accumulated data. The SAP will provide a detailed and expanded description of the statistical methods outlined in this protocol. Additional analyses, such as in important subgroups, will be described.

8.1 Sample size and power determination

The sample size was determined based on the primary endpoint: overall survival. Planned enrollment for this study is approximately 750 subjects.

Under the null hypothesis, median survival is assumed to be 10 months on ^{177}Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median overall survival on active is assumed to be 13.7 months for a HR of 0.7306.

Based on a non-linear patient accrual profile over 13 months and a follow up of 24 months (or until the the overall censoring rate for survival reduces to a level identified in the SAP), a total of 750 patients randomized will yield 489 events.

With two interim analyses at 50% (243/489, expected approximately 16.5 months after first patient randomized) and 70% (344/489, expected approximately 20.5 months after first patient randomized) events with adjusted 1-sided p-values of 0.00153 and 0.00690 respectively and a 1-

sided p-value in the final analysis of 0.02266, this trial has 90% overall power and an overall Type I error rate of 0.025 1-sided.

The observed HRs that will meet the stated p-value thresholds at the first and second interim analyses, and at the final analysis, are 0.669, 0.754 and 0.825, respectively (corresponding to 4.9-month, 3.3-month, and 2.1 month increases in median overall survival assuming median OS on best supportive/best standard of care of 10 months). The cumulative probabilities of stopping at the first and second interims under the alternative hypothesis are 35.4% and 61.3% respectively.

8.2 Analysis populations

Analysis datasets are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients. Patient efficacy data in this dataset will be summarized by randomized treatment.
- **Response Evaluable Analysis Set**: The subset of patients in the FAS with evaluable disease by RECIST at baseline. Soft tissue response as measured by RECIST will be assessed in this dataset.
- **Safety Analysis Dataset**: There will be two safety datasets
    - The subset of patients who received as least one dose of ^{68}Ga-PSMA-11.
    - The subset of patients in the FAS who received as least one dose of randomized therapy. Patient safety data in this dataset will be summarized by treatment received.

8.3 Demographics and baseline disease characteristics

Demographic and baseline disease characteristic data will be summarized for each treatment with frequency distributions and/or descriptive statistics (mean, standard deviation, median, range, and/or relevant percentiles). Formal statistical tests comparing treatment groups will not be provided.

8.4 Patient disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. Reporting of patient disposition will include:

- A summary of data on patient discontinuation
- A summary of data on overall qualification status of all patients
- An account of all significant protocol deviations

All patients enrolled in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins, will be specified.

8.5 Efficacy analyses

8.5.1 Primary efficacy analysis

Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause.

Patients who are lost to follow-up or are alive at the time of analysis will be censored at the time they were last known to be alive or at the date of event cut-off for OS analysis. OS data will be displayed using Kaplan Meier curves from which median OS will be estimated for both treatment arms.

A stratified Cox proportional hazards regression model will be used to analyze OS in the FAS dataset. The model will include a single covariate for randomized treatment and will be stratified for the randomization stratification factors. The HR (active: control), its 95% confidence interval, and the associated 2-sided p-value will be presented. A supportive analysis will be provided via a stratified log-rank test, stratifying again for the randomization stratification factors.

8.5.2 Secondary efficacy analyses

Key secondary endpoints

Key secondary endpoints will be subject to Type I error control. These endpoints are:

1. rPFS
2. RECIST ORR and DCR
3. Time to SSE

Time to SSE and rPFS will be analyzed using a Cox regression model in the same manner as described for the primary endpoint. Objective response and disease control rate will be analyzed using logistic regression with a single covariate for randomized treatment and stratification for the randomization stratification factors. The odds ratio (active: control), its 95% confidence interval and associated 2-sided p-value will be presented. The DOR for binary response endpoints will also be summarized and presented using Kaplan-Meier curves.

To control the overall Type I error rate, if the primary endpoint is met, then the key secondary endpoints will be assessed using the Hochberg closed test procedure. This procedure is reasonable given the positive correlation between the 3 key secondary endpoints.

Additional Secondary Endpoints

Additional Secondary Endpoints will be assessed at the nominal 5% level, i.e. there will be no alpha control applied. These endpoints are:

1. To evaluate the safety and tolerability of ^{177}Lu-PSMA-617
2. Aspects of HRQoL will be self-reported by patients (or via interview format) using the EQ-5D-5L and FACT-P questionnaires, and pain will be assessed by patients using the BPI-SF.

3. Health economics
4. PFS is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
5. Biochemical response endpoints:
    d. Proportion of subjects who are PSA responders, defined as a patient who has achieved a ≥50% decrease from baseline that is confirmed by a second PSA measurement ≥4 weeks.
    e. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

Event-free survival endpoints will be analyzed using a Cox regression model in the same manner as described for the primary endpoint. Disease control rate DCR will be analyzed in the same manner as objective response rate and HRQoL will be analyzed in the same manner as pain score over time. Time to pain response will be analyzed using mixture distribution methodology akin to that described by Ellis et al 2008.

8.6 Safety analyses

8.6.1 Extent of exposure

The duration of exposure and dose intensity will be calculated. The relationship between dose intensity, duration of exposure, and frequency and severity of adverse events will be explored by data tabulation.

8.6.2 Analysis of adverse events

The frequency of treatment emergent adverse events (TEAEs) and SAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. The maximum NCI CTCAE grade and frequency of AEs will be summarized.

A ^{68}Ga-PSMA-11 TEAE is defined as an AE that was not present prior to dosing with ^{68}Ga-PSMA-11 but appeared following dosing, or was present at time of initial dosing but worsened during or after dosing. The treatment-emergent period will be defined as the period from the date of the first dose of ^{68}Ga-PSMA-11 up to 6 days after the date of the initial dose of ^{68}Ga-PSMA-11 or the first dose of ^{177}Lu-PSMA-617 for the investigational arm and Cycle 1 Day 1 for the best supportive/best standard of care-only arm.

A ^{177}Lu-PSMA-617 TEAE is defined as an AE that was not present prior to treatment with ^{177}Lu-PSMA-617 but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated). The treatment-emergent period will be defined as the period from the date of the first dose of ^{177}Lu-PSMA-617 up to 30 days after the date of the last dose of

^{177}Lu-PSMA-617 or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

Adverse events leading to permanent discontinuation of study drug and/or leading to death will be listed and tabulated.

8.6.3 Analysis of laboratory assessments

Laboratory values and change from baseline will be summarized by visit and treatment using descriptive statistics. Shift tables of the worst on-study laboratory toxicity based on CTCAE v5.0 grading relative to baseline will be presented by treatment group. Subject listings of laboratory toxicities ≥ Grade 3 will be provided.

8.6.4 Analysis of vital sign data

Vital sign data (observed and change from baseline) will be summarized using descriptive statistics by time point and treatment. Abnormal findings from physical examinations will be assessed for clinical significance which will be included in the AE listings and summaries.

8.7 Interim analyses

8.7.1 Interim efficacy analyses

As described above in Section 8.1, two formal interim efficacy analyses are planned at 50% and 70% of the total planned number of events. The purpose of these interim analyses is to allow early stopping for efficacy should sufficient statistical evidence be found to reject the null hypothesis of no survival effect. There will be no assessment for futility.

These interim analyses will be overseen by a fully Independent Data Monitoring Committee (IDMC) who may recommend stopping the study for superior efficacy at the first or second interim if the corresponding pre-specified 1-sided p-value threshold is met. An IDMC Charter will be approved and finalized by the IDMC members prior to the initiation of any interim analysis.

The IDMC can recommend a course of action, but the sponsor will make the final decision to continue or stop the trial based on either interim analysis.

8.7.2 Interim safety analyses

Safety monitoring interim analyses will be conducted quarterly by the IDMC. These analyses will commence following the completion of the first three months of study accrual.

8.8 Criteria for termination of trial

Safety data will be reviewed on an ongoing basis by an IDMC who will provide recommendations as necessary to the sponsor regarding the ongoing conduct of the study. The trial may also be terminated due to an early stop due to efficacy, completion of study enrollment and treatment/follow up.

9. ACCESS TO SOURCE DATA/DOCUMENTS

During the course of the study, a representative of Endocyte or its designee will be contacting and/or visiting the study sites to monitor the progress of the study. Contacts with the investigator and on-site visits for the purpose of data audits, including the comparison of source documents with case report forms (CRFs) and study agent accountability logs, will occur. The principal investigator or his/her representative will need to be available to the representative of Endocyte or its designee during these visits.

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, Endocyte, its designee, or responsible government agencies (as required by law) may review or copy source documents in order to verify case report form (CRF) data.

10. ETHICS

10.1 Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)

The investigator will obtain approval from the IRB/IEC/REB of the proposed clinical protocol and ICF for study recruitment and the approval will be provided to Endocyte or its designee prior to beginning the clinical trial. The only circumstance in which a deviation from the IRB/IEC/REB-approved clinical protocol/ICF may be initiated in the absence of prospective IRB/IEC approval is to eliminate an apparent immediate hazard to the research participants. In such circumstances, the investigator will promptly notify the IRB/IEC/REB of the deviation.

The investigator will promptly notify Endocyte of any regulatory inspection relating to this study, including either the institution or the IRB/IEC/REB, and will promptly provide Endocyte with a copy of any inspection report.

10.2 Informed consent

The investigator will make certain that an appropriate informed consent process is in place to ensure that potential participants, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research participants. The investigator, or his/her authorized designee, will obtain the written, signed ICF of each participant, or the participant's authorized representative, prior to performing any protocol-specific procedures on the participant. The date and time that the participant, or the participant's authorized representative, signs the ICF and a narrative of the issues discussed during the informed consent process will be documented in the participant's case history. The investigator will retain the original copy of the signed ICF, and a copy will be provided to the participant, or to the participant's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled participants are adequately addressed and

that the participants are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled participants for continued participation in the clinical study.

10.3 Health Insurance Portability and Accountability Act

Preparation of the Health Insurance Portability and Accountability Act (HIPAA) authorization form is the responsibility of the investigator and must include all elements required by the United States (US) Department of Health and Human Service's Privacy Rule. Prior to the beginning of the study, the investigator must have the IRB or the appropriate institution privacy board's written approval/favorable opinion of the HIPAA authorization form.

The HIPAA authorization must be signed and personally dated by the participant or their legally acceptable representative and by the person who obtained the authorization.

For sites located outside of the US, local regulations regarding protection of individually identifiable health information must be followed.

10.4 Confidentiality

All records will be kept confidential and the participant's name will not be released at any time. Participant records will not be released to anyone other than Endocyte or its designee(s) and responsible government agencies. Data sets for each participant will be identified by a unique number. If participant records are sent to Endocyte or its affiliates or designees, the participant's name or other identifying information will be masked and participant registration number or other unique identifier substituted.

11. COMPLIANCE AND QUALITY CONTROL

Independent auditing of the clinical study for protocol and GCP compliance may be conducted periodically at selected clinical sites by the Endocyte, Inc. Quality Assurance.

The purpose of the sponsor's audit is to evaluate trial conduct and compliance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements.

Site monitoring visits will be conducted periodically at each clinical site. During site monitoring visits the following but not exhaustive list of points will be reviewed: patient informed consent, patient recruitment and follow-up, AE reporting including SAE documentation, outcome events documentation and reporting, investigational drug allocation, storage and accountability, concomitant therapy use, and quality of data.

11.1 Compliance with Monitoring and Audits

Representatives of Endocyte or its designee must be allowed to visit (scheduled in advance) all study site locations periodically to assess the data, quality, and study integrity. On site, they will review study records and directly compare them with CRFs and discuss the conduct of the study

with the investigator and verify that the facilities remain acceptable. It is the responsibility of the investigator (or designee) to be present or available for consultation during such monitoring visits.

In addition, the study may be evaluated by Endocyte (or designee's) internal auditors and government inspectors who must be allowed access to CRFs, source documents, investigational medication records, and other study files. The sponsor's (or designee's) audit reports will be kept confidential to the extent permitted by law. The investigator must notify Endocyte promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Endocyte. The investigator agrees to promptly take any reasonable steps that are requested by Endocyte as a result of monitoring or auditing activities to address deficiencies in study conduct or documentation. In the event that Endocyte is unable to secure compliance with the Statement of investigator or study protocol and prematurely terminates a trial site, Endocyte will notify the FDA (as required by 21 CFR § 312.56) the site's IRB/IEC/REB, and other regulatory authorities, as required.

12. DATA HANDLING, RECORD KEEPING, AND COMPLIANCE

12.1 Investigational medicinal product accountability

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug destroyed.

12.2 Breaking the blind

Not applicable.

12.3 Data collection forms and source document identification

All source data will be retained by the trial site to ensure that, if requested, a monitor, auditor, or regulatory agency has access to the source documents.

Source data are the clinical findings and observations, laboratory and test data, and other information contained in source documents. Source documents are the original records (and certified copies of original records) including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, biopsy reports, ultrasound reports, pharmacy records, or any other similar reports or records of any procedures performed in accordance with the protocol. Source documentation may also include any sponsor CRF when source data is recorded directly onto a CRF.

The health-related quality of life questionnaires will utilize electronic Clinical Outcome Assessments (eCOA) technology for direct entry of the patient's responses. The eCOA will serve as source data.

A CRF will be completed for each participant enrolled into the clinical study. Patients are to be identified by, year of birth, patient screening number and patient enrollment number. Information recorded on the CRF must match the source data recorded on the source documents.

The investigator will review, approve, and sign/date completed CRFs. Their signature serves as attestation ensuring that all clinical and laboratory data entered on the CRF are complete, accurate, and authentic. This review and sign-off may be delegated to a qualified physician appointed as a sub-investigator by the principal investigator. The transfer of duties must be recorded on the Delegation Log (kept on file at the site) and all sub-investigators must be listed on FDA Form 1572 or equivalent regulatory statement. The investigator must ensure that all sub-investigators are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study agent(s).

12.4 Record maintenance and retention

The investigator will maintain records in accordance with GCP guidelines including the following:

- IRB/IEC/REB correspondence (including approval notifications) related to the clinical protocol, including copies of adverse event reports and annual or interim reports
- All versions of the IRB/IEC/REB approved clinical protocol and corresponding ICFs and, if applicable, participant recruitment advertisements
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol and laboratory certification
- Instructions for on-site preparation and handling of the investigational drug, study treatment, and other study-related materials if not addressed in the clinical protocol;
- Participant screening and enrollment logs and signed ICFs
- Investigational drug accountability records, including documentation of drug return or destruction
- A summary of the final clinical study results

12.5 Archiving

Endocyte and the investigator will retain the records and reports associated with the clinical trial as required by local regulatory requirements after the marketing application is approved for the investigational drug. If a marketing application is not submitted or approved for the investigational drug the information will be retained until two years after investigations under the Investigational New Drug Application/Clinical Trial Application have been discontinued and the FDA/EMA/CA notified.

13. PUBLICATION POLICY

Endocyte and the investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Endocyte and the investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by the investigators or their personnel and associates resulting from or relating to this study must be submitted to Endocyte for review 60 days before submission for publication or presentation.

If the proposed publication or presentation contains patentable patient matter, which, at Endocyte's sole discretion, warrants intellectual property protection, Endocyte may delay any publication or presentation for up to 60 days after approval for the purpose of pursuing such protection.

14. REFERENCES

Ahmadzadehfar et al 2016
Ahmadzadehfar H, Eppard E, Kürpig S, Fimmers R, Yordanova A, Schlenkhoff CD, et al. Therapeutic response and side effects of repeated radioligand therapy with 177Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. Oncotarget. 2016;7(11):12477-88.

Ahmadzadehfar et al 2015
Ahmadzadehfar H, Rahbar K, Kürpig S, Bögemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with 177Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. EJNMMI Research. 2015;5:36.

Azad et al 2015
Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of Enzalutamide Following Abiraterone Acetate in Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer Patients. European Urology 2015, 67 23-29.

Badrising et al 2014
Badrising S, van der Noort V, van Oort IM, et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. Cancer 2014; 120:968-75.

Benešová et al 2015
Benešová M, Schäfer M, Bauder-Wüst U, Afshar-Oromieh A, Kratochwil C, Mier W, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. J Nucl Med. 2015;56(6):914–20.

Brasso et al 2015
Brasso K, Thomsen FB, Schrader AJ, Schmid SC, Lorente D, Retz M, Merseburger AS, von Klot CA, Boegemann M, de Bono J. Enzalutamide Antitumour Activity Against Metastatic

Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis. European urology. 2015;68(2):317-24.

Bray et al 2012
Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013 Mar 1;132(5):1133-45. doi: 10.1002/ijc.27711. Epub 2012 Jul 26.

Bostwick et al 1998
Bostwick DG, Pacelli A, Blute M, Roche P, and Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer. 1998;82:2256-61.

Cella et al 1993
Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993 Mar;11(3):570-9.

Cella et al 2009
Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy--Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. Value Health. 2009 Jan-Feb;12(1):124-9.

Cheng et al 2015
Cheng HH, Nadal R, Azad A, Gulati R, et al. Activity of enzalutamide in men with metastatic castration resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. Prostate Cancer Prostatic Dis. 2015; 18(2): 122–127. doi:10.1038/pcan.2014.53.

Cleeland 2009
Cleeland, CS. The Brief Pain Inventory User Guide. 2009. Available at: www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf.

Das et al 2016
Das T, Guleria M, Parab A, Kale C, Shah H, Sarma HD, et al. Clinical translation of (177)Lu-labeled PSMA-617: Initial experience in prostate cancer patients. Nucl Med Biol. 2016; 43(5): 296–302.

Delker et al 2016
Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2016;43(1):42-51.

Ellis et al 2008
Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. Contemp Clin Trials. 2008 Jul;29(4):456-65.

Emmett et al 2017
Emmett L, Willowson K, Violet J, Shin J, Blanksby A, and Lee J. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. J Med Radiat Sci. 2017 Mar; 64(1):52–60.

Esper et al 1997
Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology. 1997 Dec;50(6):920-8.

EuroQoL Group 1990
EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199-208.

EuroQoL Group 2015
EuroQol Group. EQ-5D-5L User Guide Basic information on how to use the EQ-5D-5L instrument. April 2015, Version 2.1. Retrieved from https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

Ferdinandus et al 2017
Ferdinandus J, Eppard E, Gaertner FC, Kürpig S, Fimmers R, Yordanova A, et al. Predictors of Response to Radioligand Therapy of Metastatic Castrate-Resistant Prostate Cancer with 177Lu-PSMA-617. J Nucl Med. 2017 Feb;58(2):312-319.

Ferlay et al 2013
Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on day/month/year.

Flaig et al 2016
Flaig TW, Potluri RC, Ng Y, Todd MB, and Mehra M. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. Cancer Med. 2016;5(2):182-91.

Ghosh and Heston 2004
Ghosh A and Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004;91:528–39.

Haberkorn et al 2016
Haberkorn U, Eder M, Kopka K, Babich JW, and Eisenhut M. New Strategies in Prostate Cancer: Prostate-Specific Membrane Antigen (PSMA) Ligands for Diagnosis and Therapy. Clin Cancer Res. 2016 Jan 1;22(1):9-15.

Haug et al 2016
Haug AR, Shariat S, Eidherr H, Vraka C, Wadsak W, Mitterhauser M, et al. Initial experience with aggressive treatment of metastastic prostate cancer using 3 cycles of 7.4 GBq [177Lu]-PSMA every 4 weeks. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S212 EPW11.

Hillier et al 2009
Hillier SM, Maresca KP, Femia FJ, Marquis JC, Foss CA, Nguyen N, et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. Cancer Res. 2009;69(17), 6932–40.

Hofman et al 2017
Hofman MS, Sandhu S, Eu P, Price J, Akhurst T, Iravani A, et al. Lutetium-177 PSMA (LuPSMA) theranostics phase II trial: Efficacy, safety and QoL in patients with castrate-resistant prostate cancer treated with LuPSMA. [abstract/presentation] In 2017 European Society for Medical Oncology Annual Meeting; 2017 Sep 8-12; Madrid, Spain. Ann Oncol 2017; 28 (suppl_5):v269-v294.

Kirby et al 2011
Kirby M, Hirst C, and Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract. 2011 Nov;65(11):1180-92.

Kulkarni et al 2016
Kulkarni HR, Singh A, Schuchardt C, Niepsch K, Sayeg M, Leshch Y, et al. PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. J Nucl Med. 2016 Oct;57(Suppl 3):97S-104S.

Kratochwil et al 2015
Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benešová M, Mier W, et al. [^{177}Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42(6):987–88.

Kratochwil et al 2016
Kratochwil C, Giesel FL,Stefanova M, Benešová M, Bronzel M, Afshar-Oromieh A, Mier W, Eder M, Kopka K, Haberkorn U. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with 177Lu-labeled PSMA-617. J Nucl Med. 2016;57(8):1170-1176.

Leuschner 2016
Leuschner J. Subchronis toxicity study of PSMA-617 by intravenous administration to male CD® rats. LPT Report No. 32508 2016, November 12, 2016.

Loriot et al 2013
Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, … and Massard C. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Annals of Oncology 2013 24: 1807–1812. doi:10.1093/annonc/mdt136

Mannweiler et al 2009
Mannweiler S, Amersdorfer P, Trajanoski S, Terrett JA, King D, and Mehes G. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. Pathol Oncol Res. 2009 June;15(2):167–72.

Noonan et al 2013
Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Annals of Oncology 2013 24: 1802–1807. doi:10.1093/annonc/mdt138

Rabin 2001
Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001 Jul;33(5):337-43.

Rahbar et al 2016a
Rahbar K, Bode A, Weckesser M, Avramovic N, Claesener M, Stegger L, et al. Radioligand Therapy With 177Lu-PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer. Clin Nucl Med. 2016a;41(7):522-528.

Rahbar et al 2016b
Rahbar K, Schmidt M, Heinzel A, Eppard E, Bode A, Yordanova A, et al. Response and Tolerability of a Single Dose of 177Lu-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis. J Nucl Med. 2016b;57(9):1334-38.

Rahbar et al 2017
Rahbar K, Ahmadzadehfar J, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. J Nucl Med. 2017;58(1):85-90.

Rahbar et al 2018
Rahbar K, Boegemann M, Yordanova A, Eveslage M, Schäfers M, Essler M, Ahmadzadehfar H. PSMA targeted radioligand therapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. Eur J Nucl Med Mol Imaging. 2018 Jan;45(1):12-19.

Rajasekaran et al 2003
Rajasekaran SA, Anilkumar G, Oshima E, Bowie JU, Liu H, Heston WD, et al. A Novel Cytoplasmic Tail MXXXL Motif Mediates the Internalization of Prostate-specific Membrane Antigen. Mol Biol Cell. 2003;14(12):4835-4845.

Rathke et al 2017
Rathke H, Giesel FL, Flechsig P, Kopka K, Mier W, Hohenfellner M, Haberkorn U, Kratochwil C. Repeated Lu-177-PSMA-617 radioligand therapy using treatment activities up to 9.3 GBq. J Nucl Med. 2017 Aug 10. pii: jnumed.117.194209. doi: 10.2967/jnumed.117.194209. [Epub ahead of print]

Rathore et al 2016
Rathore H, Shah H, Aland P, Chaudhuri P, Bharadwaj T, Kale C, et al. Assessment of response, clinical evaluation and toxicity of radioligand therapy (RLT) with 177-Lutetium-DKFZ-617-labelled Prostate specific membrane antigen (177-Lu-DKFZ-617-PSMA) for metastatic castrate

resistant prostate cancer (mCRPC): An initial experience in Jaslok. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S414 EP482.

Ross et al 2003
Ross JS, Sheehan CE, and Fisher H. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res. 2003;9:6357–62.

Saad et al 2004
Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone-Refractory Prostate Cancer. J Natl Cancer Inst. 2004;96(11):879–82.

Scher et al 2015
Scher HI, Solo K, Valant J, Todd MB, and Mehra M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. PLoS One. 2015 Oct 13;10(10):e0139440.

Scher et al 2016
Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Work Group 3. J Clin Oncol 2016;34(12):1402–18.

Siegel et al 2017
Siegel RL, Miller KD, and Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.

Smith et al 2016
Smith M, De Bono J, Sternberg C, Le Moulec S, Oudard S, De Giorgi U, et al. Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. J Clin Oncol. 2016;34:3005-13.

Soydal et al 2016
Soydal C, Ozkan E, Nak D, and Kucuk ON. The First Experience on Lutetium (lu)-177 Prostate Specific Antigen (PSMA) Treatment in Castration Resistant Prostate Cancer Patients. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S415 EP485.

Webster et al 2003
Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes. 2003 Dec 16;1:79.

Wegen et al 2016
Wegen S, Eppard E, Kürpig S, Essler M, Yordanova A, Hauser S, et al. Treatment response according to PSA changes in patients undergo more than one cycle of 177Lu-PSMA-617 therapy. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S213 EPW14.

Weinfurt et al 2005
Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, et al. The significance of skeletal-related events for the health related quality of life of patients with metastatic prostate cancer. Ann Oncol. 2005;16(4):579–84.

Yadav et al 2017
Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, et al. 177Lu-DKFZ-PSMA-617 therapy with metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. Eur J Nucl Med Mol Imaging. 2017;44(1):81-91.

Zielinski et al 2014
Zielinski RR, Azad AA, Chi KN, Tyldesely S. Population-based impact on overall survival after the introduction of docetaxel as standard therapy for metastatic castration resistant prostate cancer. Can Urol Assoc J. 2014 Jul;8(7-8):E520-3.

Appendix 1 Schedules of Assessments

Table 3 Schedule of assessments: ^{177}Lu-PSMA-617 plus best supportive/best standard of care arm (Cycle 1)

Study Period:	Cycle 1					
Cycle Week:	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
Cycle Day:	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**
Concomitant medication review	X----------					----------X
AE monitoring[a]	X----------					----------X
Weight	X[b]					
ECOG	X[b]					
Directed physical exam	X[b]					
Vital signs[c]	X[b]					
EQ-5D-5L	X[d,f]					
FACT-P	X[d,f]					
BPI-SF	X[d,f]					
Administer ^{177}Lu-PSMA-617	X					
Best supportive/best standard of care	As per physician's orders					
Hematology[e]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Chemistry[e]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Serum testosterone	X[b]					
PSA	X[b]					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (± 4 days) after first dose of ^{177}Lu-PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days) through the End of Treatment visit.					

[a] Adverse event monitoring for treatment-emergent ^{177}Lu-PSMA-617 events will commence with initial dosing of ^{177}Lu-PSMA-617

[b] Within 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 8, 15, 22, 29, and 36.

[c] Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1) and at 15 minutes before, 30 minutes post, and 60 minutes post ^{177}Lu-PSMA-617 administration.

[d] To be completed prior to drug administration on Day 1.

[e] Hematology and chemistry to be done every week for Cycle 1 only.

[f] HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

Table 4 Schedule of assessments: ^{177}Lu-PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Study Period:	**Cycles 2-6***						**After Cycle 6***	**End of Treatment[g]**	**Long-term follow-up**
Cycle Week:	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Every 8 weeks (± 1 week)**		**Every 3 months (± 1 month)**
Cycle Day:	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**			**Collect:** • Hematology • Chemistry • Survival • New treatment: • Start/stop dates • Best response • Type of response • AE assessment
Concomitant medication review	X----------X[a]						X[a]	X	
AE monitoring[b]	X----------X[a]						X[a]	X	
Weight	X[c]						X[c]	X	
ECOG	X[c]						X[c]	X	
Directed physical exam	X[c]						X[c]	X	
Vital signs[d]	X[c]						X[c]	X	
EQ-5D-5L	X[e,h]						X[e,h]	X[h]	
FACT-P	X[e,h]						X[e,h]	X[h]	
BPI-SF	X[e,h]						X[e,h]	X[h]	
Administer ^{177}Lu-PSMA-617	X								
Best supportive/ best standard of care	As per physician's orders						As per physician's orders		
Hematology[f]	X[c]		X[c]		X[c]		X[c]	X	
Chemistry[f]	X[c]		X[c]		X[c]		X[c]	X	
Serum testosterone	X[c]						X[c]	X	
PSA	X[c]						X[c]	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (± 4 days) after first dose of ^{177}Lu-PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days) through the end of treatment visit								

[*] After the Cycle 4 dose of ^{177}Lu-PSMA-617 and prior to Cycle 5 Day 1, the investigator should determine if:
- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- has shown good tolerance to the ^{177}Lu-PSMA-617 treatment.

If the patient meets the criteria above, and agrees to continue with additional treatment of ^{177}Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu-PSMA-617 treatment, then no additional doses of ^{177}Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ^{177}Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

[a] Phone evaluation is allowed during Weeks 2, 4, and 6.

[b] Adverse event monitoring for treatment-emergent ^{177}Lu-PSMA-617 events will commence with initial dosing of ^{177}Lu-PSMA-617 and continue up to and including 30 days after the last dose of ^{177}Lu-PSMA-617.

[c] Within 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 15, and 28.

[d] Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1) and at 15 minutes before, 30 minutes post, and 60 minutes post ^{177}Lu-PSMA-617 administration.

[e] To be completed prior to drug administration (if applicable) on Day 1.

[f] For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every 8 weeks (±1 week). If at any time, WBC count $<3.0 \times 10^9$/L, ANC is $<1.5 \times 10^9$/L, platelet count is $<100 \times 10^9$/L or hemoglobin level is <9 g/dL, hematologic parameters (i.e., CBC with differential analysis) should be done no less frequently than once each week until resolution to Grade 1 or baseline. If at any time there is a ≥ Grade 2 related chemistry lab result, chemistry should be done no less frequently than once each week until resolution to Grade 1 or baseline.

[g] To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose of ^{177}Lu-PSMA-617 or best supportive/best standard of care, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study

[h] HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

AE = adverse event; ANC= absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; WBC = white blood cell

Table 5 Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)

Study Period:	Cycle 1					
Cycle Week:	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
Cycle Day:	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**
Concomitant medication review	X----------					X
AE monitoring[b]	X----------					X
Weight	X[a]					
ECOG	X[a]					
Directed physical exam	X[a]					
Vital signs[c]	X[a]					
EQ-5D-5L	X[d,f]					
FACT-P	X[d,f]					
BPI-SF	X[d,f]					
Best supportive/ best standard of care	As per physician's orders					
Hematology[e]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Chemistry[e]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Serum testosterone	X[a]					
PSA	X[a]					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (± 4 days) after first dose of best supportive/best standard of care for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days) through the End of Treatment visit					

[a] Within 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 8, 15, 22, 29, and 36.
[b] Adverse event monitoring will begin Cycle 1 Day 1
[c] Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1).
[d] To be completed prior to any drug administration (if applicable) on Day 1.
[e] Hematology and chemistry to be done every week for Cycle 1 only.
[f] HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

Table 6 Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU)

Study Period:	**Cycles 2-6**						**After Cycle 6**	**End of Treatment[f]**	**Long-term follow-up**
Cycle Week:	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Every 8 weeks (± 1 week)**		**Every 3 months (± 1 month)**

Cycle Day:	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**			**Collect:**
									• Hematology
									• Chemistry
									• Survival
									• New treatment:
									  • Start/stop dates
									  • Best response
									  • Type of response
									• AE assessment

Concomitant medication review	X----------X[a]						X[a]	X	
AE monitoring	X----------X[a]						X[a]	X	
Weight	X[b]						X[b]	X	
ECOG	X[b]						X[b]	X	
Directed physical exam	X[b]						X[b]	X	
Vital signs[c]	X[b]						X[b]	X	
EQ-5D-5L	X[d,g]						X[d,g]	X[d,g]	
FACT-P	X[d,g]						X[d,g]	X[d,g]	
BPI-SF	X[d,g]						X[d,g]	X	
Best supportive/best standard of care	As per physician's orders						As per physician's orders		
Hematology[e]	X[b]		X[b]		X[b]		X[b]	X	
Chemistry[e]	X[b]		X[b]		X[b]		X[b]	X	
Serum testosterone	X[b]						X[b]	X	
PSA	X[b]						X[b]	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (± 4 days) after first dose of best supportive/best standard of care for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days) through the end of treatment visit								

[a] Phone evaluation is allowed during Weeks 2, 4, and 6.
[b] Within 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 15, and 29.

[c] Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1).
[d] To be completed prior to drug administration (if applicable) on Day 1.
[e] For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every 8 weeks (± 1 week). If at any time, WBC <3.0 x 10^9/L, ANC is <1.5 x 10^9/L, platelet count is <100 x 10^9/L or hemoglobin level is <9 g/dL, hematologic parameters (i.e., CBC with differential analysis) should be done no less frequently than once each week until resolution to Grade 1 or baseline. If at any time there is a Grade 2 related chemistry lab result, chemistry should be done no less frequently than once each week until resolution to Grade 1 or baseline.
[f] To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose of best supportive/best standard of care, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study.
[g] HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; WBC = white blood cell count

Appendix 2 Suggested treatment guidelines

The following are suggested guidelines for clinical support during ^{177}Lu-PSMA-617 administration. They are to be used at the discretion of the investigator.

- Cooling the salivary glands from 30 min. before and up to 4 hours after the ^{177}Lu-PSMA-617 injection for reducing the risk of salivary glands radiation injuries is optional and depends on center practice.
- 500 mL of 0.9% (i.e., normal) saline may be infused at a rate of 125 mL/hour to begin after administration of ^{177}Lu-PSMA-617. Additionally, fluid intake should be encouraged on the day of treatment.
- In patients with high tumor burden or gout allopurinol may be started within 7 days and up to 10 days following ^{177}Lu-PSMA-617 therapy

Appendix 3 Principal Investigator Signature

I have read this clinical protocol, no. PSMA-617-01, in its entirety and:

- I agree to implement and conduct this clinical study diligently and in strict compliance with the protocol, good clinical practices, and all applicable national, federal, and local laws and/or regulations.
- I agree that this clinical protocol will not be modified by me or any member of my staff without the written consent of Endocyte, Inc. and, if required, I will receive approval of these modifications by my institution's IRB/REB/Independent Ethics Committee (IEC).
- I certify that neither I nor any member of my staff has been disqualified or debarred by the Food and Drug Administration (FDA), European or any other regulatory bodies for clinical investigations or any other purpose.
- I understand that this clinical protocol and the accompanying clinical Investigator's Brochure contains trade secrets and/or commercial information that are privileged and/or confidential and may not be disclosed unless such disclosure is required by national, federal, or local laws and/or regulations.

Pursuant to 21 CFR § 312.53(c), each US investigator will complete and sign FDA Form 1572, Statement of Investigator, prior to participating in the study. The completed form, along with a curriculum vitae, will be returned to Endocyte and maintained on record.

Form FDA 1572, Statement of Investigator, which must be completed, is available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf

Principal Investigator Signature	Date
Name (Printed)	
Title (Printed)	

Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

Eastern Cooperative Oncology Group Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.
**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *Journal of Chronic Diseases*; 1960:11:7-33.

Appendix 5 Common Terminology Criteria for Adverse Events

The complete NCI CTCAE (version 5.0) can be found at the following site:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

Appendix 6 Response Evaluation Criteria in Solid Tumors

The latest RECIST guidelines (version 1.1) can be found at the following site:
http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf

Appendix 7 Prostate Cancer Working Group 3 Recommendations

The sections that apply to this trial are the criteria for prostate-specific antigen (PSA) response and progression, and the criteria for bone lesion "prevent/delay end points" (progression). It is based on the PCWG3 recommendations. Please note that not all the recommendations listed below are applicable to this patient population or to the specifics of this study.

Variable	PCWG3 (2016)
PSA	• Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drug • Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression • Ignore early rises (prior to 12 weeks) in determining PSA response **For control/relieve/eliminate endpoints:** • Describe absolute changes in PSA over time from baseline to best response **For delay/prevent endpoints: Decline from baseline:** • Record time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend) **No decline from baseline:** • PSA progression ≥25% and ≥2 ng/mL after 12 weeks
Soft-tissue lesions	**For control/relieve/eliminate end points:** Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats: • Record up to 5 lesions per site of disease • Record changes in nodal, lung, liver adrenal and central nervous system (CNS) sites separately • Only report changes in lymph nodes that were ≥1.5 cm in diameter in short axis at baseline • Record changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separately • Only report changes in visceral lesions (liver, lung, adrenal, CNS) that were ≥1.0 cm in the longest dimension • Record complete elimination of disease at any site separately • Confirm favorable change with second scan • Record changes using waterfall plot **For delay/prevent end points:** • Record changes in nodal and visceral disease separately • Record up to 5 lesions per site of spread • Use RECIST 1.1 criteria for progression, but clearly record type of progression (growth of existing lesions vs development of new lesions) separately by site. With additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. (Particularly important when anticipated effect on PSA is delayed or for biologic therapies) • Previously normal (<1.0 cm) lymph nodes must have grown by ≥5 mm in the short axis from baseline or nadir and be ≥1.0 cm in the short axis to be considered to have progressed. Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable. For existing pathologic adenopathy (≥1.5 cm), progression is defined per RECIST 1.1

Bone	For control/relieve eliminate end points: • Record outcome as new lesions, no new lesions or resolved lesion • First scheduled reassessment: o No new lesions: continue therapy o New lesions: perform a confirmatory scan 6 or more weeks later • Confirmatory scan: o No new lesions: continue therapy o Additional new lesions: progression • Subsequent scheduled reassessments: o No new lesions: continue o New lesions: progression • Changes in intensity or uptake do not constitute regression or progression For prevent/delay end points (progression): • Exclude pseudoprogression in the absence of symptoms or other signs of progression • At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule) • If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented • For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan • Date of progression is the date of the scan that first documents the second lesion • Changes in intensity of uptake alone do not constitute either progression or regression • Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
Symptoms	Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use). **For control/relieve eliminate end points:** • Serial (eg, daily x 7 days) assessments at each time point can improve the stability of values Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement. **For delay/prevent end points:** Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use). Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later). Time to deterioration of physical function and/or health-related quality of life (HRQoL) scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire.

Refer to Scher et al 2016 for more details.

CNS = central nervous system; HRQoL = health-related quality of life; PCWG3 = Prostate Cancer Working Group 3; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

Appendix 8 BPI-SF (*sample only, not for patient use)*

Brief Pain Inventory (Short Form)

Time: ____ : ____ ☐ AM ☐ PM

Today's Date (day, month, year):

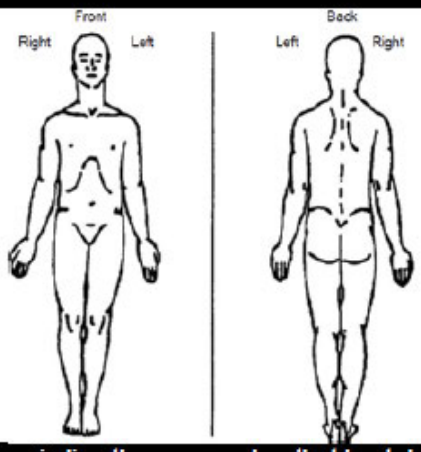
☐ JAN ☐ FEB ☐ MAR ☐ APR ☐ MAY ☐ JUN ☐ JUL ☐ AUG ☐ SEP ☐ OCT ☐ NOV ☐ DEC

__ __ - Day - __ __ __ __ Year

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that best describes how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Page 1 of 2

Today's Date (Day, Month, Year): |__|__|-|__|__|__|-|__|__|__|__|
(Example: 08-FEB-2016) DAY MONTH YEAR

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (inculdes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Please place an "X" in the appropriate box to indicate who completed the form:

☐ Patient

☐ Another person read the patient the questions and marked the form with the patient's answers

Appendix 9 EQ-5D-5L (European Quality of Life (EuroQol) – 5 Domain 5 Level scale) (*sample only, not for patient use)*

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

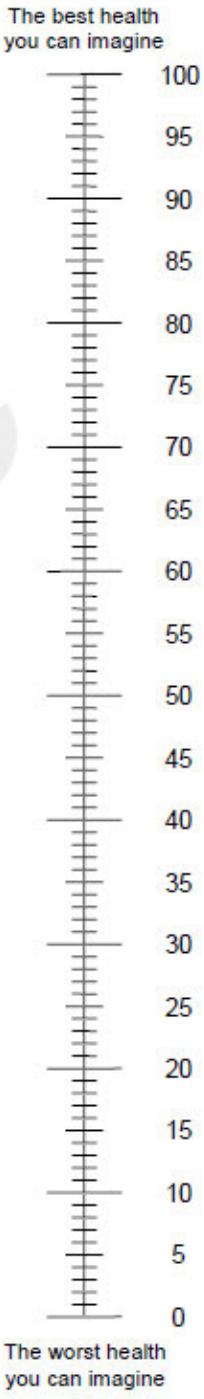
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 10 FACT-P (Functional Assessment of Cancer Therapy – Prostate) *(sample only, not for patient use)*

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

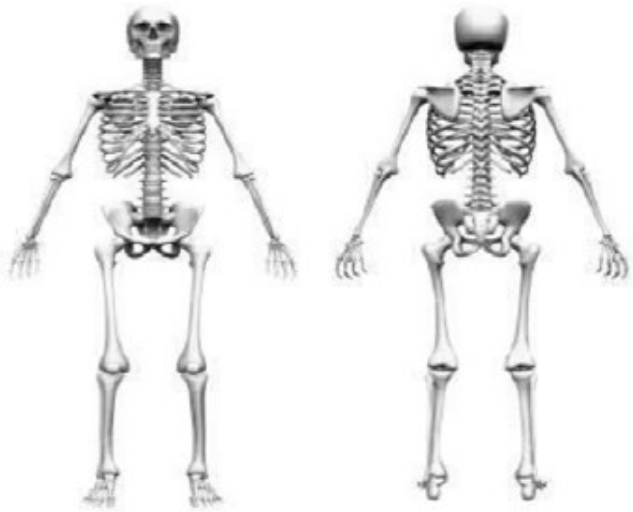
	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Appendix 11 PCCTC Bone Scan Assessment Tool

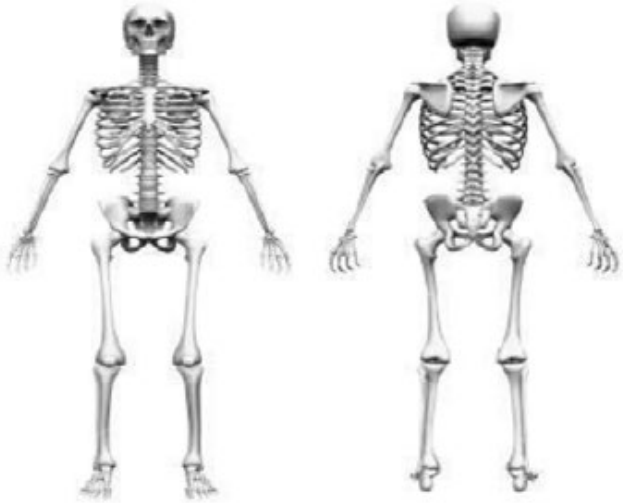
Screening Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	☐ Yes ☐ No [do not fill out the rest of the form]
If yes, indicate total number of lesions related to metastatic disease at Screening: ☐ 1 ☐ 2-4 ☐ 5-9 ☐ 10-20 ☐ >20	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

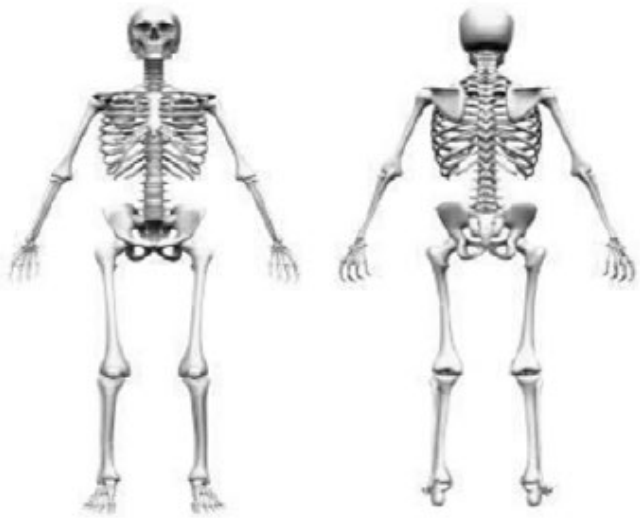
Week 8 BASELINE Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	☐ Yes ☐ No [do not fill out the rest of the form]
If yes, indicate total number of NEW lesions compared to Screening Bone Scan: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ >5	
Check Region(s) of NEW Disease Post-Screening: ☐ Skull ☐ Thorax ☐ Spine ☐ Pelvis ☐ Extremities	**Draw site(s) of NEW lesion(s) on skeleton:** 
Are there 2 or more NEW lesions at this Week 8 Bone Scan compared to the Screening Bone Scan?	☐ Yes* ☐ No
** Presence of new lesions at this time does not confirm progression*	
Clinical Impression: ☐ Improved ☐ Stable ☐ Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Week 16 Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	☐ Yes ☐ No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ >5	
Check Region(s) of NEW Disease Post-Screening: ☐ Skull ☐ Thorax ☐ Spine ☐ Pelvis ☐ Extremities	**Draw site(s) of NEW lesion(s) on skeleton:** 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?	☐ Yes ☐ No [Not PD]
Were there 2 or more NEW lesions at the Week 8 Bone Scan compared to the Screening Bone Scan *AND* were there 2 or more NEW lesions compared to the Week 8 Bone Scan?	☐ Yes [PD] ☐ No [Not PD]
Clinical Impression: ☐ Improved ☐ Stable ☐ Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Week ☐ 24 ☐ 36 ☐ 48 ☐ 60 ☐ 72 ☐ 84 ☐ ___ **Scan**

Bone Scan Date:	__ __ - __ __ __ - __ __ __ __ D D M M M Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	☐ Yes ☐ No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ >5	
Check Region(s) of NEW Disease Post-Screening: ☐ Skull ☐ Thorax ☐ Spine ☐ Pelvis ☐ Extremities	**Draw site(s) of NEW lesion(s) on skeleton:** 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?	☐ Yes ☐ No [Not PD]
Does this bone scan confirm (2+2) the presence of 2 or more new lesions seen since the Week 8 Bone Scan?	☐ Yes [PD] ☐ No [Not PD]
Clinical Impression: ☐ Improved ☐ Stable ☐ Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

ENDOCYTE
A Novartis Company

PROTOCOL NO. PSMA-617-01:

VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF ^{177}LU-PSMA-617 IN THE TREATMENT OF PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)

Clinical Protocol No.:	PSMA-617-01
Version No.:	4.0
Date:	08 July 2019
IND No.:	133,661 (^{177}Lu-PSMA-617) 133,925 or site equivalent (^{68}Ga-PSMA-11)
EudraCT No.	2018-000459-41
Phase of Study:	Phase 3
Investigational Products:	^{177}Lu-PSMA-617; ^{68}Ga-PSMA-11
Sponsor:	Endocyte, Inc., A Novartis Company 3000 Kent Avenue - Suite A1-100 West Lafayette, Indiana 47906-1075 (765) 463-7175
Medical Officer:	[redacted] 8910 Purdue Road, Suite 250 Indianapolis, Indiana 46268 [redacted]

Approval:

[signed electronically in MasterControl]

Medical Officer Signature *Date*

Site Principal Investigator Signature

The investigator signature page is provided in Appendix 3 along with a link to form FDA 1572 or equivalent if the site is outside of the United States.

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Revision History

Version No.	Date	Summary of Changes
1.0	22 March 2018	Not applicable; initial clinical trial protocol.
1.1	03 July 2018	GB only amendment: AE assessment timing to start from consent. Added wording regarding birth control
1.2	26 September 2018	DE only amendment: AE assessment timing to start from consent. Added wording regarding birth control
2.0	16 January 2019	Incorporated GB and DE only amendment changes. Added statement of compliance as required by Sweden. Incorporated the addition of the alternative primary endpoint of rPFS and update to 1 rPFS analysis and 1 overall survival analysis. Clarified inclusion of and timing of start for best supportive/best standard of care. Clarified inclusion/exclusion criteria. Clarified procedures and timing Clarified progression of disease is not considered an AE or SAE. Clarified start and end timing for ^{68}Ga-PSMA-11 TEAEs, ^{177}Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.
3.0	01 April 2019	• Updated sponsor name. • Updated background information data. • Clarified rPFS is an alternate primary endpoint. • Clarified inclusion/exclusion criteria and added specific criteria regarding best supportive/best standard of care options to be identified for patients as part of eligibility. • After Cycle 6, visits are now every 12 weeks (+/- 4 days) • Additional details regarding long-term follow were added including a second consent to be signed by patients who withdraw consent or leave the active part of the study for any reason other than radiographic disease progression. This now includes radiographic follow up. • Plasma testosterone was added as an acceptable form of testosterone testing. • Window for QOL and Pain questionnaires added. • Updated reference section
4.0	08 July 2019	• Increased total number of patients randomized in the study by 64 to ensure sufficient events in order to maintain power for total enrollment of 814 patients. • Details for confirmatory analysis of OS (based on all randomized patients on an Intent to Treat (ITT) basis i.e., all patients enrolled since the start of the study) and the rPFS analysis based on randomized patients on or after March 5th, 2019 were added.

		• Adjusted the allocation of alpha between rPFS and OS while still maintaining the original power for both rPFS (approximately 85%) and OS (90%). Allocated alpha=0.004 to rPFS, 0.001 to interim OS and alpha of 0.02 to 0.025 for OS. Previously, allocation was rPFS=0.001 and OS=0.023. • Additional imaging analyses details were added for study ^{68}Ga PSMA 11 scan data and the role of the Independent Review with reviewer variability assessment, as well as Quantitative Analysis was added to assess tumor burden and tumor characteristics with rPFS, OS, and other response measures, as determined by PCWG3 criteria. • Further clarification on the start and end timing for ^{68}Ga-PSMA-11 TEAEs, ^{177}Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs. • Additional wording to clarify intent to collect radiographic imaging for patients who stop treatment for reasons other than radiographic progression,

Clinical Trial Summary

Protocol title:	VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)
Clinical phase:	Phase 3
Objectives:	The primary objective of this study is to compare the two alternate primary endpoints of radiographic progression-free survival (rPFS) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ^{177}Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/best standard of care alone. Key secondary objectives are an arm-to-arm comparison of the following: • Response Evaluation Criteria in Solid Tumors (RECIST) response • Time to a first symptomatic skeletal event (SSE) Additional Secondary Objectives: • Safety and tolerability of ^{177}Lu-PSMA-617 • Health-related quality of life (HRQoL; EQ-5D-5L, FACT-P and Brief Pain Inventory – Short Form (BPI-SF)) • Health economics • Progression-free survival (PFS) (radiographic, clinical, or prostate-specific antigen [PSA] progression-free survival) • Biochemical response as measured by PSA. Alkaline phosphatase [ALP] levels and lactate dehydrogenase [LDH] levels will also be measured.
Study design:	Patients with PSMA positive scans will be randomized in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 plus best supportive/best standard of care or to receive best supportive/best standard of care only. Best supportive/best standard of care will be determined by the treating physician/investigator but will exclude investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radioisotopes, and hemi-body radiotherapy. Novel androgen axis drugs [NAADs] (such as abiraterone or enzalutamide) are allowed. The care of cancer patients must include cancer specialists accomplished in the care of patients with advanced prostate cancer, (e.g., medical, radiation oncologists) with a clear understanding of the PCWG3 2+2 rules for progression, management of adverse events (AEs) related to the natural course of the disease, as well as pre-existing AEs and study-related AEs. The study is open-label and patients will be monitored throughout the 6 to 10-month treatment period for survival, disease progression, and adverse events. rPFS will be analyzed in these patients once 364 events have accrued. At time of the rPFS primary analysis, there will also be an interim analysis of OS. When a patient discontinues from the treatment portion of the study, they will have an end of treatment visit and will then continue to be followed in long-term follow-up. A long-term follow-up period will include the collection of rPFS survival and information about new treatments, along with the patient's response to these treatments, adverse events assessment, and hematology and chemistry testing. During follow-up, patients will be contacted every 3 months (±1 month) via phone, email, or letter for up to 24 months or until 508 deaths have occurred. Patients who withdraw their consent to participate in the treatment portion of the study or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which

	may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs). These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (e.g. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates. An End of Treatment visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.). This visit should occur approximately 30 days from the last dose of ^{177}Lu-PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study. The planned enrollment for this study is 814 patients.
Study population:	The study population includes patients with progressive PSMA-positive mCRPC who received at least one novel androgen axis drug [NAAD] (such as enzalutamide or abiraterone) and were previously treated with 1 to 2 taxane regimens. Patients treated with only 1 prior taxane regimen are eligible if the patient is unwilling or the patient's physician deems the patient unsuitable to receive a second regimen.
Investigational product:	Patients randomized to receive the investigational product will receive 7.4 GBq (±10%) ^{177}Lu-PSMA-617 intravenously every 6 weeks (±1 week) for a maximum of 6 cycles. After 4 cycles, patients will be assessed for (1) evidence of response, (2) residual disease, and (3) tolerance to ^{177}Lu-PSMA-617. If the patient meets the criteria above and agrees to continue with additional treatment of ^{177}Lu-PSMA-617 radioligand therapy, the investigator may administer 2 additional cycles. A maximum of 6 cycles of radioligand therapy is allowed. After the last cycle of ^{177}Lu-PSMA-617, patients can continue best supportive/best standard of care alone. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu-PSMA-617 treatment, then no additional doses of ^{177}Lu-PSMA-617 will be administered after Cycle 4. These patients can continue on best supportive/best standard of care alone after Cycle 4.
Assessment schedule:	Radiographic imaging will be done every 8 weeks (±4 days) during the first 24 weeks of treatment and every 12 weeks (± 4 days) thereafter, regardless of treatment delays, through the End of Treatment visit. The previous 2 PSA values will be noted before randomization. Serum/plasma testosterone and PSA levels will be measured up to 3 days prior to Day 1 of each cycle. Hematology and chemistry will be done weekly during Cycle 1 (up to 3 days prior to each time point) and up to 3 days prior to Days 1, 15, and 29 in Cycles 2 to 6 (i.e. every two weeks). After Cycle 6, hematology and chemistry will be done every 12 weeks (±4 days) until the patient starts long term follow up. Patients will complete the BPI-SF, EQ-5D-5L and FACT-P questionnaires about their pain level and HRQoL during screening and prior to treatment on Day 1 of each cycle and through the End of Treatment visit. Patients will be monitored throughout the study for SSEs.
Statistical methodology:	Subsequent to the implementation of measures to minimize early dropouts from the best supportive/best standard of care alone arm, the primary analysis of rPFS will focus on patients randomized on or after March 5th, 2019; rPFS will be analyzed in these patients once 364 events have accrued and the alpha level applied will be 0.004 1-sided. At time of the rPFS analysis, there will be an interim analysis of OS and the alpha level applied will be 0.001 1-sided; unlike rPFS, the analysis of OS will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final

	analysis of OS will be performed when 508 deaths have accrued and the alpha level applied will be 0.02 1-sided. This trial has at least 90% overall power and an overall Type I error rate of at most 0.025 1-sided.
Duration of Study:	Total duration of the study will be approximately 38 months.

List of Abbreviations and Definitions

Abbreviation	Term/Definition
ANC	Absolute neutrophil count
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
BPI-SF	Brief Pain Inventory – Short Form
CFR	United States Code of Federal Regulations
CR	Complete response
CRF	Case Report Form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease control rate
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EQ-5D-5L	European Quality of Life (EuroQol) – 5 Domain 5 Level scale
EudraCT	European Union Drug Regulating Authorities Clinical Trial
FACT-P	Functional Assessment of Cancer Therapy – Prostate
GCSF	Granulocyte colony-stimulating factors
FDA	Food and Drug Administration
FAS	Full Analysis Set
^{68}Ga	Gallium-68
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous

Abbreviation	Term/Definition
LDH	Lactate dehydrogenase
^{177}Lu	Lutetium-177
mCRPC	Metastatic castration-resistant prostate cancer
NAAD	Novel androgen axis drug (such as abiraterone or enzalutamide)
ORR	Overall response rate
OS	Overall survival
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SSE	Symptomatic Skeletal Event
TEAE	Treatment-emergent adverse event
SOD	Sum of the diameter
ULN	Upper limit of normal
US	United States
WBC	White blood cell
^{90}Y	Yttrium-90

The following clinical protocol describes the scientific rationale, objectives, design, statistical considerations, and organization of the planned trial including the plan to assure the safety and health of the trial participants. Additional details for conducting the clinical trial are provided in documents referenced in the protocol, such as an Investigator's Brochure (IB), the Pharmacy Manual, or in the Appendices.

The format and content of this clinical trial protocol complies with the Guideline for Good Clinical Practice (GCP) [E6(R2)] issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as well as applicable local regulations, i.e. LVFS 2011:19 (Sweden), and the latest version of the Declaration of Helsinki. The study will be conducted according to this clinical trial protocol.

The term subject, participant, and patient are used interchangeably throughout this protocol and are used to denote an individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1. INTRODUCTION

1.1 Background information

Prostate cancer and unmet medical need

An estimated 1.1 million men worldwide were diagnosed and 307,000 died due to prostate cancer in 2012. Almost 70% of the cases are diagnosed in more developed regions due to the use of prostate-specific antigen (PSA) testing, but there is only modest variation in mortality rates globally which is driven by metastatic, and often castration-resistant disease (Ferlay et al 2013, Bray et al 2012).

There is an urgent need for more effective treatments to improve outcomes for patients with metastatic castration-resistant prostate cancer (mCRPC). Prostate cancer is the third leading cause of cancer mortality in United States (US) men (Siegel et al 2017), driven by prostate cancer patients who no longer respond to hormonal therapy. Once patients reach the mCRPC stage, their expected overall survival is low as was seen in the randomized phase 3 study of cabozantinib vs prednisone in men with mCRPC who had received prior docetaxel and abiraterone acetate and/or enzalutamide; the median overall survival of the prednisone control arm was 9.8 months (Smith et al 2016). Post-docetaxel mCRPC patients have an annual death rate of 73% (Scher et al 2015).

The median age at diagnosis of mCRPC is 70 years (Flaig et al 2016). Metastatic prostate cancer has a predilection for bone. As a result, approximately 90% of mCRPC patients develop bone metastases (Kirby et al 2011), and 49% of them will develop a serious skeletal event within 2 years (Saad et al 2004). Common presentations include bone pain, bone marrow failure, fatigue, or complications such as fractures and cord compression. These presentations typically require radiation or bone surgery, which can significantly impair physical, emotional, and functional well-being (Weinfurt et al 2005). These patients, many of whom are elderly, can be extremely symptomatic and at risk of serious oncological complications. They can be a considerable challenge in the clinic due to the symptoms of metastatic soft tissue and visceral disease, general frailty, bone marrow impairment, and because they have exhausted approved

agents. In mCRPC patients facing advanced illness with little hope for a cure, the focus of treatment shifts from active anti-cancer treatment to palliative care for relief of physical symptoms, maintaining function, and attempting to improve their health-related quality of life (Cella et al 2009). Therefore, in addition to tracking essential clinical outcomes, it is also important to assess and evaluate changes in HRQoL of such fragile patients as they receive treatment.

Several agents have been approved for the treatment of mCRPC, and NCCN, ASCO, ESMO, and APCCC guidelines provide some consensus and guidance for their use. Regardless, none of these therapies are proven to prolong survival after enzalutamide or abiraterone. In practice, abiraterone acetate or enzalutamide are often used in the first-line mCRPC setting; Sipuleucel-T is best used in mildly asymptomatic small volume disease; and ^{223}Radium is used to treat men with bone-only disease. Taxane-based chemotherapy is most often used today after abiraterone or enzalutamide and for symptomatic patients, particularly with visceral disease. Docetaxel is used more commonly that cabazitaxel. Because both agents have a typical chemotherapy side effect profile, they are often not considered for patients due to comorbidity, poor hematological reserve, or patient refusal (Zielinski et al 2014).

Six small published series with a total of 499 patients have examined the efficacy of either abiraterone or enzalutamide in men previously exposed to a taxane and either abiraterone or enzalutamide. These modern hormonal agents produced only modest activity, including PSA decline >50% in 4% to 22% of patients, a median PFS of 2.7 to 4.6 months and a median OS of 7.2 to 12.2 months (Azad et al 2015, Cheng et al 2015, Badrising et al 2014, Brasso et al 2015, Loriot et al 2013, Noonan et al 2013). It's important to note that this is in contrast with the level of anti-tumor activity demonstrated in the pivotal clinical trials for these agents that led to approval. In that setting, patients had only received prior docetaxel and had not been exposed to prior therapy with either abiraterone or enzalutamide. As these modern hormonal agents have been used in earlier lines of therapy, the use of a second agent following docetaxel has resulted in diminished efficacy, likely due to cross resistance.

Therefore, there are limited options available to patients who fail or refuse taxane-based chemotherapy, particularly if alternative agents currently approved in this setting (abiraterone and enzalutamide) have been used earlier in the disease.

Prostate-specific membrane antigen

Prostate-specific membrane antigen (PSMA) is a transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II. PSMA is highly overexpressed in nearly all prostate cancers, but has restricted, and several hundred-fold lower, expression in some normal tissues such as the duodenal mucosa, proximal renal tubules, and salivary glands (Bostwick et al 1998, Ghosh and Heston 2004, Mannweiler et al 2009). Additionally, PSMA overexpression also correlates with advanced, high-grade, metastatic, androgen-independent disease (Ross et al 2003). The differential expression of PSMA from tumor to non-tumor tissue has resulted in numerous targeted strategies involving both disease localization using radioactive imaging as well as therapeutic intervention, and therefore may be an attractive target for men with mCRPC.

In addition to the expression pattern, the functionality of PSMA plays an equally important role in its value as a tumor-specific targeting mechanism. Specifically, the binding of a high affinity

ligand to PSMA, such as the targeting moiety in ^{177}Lu-PSMA-617, leads to internalization through endocytosis and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003). This functional feature of PSMA allows for the development of low-molecular-weight targeted radiopharmaceuticals with favorable pharmacokinetic and tumor penetration properties, rather than being restricted to antibody-based targeting strategies (Haberkorn et al 2016).

The result of both selective expression and ligand-based uptake using PSMA as a target is a reduction in background uptake and off-target toxicities as well as an increase in the amount of radioactivity that localizes at the tumor site.

^{177}Lu-PSMA-617 mechanism of action

The novel PSMA-targeted radioligand therapy ^{177}Lu-PSMA-617 consists of the PSMA-binding ligand [redacted], ^{177}Lu-PSMA-617 exhibits high PSMA binding affinity and internalization, prolonged tumor retention, and rapid kidney clearance (Benešová et al 2015). PSMA-617 was uniquely developed for both imaging and radioligand therapy of prostate cancer and can be radiolabeled with gallium-68 (^{68}Ga), lutetium-177 (^{177}Lu), indium-111, copper-64, scandium-44, actinium-225, or yttrium-90 (^{90}Y).

^{177}Lu, the radioactive cargo being delivered by PSMA-617, has physical properties that make it an ideal radionuclide for the treatment of mCRPC. ^{177}Lu is a medium- ‑ energy β ‑ -emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2 mm. The shorter β ‑ range of ^{177}Lu provides better irradiation of small tumors, in contrast to the longer β-range of ^{90}Y (Emmett et al 2017). The shorter path length also acts to direct the energy within the tumor rather than in the surrounding normal tissues, while the path length is still sufficient to create bystander and crossfire effects within the tumor lesion. ^{177}Lu has a relatively long physical half-life of 6.6 days that combines with the intratumoral retention of ^{177}Lu-PSMA-617 to reduce the necessary dosing frequency. It is these physical properties, and the benefit of PSMA-targeting, that allow for the delivery of effective activities of ^{177}Lu to prostate cancer cells.

^{177}Lu-PSMA-617 for metastatic castration-resistant prostate cancer

The novel therapeutic drug ^{177}Lu-PSMA-617 was developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ) in collaboration with University Hospital Heidelberg for the treatment of patients with metastatic prostate cancer (Kulkarni et al 2018

Kulkarni HR, Langbein T, Atay C, Singh A, Schuchardt C, Lehmann C, Pomper M, Pienta KJ, Baum RP. Safety and long-term efficacy of radioligand therapy using Lu-177 labeled PSMA ligands in metastatic prostate cancer: A single center experience over 5 years. Cancer Research. 2018 Jul;78(13):CT015.

Kratochwil et al 2015, Hillier et al 2009). Based on preclinical data that demonstrated high PSMA binding affinity and compound internalization, prolonged tumor uptake, rapid kidney clearance, and high tumor-to-background ratio, ^{177}Lu-PSMA-617 proceeded into clinical development at investigative sites in Germany.

Data evaluations based on compassionate use according to the German Medicinal Product Act, AMG §13 2b, Clinical Trial Notification (Australia) regulations, and other countries where

expanded access programs are in place per local regulations, reported a favorable safety profile and promising results for PSA response rates of systemic radioligand therapy with ^{177}Lu-PSMA-617 in patients with mCRPC.

Dosimetry data suggest that ^{177}Lu-PSMA-617 is targeted to PSMA-expressing tissue, which may include the salivary glands, kidneys, and small and large bowel. The highest exposure is to salivary glands, however in the prospective study xerostomia appears low grade and occurs at a rate of approximately 87% in treated patients. Clearance of ^{177}Lu PSMA-617 from the kidney occurs rapidly. To date nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. The exposure to normal bone marrow tissue is predictably low as it does not express PSMA and corresponds with normal plasma clearance. There was some evidence of reversible hematological toxicity that occurred following ^{177}Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 67% respectively.

The first published clinical series of ^{177}Lu-PSMA-617 consisted of 10 patients (Ahmadzadehfar et al 2015) treated between November 2013 and January 2014, with 5.6 GBq/150mCi (4.1–6.1 GBq/110–165 mCi). PSA decline >50% occurred in 50% of subjects, which increased to 60% after 2 cycles of 6 GBq/160 mCi (4.1–7.1 GBq/110–190 mCi). The level of PSA decline >50% (most commonly used to assess tumor response in these studies) has remained remarkably consistent across several clinical series when 2 or more doses of ≥6 GBq/160 mCi are given.

Hofman presented the first prospective open-label, single-arm, non-randomized Phase 2 study of ^{177}Lu-PSMA-617 in 50 metastatic castration-resistant prostate cancer patients dosed with up to 4 cycles of 4–8 GBq/110–220 mCi administered every 6 weeks (Hofman et al 2018, Hofman et al 2019). The primary endpoints of this study were to evaluate both safety and efficacy, as measured by PSA response, bone pain score, quality of life measurements, imaging response and survival.

Of the screened patients, 70% were identified as PSMA-positive via PET imaging and eligible for treatment. Most subjects had been exposed to at least 1 taxane chemotherapy and either abiraterone or enzalutamide in the mCRPC setting. In this heavily pre-treated patient population with few therapeutic alternatives, 64% of patients on ^{177}Lu-PSMA-617 showed a PSA response defined by a reduction in PSA of at least 50%, and 44% had a reduction of PSA of 80% or more. In 27 patients with measurable disease, the objective response rate in measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was 56% (complete response [CR] and partial response [PR]). Median overall survival was 13.3 months (95% confidence interval [CI] 10.5-18.0). Therapy with ^{177}Lu-PSMA-617 was well tolerated. These safety and efficacy data also translated into significantly improved quality of life scores and reduction in pain scores.

In summary, over 40 compassionate use publications and prospective Phase 2 clinical trial data describe the use of ^{177}Lu-PSMA-617 in patients who have been exposed to approved agents. In the post-taxane, post-androgen axis inhibitor setting ^{177}Lu-PSMA-617 has demonstrated a well-established, predictable, well tolerated safety profile. Clinical series indicate the most common side effects, predominately Grade 1-2, of ^{177}Lu-PSMA-617 treatment are dry mouth, nausea, vomiting, diarrhea, constipation, fatigue, anemia, thrombocytopenia and neutropenia. The

incidence of Grade 3/4 toxicity in the series were very low, and mainly restricted to reversible hematological events. Efficacy has been demonstrated on multiple clinically significant endpoints, including PSA response, soft tissue lesion response measured by RECIST, PFS, OS, pain and quality of life. No standard dose and schedule have been developed.

The preliminary clinical evidence indicates ^{177}Lu-PSMA-617 may demonstrate clinical benefit in patients with mCRPC in a setting where patients had been exposed to chemotherapy and NAADs and there is no recommended standard of care.

This Phase 3 study will assess the efficacy of ^{177}Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC by measuring overall survival and rPFS in a randomized, prospective, open-label trial.

1.2 Summary of nonclinical studies with clinical significance

***In vitro* PSMA affinity and internalization studies**

According to Benešová et al, the results of the binding assay of PSMA-617 in PSMA-positive LNCaP cells demonstrated a very high binding affinity, with an equilibrium dissociation constant (K_i) value of 2.34 ± 2.94 nM. The internalization of PSMA-617 is highly effective with an internalized fraction of 17.51 ± 3.99 percent of the added activity/10^6 LNCaP cells (n = 3) at 37°C (Benešová et al 2015).

Organ distribution in mice bearing PSMA-positive LNCaP tumors

The organ distribution with ^{177}Lu-PSMA-617 in mice showed a high specific uptake in LNCaP tumors and in the murine kidneys, as expected. Importantly, the high initial kidney uptake is almost completely cleared within 24 hours whereas the tumor uptake remained high or even tended to slightly increase during that time frame. Other organs such as the liver, lung and spleen demonstrated low uptake at 24 hours after injection (Benešová et al 2015).

Biodistribution in Wistar rats

Pharmacokinetic evaluation of ^{177}Lu-PSMA-617 in normal healthy male Wistar rats exhibited major renal clearance with no significant uptake in any of the major organ/tissue (Das et al 2016). More than 80% of the injected activity was excreted within 3 hours post-injection. Retention of residual activity was observed in intestine, liver, kidneys and skeleton at 24 hours post-administration. However, uptake in these organs, except skeleton, was observed to gradually decrease with the time.

Repeat-dose toxicity in Wistar rats

The toxicity of non-radioactive PSMA-617 administered once weekly by intravenous (IV) administration to male Wistar rats over 22 days was tested in a toxicology study. The animals were treated with 40, 160, or 400 µg PSMA-617/kg b.w. by IV bolus injection on test days 1, 8, 15, and 22. The control group was treated with physiological saline. The no-observed-adverse-effect-level was found to be above 400 µg PSMA-617/kg body weight administered once weekly by IV bolus injection (Leuschner 2016). The estimated mass of the PSMA-617 precursor which is applied per treatment cycle is likely to be approximately 150 to 250 µg. Using the NOAEL for repeat dosing of PSMA-617 of 400 µg/kg in rats, this accounts for a safety margin of approximately 16-27-fold, assuming that the average patient has a body surface are of 1.7 m^2. However, considering that a more intensive dosing schedule was tested in rats, relative to the

proposed, and well-studied, clinical regimen of once every 6 to 8 weeks, this safety margin may be a conservative estimate.

1.3 Summary of known and potential risks and benefits

Preclinical work, dosimetry studies, and clinical experience with ^{177}Lu-PSMA-617 since 2013, suggest positive response rates and a favorable safety profile in patients with mCRPC (Kratochwil et al 2016, Rahbar et al 2017, Kulkarni et al 2016, Haug et al 2016, Rathke et al 2017, Soydal et al 2016, Rathore et al 2016, Rahbar et al 2016a, Ahmadzadehfar et al 2016, Fendler et al 2017

Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S, Herrmann K. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017 Jun;44(6):1014-1024.

Ferdinandus et al 2017, Rahbar et al 2016b, Yadav et al 2017).

Dosimetry studies have confirmed that ^{177}Lu PSMA-617 is targeted and normal tissues that express PSMA are exposed to radiation (Delker et al 2016). These tissues are salivary glands, renal, and small and large bowel. Renal absorbed dose is cleared rapidly, and exposure appears similar to that seen with ^{177}Lu-DOTATATE. The exposure to normal bone marrow tissue should be low and correspond with normal plasma clearance.

Nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. There was some evidence of reversible hematological toxicity that occurred following ^{177}Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 67% respectively. Rahbar (2017) reported ^{177}Lu-PSMA-617 was associated with asymptomatic Grade 3 or 4 leukopenia, anemia, thrombocytopenia in 3%, 10%, 4%, respectively. Mild reversible xerostomia occurred in 8% of subjects. No significant diarrhea or renal impairment were reported from a retrospective review of doctor reports (Rahbar et al 2017).

Dr. Hofman recently presented results from the first prospective clinical trial with ^{177}Lu-PSMA-617 (Hofman et al 2019). In the trial, 50 mCRPC patients were dosed with up to 4 cycles of 4–8 GBq. Prospective common toxicity criteria for adverse events (CTCAE) v4 safety data was defined. He found his regimen to be well-tolerated. The most common non-hematological toxicities attributed to ^{177}Lu-PSMA-617 occurring in >25% of patients included transient G1-2 dry mouth (66%), G1-2 nausea (48%), G1-3 fatigue (38%), and G1-2 vomiting (26%). The most common hematological toxicities attributed to ^{177}Lu-PSMA-617 occurring in >25% of patients included G1-3 lymphocytopenia (72%), G1-4 thrombocytopenia (38%), G1-3 neutropenia (30%) and G1-3 anemia (28%). G3-4 toxicities attributed to ^{177}Lu-PSMA-617 were infrequent with lymphocytopenia (32%), thrombocytopenia (10%), anaemia (10%), neutropenia (6%) and fatigue (2%).

Potential risks of ^{177}Lu-PSMA-617 include the effects of radiological toxicity, namely xerostomia, fatigue, myelosuppression and mild nausea and vomiting.

Additional details of the nonclinical and clinical experience with ^{177}Lu-PSMA-617 are provided in the IB.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 Trial objectives

2.1.1 Primary objective

The primary objective of this study is to compare the two alternate endpoints of radiographic progression free survival (rPFS) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive 177Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone.

2.1.2 Key secondary objectives

Key secondary objectives are an arm-to-arm comparison of the following:

1. RECIST response to include:
    a. Overall Response Rate (ORR) as measured by RECIST v1.1 criteria
    b. Disease control rate (DCR) as measured by RECIST v1.1 criteria
2. Time to a first symptomatic skeletal event (SSE)

2.1.3 Additional secondary objectives

1. Safety and tolerability of ^{177}Lu-PSMA-617
2. Periodic assessment of health-related quality of life to evaluate impact of intervention on patient well-being (HRQoL; EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF])
3. Health Economics
4. Progression-free survival (PFS) (radiographic, clinical, or PSA progression-free survival)
5. Biochemical response as measured by PSA. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

2.2 Trial endpoints

2.2.1 Alternate Primary endpoints

rPFS and OS are designated as alternate primary endpoints. rPFS is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. OS is defined as the time from randomization to the date of death from any cause.

rPFS will be assessed locally by each site. Additionally, patient scans will be collected for independent central review. The independent central review will be used to support the primary rPFS analysis. The local rPFS assessment will be supportive.

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either the primary analysis of rPFS **or** OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. Alpha allocation and recycling is used to ensure control of the overall Type I error rate.

2.2.2 Key Secondary endpoints

The key secondary endpoints include the following:

1. RECIST response to include:
    a. Objective response rate (ORR) (CR + PR) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions. Duration of Response (DOR) will also be measured in patients with a CR or PR from date of first response to the date of RECIST progression or death.
    b. Disease Control Rate (DCR) (CR + PR + stable disease [SD]) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions.
2. The time to a first SSE 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.

2.2.3 Additional Secondary endpoints

1. To evaluate the safety and tolerability of ^{177}Lu-PSMA-617
2. Aspects of HRQoL will be reported using the EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF]
3. Health economics
4. Progression-free survival is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
    a. Radiographic progression is defined as the date of radiographic disease progression as outlined in the Prostate Cancer Working Group 3 (PCWG3) Guidelines.
    b. Unequivocal clinical progression. Unequivocal evidence of clinical progression is defined as:
        - Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy

- Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status to ≥ Grade 3 and/or in the opinion of the investigator ECOG deterioration indicates clinical progression
- In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

c. PSA progression is defined as the date that a ≥ 25% increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance). Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.

5. Biochemical response endpoints:

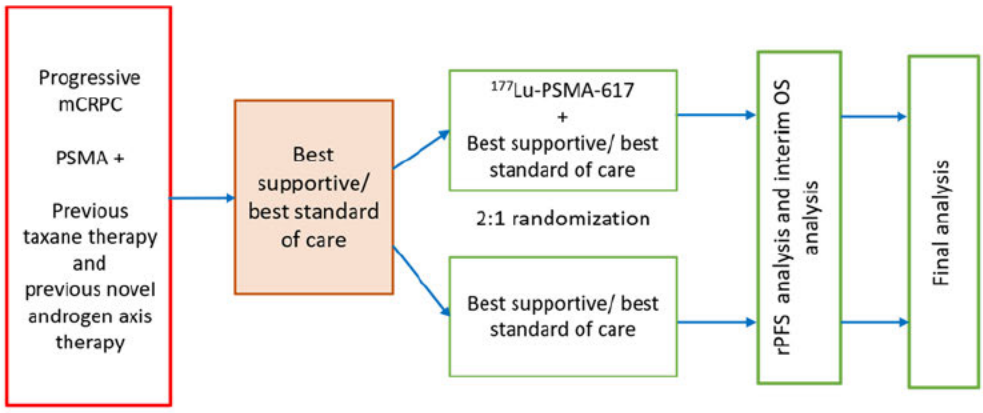
a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a ≥50% decrease from baseline that is confirmed by a second PSA measurement ≥4 weeks.

b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

3. TRIAL DESIGN

3.1 Overview of the clinical trial design

This is a Phase 3, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in addition to best supportive/best standard of care as compared to best supportive/best standard of care alone (Figure 1).



Stratification Factors
- Serum lactate dehydrogenase (LDH) (≤260 IU/L vs. >260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0-1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care (yes vs. no)

Alternate Primary Endpoints
- Overall survival
- Radiographic progression-free survival (rPFS)

Key Secondary Endpoints (with α control)
- RECIST response
- Time to first symptomatic skeletal event (SSE)

Additional Secondary Endpoints
- Safety and tolerability
- Health-related quality of life (HRQoL; EORTC QLQ-C30 and Brief Pain Inventory – Short Form (PI-SF))
- Health economics
- Progression-free survival (PFS) (radiological, clinical or PSA progression)
- Biochemical response: PSA levels, alkaline phosphatase levels and lactate dehydrogenase levels

Figure 1 Diagram of trial design

ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

Best supportive/best standard of care includes available care for the eligible patient according to best institutional practice and at the discretion of the investigator. Novel androgen axis drugs [NAADs] (i.e., enzalutamide or abiraterone) are allowed.

Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223) or hemi-body radiotherapy treatment may not be administered on study.

At screening, potential subjects will be assessed for eligibility and will undergo a ^{68}Ga-PSMA-11 PET/computed tomography (CT) scan to evaluate PSMA positivity. Only patients with PSMA-positive cancer will be randomized in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 plus best supportive/best standard of care (investigational arm) or to receive best supportive/best standard of care alone (BS/BSC-only arm). Randomization will be stratified by 4 factors (Section 3.4.3).

Patients randomized to the investigational arm must begin ^{177}Lu-PSMA-617 dosing within 28 days after randomization. These patients will receive best supportive/best standard of care and 7.4 GBq (±10%) ^{177}Lu-PSMA-617 once every 6 weeks (±1 week) for a maximum of 6 cycles.

After the Cycle 4 dose of ^{177}Lu-PSMA and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and

- Has shown good tolerance to the ^{177}Lu-PSMA-617 treatment.

If the patient meets all of the criteria above, and agrees to continue with additional treatment of ^{177}Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet any of the criteria or does not agree to additional ^{177}Lu-PSMA-617 treatment, then no additional doses of ^{177}Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ^{177}Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

Best supportive/best standard of care for each patient will be selected at the discretion of the patient's physician, prior to randomization and will be administered per the physician's orders and continued until the patient comes off the treatment part of the study and enters the long-term follow-up stage.

A patient may choose to discontinue randomized treatment part of the study at any time. If a patient chooses only to discontinue from the randomized treatment in the study for a reason other than radiographic progression, the patient will be asked to confirm if they consent to continue to be followed for long-term safety, rPFS, and survival follow-up. The patient will continue to be followed for long term follow up unless they specifically withdraw consent from long term follow-up of the study. An End of Treatment (EOT) visit should occur once a patient discontinues randomised treatment for any reason (patient or investigator decision, going on to long term follow up, etc.).

The EOT visit should occur approximately 30 days from the last dose of ^{177}Lu-PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

If a patient discontinues randomized treatment for any reason other than radiographic progression, they will be asked for permission to continue collecting radiographic images (bone scans and CT scans and/or MRIs) for the purpose of continuing to assess rPFS.

After the EOT visit, patients will enter the long-term follow-up period. The long-term follow-up period will include the collection of rPFS (if discontinuing for reasons other than radiographic progression), survival and information about new treatments, along with the patient's response to these treatments, adverse events assessment, and results of hematology and chemistry testing. During follow-up, patients will be followed for safety and survival. They will be contacted every 3 months (±1 month) via phone, email, or letter for up to 24 months or until 508 deaths have occurred.

Patients who withdraw their consent to participate in the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact

person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

This study will enroll approximately 814 patients involving about 110 sites worldwide.

3.1.1 Study design update

The trial was originally designed to randomize 750 patients, targeting the primary analysis of rPFS with 457 events, an interim analysis of OS, to be conducted contemporaneously with the primary analysis of rPFS, and a final analysis of OS with 489 deaths.

However, shortly after commencement of the trial, a high, early dropout rate amongst those randomized to BS/BSC only became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients which consequently could result in bias in the analysis of rPFS. Remedial measures to curtail this phenomenon were implemented and made effective on March 5th, 2019. As part of the plan to address the early withdrawal of consent in the BS/BSC-only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after March 5th, 2019; therefore, rPFS will be analyzed in these patients once 364 events have accrued. At time of the rPFS primary analysis, there will also be an interim analysis of OS; this OS analysis will be on an intent to treat (ITT) basis and will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final ITT analysis of the OS primary objective will be performed when 508 deaths have accrued. To achieve these analyses, the total number of subjects randomized into the trial was increased from N=750 to N=814. The revisions described do not alter the hypothesized treatment effects for rPFS and OS upon which the study was originally powered.

3.2 Rationale for the study design

The primary objective of this study is to compare the two alternate endpoints of rPFS and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ^{177}Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone. The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either rPFS **or** OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. Secondary endpoints have been defined by PCWG3 as well as FDA and EMEA guidance. In view of the highly symptomatic nature of advanced mCRPC both validated pain (BPI-SF) and HRQoL (EQ-5D-5L and FACT-P) measurements will be collected using various questionnaires.

3.3 Measures taken to minimize/avoid bias

Patients will be randomized to 1 of 2 treatment arms. Randomization will be stratified to avoid bias in treatment selection (Section 3.4.3). Treatment will be open-label.

Reading of the baseline ^{68}Ga-PSMA-11 PET/CT scan will be done by central readers for consistency.

3.4 Description of the clinical trial

3.4.1 Description of investigational medicinal product

The ^{68}Ga-PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi). For background and additional details on ^{68}Ga-PSMA-11, refer to the ^{68}Ga-PSMA-11 Investigator's Brochure.

Refer to the Fendler et al 2017 publication "^{68}Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0 guideline" for an overview of ^{68}Ga-PSMA-11 recommendations. Details of the patient preparation and administration can be found in the Imaging Manual.

The ^{177}Lu-PSMA-617 solution for injection consists of a sterile solution in glass vials containing 7.4 (±0.74) GBq of ^{177}Lu-PSMA-617 at time of injection.

Refer to the ^{177}Lu-PSMA-617 IB for additional details of the investigational medicinal product including the pharmacological class and action, the dosage form including excipients, and any available packaging and labelling.

3.4.2 Dosage and rationale for dose selection

In the investigational arm, patients will receive best supportive/best standard of care regimen and IV 7.4 GBq (±10%) ^{177}Lu-PSMA-617 once every 6 weeks (±1 week) for a maximum of 6 cycles. After 4 cycles patients will be reassessed to determine if a further 2 cycles can be given for a maximum of 6 cycles (Section 3.1).

The basic principle of ^{177}Lu-PSMA-617 radioligand therapy is to systemically deliver low dose rate radiation specifically to multiple PSMA positive prostate cancer lesions, while sparing normal tissues. To date, 11 dosimetry studies have been conducted and published in over 100 patients. The results are consistent across the studies and demonstrate exposure that correlates well with the expected rapid clearance of a small molecule, and the limited distribution pattern of a PSMA-targeted radionuclide. The primary sites of non-tumor uptake were the salivary glands, lacrimal glands, and kidneys, with excretory mechanisms contributing to exposure in the kidneys where approximately 50% of the injected dose is cleared within 48 hours (Kratochwil et al 2016). PSMA-negative tissues like the bone marrow, are exposed transiently to ^{177}Lu-PSMA-617 while in circulation, however this exposure is minimized due to its rapid elimination.

^{177}Lu-PSMA-617 is well tolerated according to the clinical experience that has been documented in 42 publications, summarizing the safety and or efficacy information from over 800 subjects. Across these studies doses have ranged from 1.1-12.0 GBq, and schedules have typically followed an administration schedule of once every 4 to 12 weeks, for 1-9 cycles. The majority of these publications have used a regimen of 4 cycles of 6 GBq every 8 weeks, as published by the German Radiopharmaceutical Society in 2015. However, efficacy and safety information from the prospective phase 2 study suggested that dosing of 6-8 GBq every 6 weeks for 4 cycles was well tolerated and efficacious (Hofman et al 2018).

Clinical series now show reports of more than 4 cycles of ^{177}Lu PSMA-617 being administered safely as a means to maximize the benefit to the patient (Rahbar et al 2018, Kulkarni et al 2018, Bräuer et al 2017, Yordanova et al 2017). In addition, a recent review suggests optimal dosing of 6 cycles of ^{177}Lu-PSMA-617 administered every 6 weeks in a decreasing scale reaching a total cumulative absorbed dose of 44 GBq (Emmett et al 2017). Six fractions of 7.4 GBq, delivers a similar total dose of 44.4 GBq.

In the ANZUP1603 study in 200 Australian patients (NCT03392428), which is comparing ^{177}Lu-PSMA-617 with cabazitaxel, the dose starts at 8.5 GBq ^{177}Lu-PSMA-617 and reduces by 0.5 GBq per cycle, i.e. 8.5, 8, 7.5, 7, 6.5, 6 (cycle #6). A maximum of 6 cycles given every 6 weeks is what is being evaluated, which equates to a cumulative dose that is similar to that for this proposed study.

The clinical safety review and detailed analyses of the radiation exposure support the intended dose and frequency of ^{177}Lu-PSMA-617 administration in this clinical trial.

3.4.3 Subject allocation to treatment

Patients will be randomized by an interactive response system in a 2:1 ratio to the investigational treatment arm (^{177}Lu-PSMA-617 plus best supportive/best standard of care) or the best supportive/best standard of care-only arm using a permuted block scheme. Randomization will be stratified by the following factors:

- LDH (≤ 260 IU/L vs. > 260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0 or 1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care at time of randomization (yes vs no)

3.4.4 End of treatment visit

An EOT visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).

This visit should occur approximately 30 days from the last dose of ^{177}Lu-PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

3.4.5 Duration of Subject Participation

Patients may continue treatment until radiographic progressive disease, withdrawal of consent, the occurrence of unacceptable toxicity, or a determination by the investigator the patient is not clinically benefiting. As per the patient's physician, when the participant requires care that is not allowed on study, the participant will discontinue treatment and enter the long-term follow-up period. While the patient and/or physician may decide prematurely to cease taking randomized therapy at any time, full follow-up of all randomized patients for the intended duration of the trial is planned by design for the collection of rPFS and OS data.

It is anticipated that it will take approx. 14 months to randomize the required 814 patients in the study. After the last patient is randomized patients will be followed for up to 24 months or at least until 508 deaths have occurred. The maximum duration of the study, from first date of randomization to last follow-up, will therefore be approximately 38 months.

3.5 End of trial definition

The trial and long-term follow-up procedures are expected to continue at least until 508 deaths have occurred. Long-term follow up for safety and survival will continue for up to 24 months per patient. For timing of the rPFS and OS analyses and any rules for early statistical curtailment, refer to Section 8.1.

4. SELECTION AND DISCONTINUATION OF SUBJECTS

Written informed consent must be obtained prior to any study-related procedures. The Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the participant's financial responsibility. While full follow-up is intended in the ITT population for the planned duration of the trial, participants must also be notified that they are free to discontinue from the study at any time. The participant will be given the opportunity to ask questions and allowed time to consider the information provided. A copy of the signed written informed consent form (ICF) will be given to the participant for their review and signature.

4.1 Inclusion criteria

To qualify for enrollment, patients must meet the following criteria:

1. Patients must have the ability to understand and sign an approved ICF.
2. Patients must have the ability to understand and comply with all protocol requirements.
3. Patients must be ≥18 years of age.
4. Patients must have an ECOG performance status of 0 to 2.
5. Patients must have a life expectancy >6 months.
6. Patients must have histological, pathological, and/or cytological confirmation of prostate cancer.
7. Patients must be ^{68}Ga-PSMA-11 PET/CT scan positive, and eligible as determined by the sponsor's central reader.
8. Patients must have a castrate level of serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L).
9. Patients must have received at least one NAAD (such as enzalutamide and/or abiraterone).

10. Patients must have been previously treated with at least 1, but no more than 2 previous taxane regimens. A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane. If a patient has received only 1 taxane regimen, the patient is eligible if:

    a. The patient's physician deems him unsuitable to receive a second taxane regimen (e.g. frailty assessed by geriatric or health status evaluation, intolerance, etc.).

11. Patients must have progressive mCRPC. Documented progressive mCRPC will be based on at least 1 of the following criteria:

    a. Serum/plasma PSA progression defined as 2 consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL.

    b. Soft-tissue progression defined as an increase ≥20% in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions.

    c. Progression of bone disease: evaluable disease or new bone lesions(s) by bone scan (2+2 PCWG3 criteria, Scher et al 2016).

12. Patients must have ≥1 metastatic lesion that is present on baseline CT, MRI, or bone scan imaging obtained ≤28 days prior to beginning study therapy.

13. Patients must have recovered to ≤ Grade 2 from all clinically significant toxicities related to prior therapies (i.e. prior chemotherapy, radiation, immunotherapy, etc.).

14. Patients must have adequate organ function:

    a. Bone marrow reserve:

    - White blood cell (WBC) count $\geq 2.5 \times 10^9$/L (2.5×10^9/L is equivalent to 2.5×10^3/μL and 2.5 × K/μL and 2.5×10^3/cumm and 2500/μL) OR absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L (1.5×10^9/L is equivalent to 1.5×10^3/μL and 1.5 × K/μL and 1.5×10^3/cumm and 1500/μL)
    - Platelets $\geq 100 \times 10^9$/L (100×10^9/L is equivalent to 100×10^3/μL and 100 × K/μL and 100×10^3/cumm and 100,000/μL)
    - Hemoglobin ≥9 g/dL (9 g/dL is equivalent to 90 g/L and 5.59 mmol/L)

    b. Hepatic:

    - Total bilirubin ≤1.5 x the institutional upper limit of normal (ULN). For patients with known Gilbert's Syndrome ≤3 × ULN is permitted
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤3.0 × ULN OR ≤5.0 × ULN for patients with liver metastases

    c. Renal:

    - Serum/plasma creatinine ≤1.5 x ULN or creatinine clearance ≥50 mL/min

15. Albumin >3.0 g/dL (3.0 g/dL is equivalent to 30 g/L)

[Inclusion #16 has been removed]

17. HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial.

18. For patients who have partners of childbearing potential: Partner and/or patient must use a method of birth control with adequate barrier protection, deemed acceptable by the principle investigator during the study and for 6 months after last study drug administration.

19. The best standard of care/ best supportive care options planned for this patient:
    a. Are allowed by the protocol
    b. Have been agreed to by the treating investigator and patient
    c. Allow for the management of the patient without ^{177}Lu-PSMA-617

4.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Previous treatment with any of the following within 6 months of randomization: Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation. Previous PSMA-targeted radioligand therapy is not allowed.
2. Any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy [including monoclonal antibodies]) within 28 days prior to day of randomization.
3. Any investigational agents within 28 days prior to day of randomization.
4. Known hypersensitivity to the components of the study therapy or its analogs.
5. Other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy.
6. Transfusion for the sole purpose of making a subject eligible for study inclusion.
7. Patients with a history of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired. For patients with parenchymal CNS metastasis (or a history of CNS metastasis), baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast).
8. A superscan as seen in the baseline bone scan.
9. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.

10. Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, known active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.
11. Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. However, patients with a prior history of malignancy that has been adequately treated and who have been disease free for more than 3 years are eligible, as are patients with adequately treated non-melanoma skin cancer, superficial bladder cancer.

4.3 Subject withdrawal of consent for study or treatment

A patient may choose to withdraw his consent for participation in the study at any time. If a patient chooses only to discontinue from the randomized treatment in the study, the patient will be asked to confirm if they consent to continue to be followed for long-term safety, rPFS (if discontinuing for reasons other than radiographic progression), and survival follow-up. This may include blood work results, radiographic follow up and information about new treatments and his response to these treatments. Patients may also choose to be followed for survival only long-term follow up. This trial design is ITT so that all subjects are to be followed for up to 24 months for safety and survival or until 508 deaths have occurred. The total of 508 deaths are expected to have occurred approximately 13 months after the last patient has been randomized.

5. TREATMENT OF SUBJECTS

5.1 Treatment with the investigational medicinal product

5.1.1 Administration of ^{68}Ga-PSMA-11

For background and additional details on ^{68}Ga-PSMA-11, refer to the ^{68}Ga-PSMA-11 Investigator's Brochure. The ^{68}Ga-PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi).

Refer to the Fendler et al 2017 publication "^{68}Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0 guideline" for an overview of ^{68}Ga-PSMA-11 recommendations. Details of the patient preparation and administration can be found in the Imaging Manual.

5.1.2 Administration of ^{177}Lu-PSMA-617

Once every 6-weeks (± 1 week), 7.4 GBq (±10%) ^{177}Lu-PSMA-617 will be administered. A 7.4 GBq dose is equivalent to 200 mCi or 7400 MBq.

Treatment with ^{177}Lu-PSMA-617 must be performed in accordance with national and/or local radiation and safety requirements.

A saline flush with ≥10 mL of normal saline must be administered to ensure patency of the intravenous line before administering with ^{177}Lu-PSMA-617 administration.

^{177}Lu-PSMA-617 will be administered slowly by intravenous route and followed by a saline flush. The time of administration must be recorded. The total activity administered must be measured (GBq).

Vital signs will be collected 15(+/- 5) minutes before and at 30(+/- 5) and 60(+/- 5) minutes following administration.

Patients should also be monitored for any evidence of pain or burning sensation during the injection. Patients should be encouraged to maintain a good fluid intake on the day of treatment and following therapy.

Date and time of patient discharge following ^{177}Lu-PSMA-617 administration should be recorded.

A decision to order ^{177}Lu-PSMA-617 should be communicated to the sponsor or designee no later than 10 business days prior to the planned administration for each cycle.

5.1.3 Toxicity risk reduction and supportive care for ^{177}Lu-PSMA-617 injections

Supportive care should be provided as deemed necessary by the treating physician.

Oral hygiene
Patients should be advised to use sodium bicarbonate mouthwash during the first 3 days of each cycle.

Nausea and vomiting
Mild nausea and vomiting may occur without prophylactic therapy and antiemetic treatment is recommended. Oral or IV ondansetron (or equivalent) and/or dexamethasone or equivalent institutional anti-emetic regimen should be administered on the day of ^{177}Lu-PSMA-617 administration. If oral administration is given, it should occur at least 30 minutes before dosing and, if by injection, at least 15 minutes prior to infusing ^{177}Lu-PSMA-617.

Additionally, dexamethasone and domperidone/metoclopramide or institutional anti-emetic regimen may be administered on Days 2 and 3 of each cycle if required at the discretion of the investigator.

Other anti-emetics should be used as required as per standard clinical practice.

Additional suggested treatment guidelines
A listing of additional suggested treatment guidelines can be found in Appendix 2. These are to be used at the discretion of the investigator.

5.1.4 Management of toxicity adverse events: dosing delays and modification

Within the first few days of treatment the most common adverse events (AEs) are general fatigue and an increase in bone pain. Symptomatic hematologic toxicity may occur but is not common.

Every effort should be made to keep the treatment cycle of 6 weeks (±1 week) at the prescribed doses. Physical exams, assessment of toxicities, along with hematology and chemistry results

must all be assessed prior to dosing with ^{177}Lu-PSMA-617. At the discretion of the investigator, a dose of ^{177}Lu-PSMA-617 may be delayed or reduced. Table 1 provides dose modification recommendations. Only one reduction in administered activity is permitted. If a patient has further toxicity that would require an additional reduction in administered activity, treatment with ^{177}Lu-PSMA-617 must be discontinued. Once a dose is reduced, treatment with 177Lu-PSMA-617 should not be re-escalated.

If a treatment delay due to adverse event or toxicity management persists for >4 weeks, treatment with ^{177}Lu-PSMA-617 must be discontinued. If treatment with ^{177}Lu-PSMA-617 is discontinued due to an AE, abnormal laboratory value, or toxicity, treatment with best supportive/best standard of care may continue at the discretion of the investigator if the patient has not radiographically progressed as measured by PCWG3 criteria.

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Anemia, leukopenia, or neutropenia: • Hemoglobin <10 g/dL • WBC count <3.0 × 10^9/L • ANC <1.5 × 10^9/L	≥Grade 2	Hold ^{177}Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Manage as deemed appropriate by investigator. The use of growth factors is permitted but should be discontinued once the AE resolves to Grade 1 or baseline. Checking hematinic levels (iron, B12, and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated for anemia.
Thrombocytopenia (platelet count of < 75 x 10^9/L)	≥ Grade 2	Hold ^{177}Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Transfusions may be given as clinically indicated for thrombocytopenia.
Hematological toxicity (except lymphocytopenia that responds to medical intervention)	Grade 3 or Grade 4	Hold ^{177}Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle
Serum/plasma creatinine increased ≥40% from baseline AND calculated creatinine clearance decreased >40% from baseline		Reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle
Salivary gland toxicity	≥ Grade 2	Reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle
Non-hematological, clinically significant toxicity not otherwise stated	≥ Grade 2	Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Electrolyte or metabolic abnormalities that are correctable within a 48 hr period without sequela	≥ Grade 2	Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Gastrointestinal toxicity (not amenable to medical intervention)	≥ Grade 3	Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 2 or baseline Reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Fatigue	≥ Grade 3	Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Pain	≥ Grade 3	Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Spinal cord compression		Hold ^{177}Lu-PSMA-617 administration until the compression has been adequately treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
Fracture in weight bearing bones		Hold ^{177}Lu-PSMA-617 administration until fracture is adequately stabilized/treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
AST or ALT >5 × ULN in the absence of liver metastases		Discontinue ^{177}Lu-PSMA-617
Renal toxicity	≥ Grade 3	Discontinue ^{177}Lu-PSMA-617
Any serious AE that requires drug discontinuation or treatment delay of >4 weeks		Discontinue ^{177}Lu-PSMA-617
Any unacceptable toxicity		Discontinue ^{177}Lu-PSMA-617

Note: Hematologic parameters (i.e., CBC with differential analysis) will be monitored every week in Cycle 1 only. Cycles 2 to 6, it will be monitored every 2 weeks. After Cycle 6, it will be monitored every 12 weeks.
AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; Lu = Lutetium; PSMA = prostate-specific membrane antigen; ULN = upper limit of normal; WBC = white blood cell

5.2 Best supportive/best standard of care

The care of cancer patients must include cancer specialists accomplished in the care of patients with advanced prostate cancer, (e.g., medical, radiation oncologists) with a clear understanding of the PCWG3 2+2 rules for progression, management of AEs related to the natural course of the disease, as well as pre-existing AEs and study-related AEs.

The best supportive/best standard of care for the patient in either arm should be administered as per physician's orders and protocol at the institution, and whenever feasible, best supportive/best standard of care should be optimized for all study participants prior to randomization. Patients will continue to be treated with best supportive/best standard of care until they require a treatment regimen not allowed on this study or have radiographic progressive disease as measured by PCWG3 criteria.

Other treatments for prostate cancer, not specifically excluded as part of the study, should be used in accordance with the routine clinical practice and at the discretion of the investigator. These may include, but are not limited, to any of the interventions mentioned below.

Supportive measures (pain meds, hydration, transfusions, etc.), and ketoconazole are allowed on study.

Hormonal agents (single or combinations), estrogens including diethylstilbestrol (DES) and estradiol are allowed on study.

Luteinizing hormone-releasing hormone (LHRH) analogue for testosterone suppression including both agonists and antagonists are allowed on study.

Any corticosteroid such as dexamethasone, prednisone, etc. and 5-alpha reductases including finasteride and dutasteride is allowed on study.

Abiraterone, enzalutamide, apalutamide or any other NAAD is allowed on study.

Radiation in any external beam or seeded form is allowed on the study. This can include stereotactic body radiation therapy (SBRT) or palliative external beam or radiation involving seeds but no systemic radiopharmaceuticals. Y90 beads are allowed for approaches to liver metastasis as they are FDA approved.

Bone targeted agents including zoledronic acid, denosumab and any bisphosphonates are allowed on study.

It is important to recognize that combinations of any, and all, of the above are allowed on the study and can be modified over time as needed.

5.3 Concomitant medications/ supportive care

5.3.1 Permitted concomitant medications/ supportive care

Consideration should be given to using concomitant bone health agents such as bisphosphonates on either arm of the study. Patients receiving bisphosphonates, denosumab, zoledronic acid or similar therapy prior to randomization may be maintained on this therapy during the study. Bisphosphonates denosumab, zoledronic acid or similar therapy can be stopped or started at the discretion of the investigator throughout the study.

Patients must maintain castrate levels of serum/plasma testosterone either by chemical castration or by having had an orchiectomy.

Medications for myelosuppression
Blood transfusion or erythropoietin stimulation agents are allowed throughout the study after randomization. Routine prophylaxis with GCSF/granulocyte-macrophage colony-stimulating factor and erythropoietin is not recommended. Nevertheless, use is permitted at the investigator's discretion.

Refer to Section 5.1.4 for guidance on the management of toxicity.

5.3.2 Prohibited concomitant medications

Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g., radium-223), or hemi-body radiotherapy treatment may not be administered on study.

5.4 Monitoring treatment compliance

The investigational medicinal product will be administered only at the investigational site under the direction of the investigator. Compliance with ^{177}Lu-PSMA-617 therapy will be monitored and ensured.

5.5 Treatment discontinuation

Patients may discontinue the treatment part of the study for any of the following reasons:

- Evidence of tumor progression by radiological assessment as measured by PCWG3 criteria
- Unacceptable toxicity
- Patient non-compliance or voluntary withdrawal
- Required use of a prohibited treatment
- Evidence that the patient is no longer clinically benefiting
- At the sponsor's or investigator's discretion

Patients that discontinue treatment due to unacceptable toxicity should return to the clinic for the End of Treatment visit. Participants who discontinue ^{177}Lu-PSMA-617 due to unacceptable toxicity may continue to receive best supportive/best standard of care alone during the treatment part of the study until they discontinue the treatment part of the study and enter long term follow up.

If a patient discontinues the treatment part of the study for any reason other than radiographic progression, they will be asked for permission to continue collecting radiographic images (bone scans and CT scans and/or MRIs) for the purpose of continuing to assess rPFS.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1 Screening procedures and baseline assessments

Screening procedures and baseline assessments will be performed within 4 weeks of randomization except for baseline imaging. Any procedure or assessment done within this time frame may be accepted as the baseline procedure or assessment. Baseline medical imaging (CT with contrast/ MRI, and bone scan) is to be performed within 28 days of start of treatment. Any medical imaging done within this time frame may be accepted as the baseline imaging. The screening procedures are detailed in Table 2.

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Informed consent	As per local/central IRB/IEC/REB timing requirements but prior to the performance of any study specific procedures.
Inclusion/exclusion criteria	Refer to Section 4.1 and Section 4.2 for additional details.
Medical history	Collect medical history, including the following details about prior prostate cancer treatment(s): • Date of initial diagnosis • Approximate start and stop date of each therapy

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
	• Date and type of progression (e.g. PSA, radiological, bone, or no clinical benefit) • Site of progression (new lesions, existing lesions, or both) when available
Prior/concomitant medication review	
Full physical examination	Should be performed by a qualified medical practitioner.
Height	
Weight	
ECOG performance score	Refer to Appendix 4 for the ECOG performance score scale.
Vital signs	Includes: blood pressure, pulse, and respiratory rate
CT with contrast/MRI	CT with contrast /MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations The radiological technique used for measurement of the baseline images should also be the radiological technique used for each reassessment.
^{99m}Tc diphosphonate bone scan	Baseline and follow up radiological disease assessments must include bone scans performed with technetium-99m labeled diphosphonates as per the local standard of care for patients with prostate cancer. Use the PCCTC bone scan assessment tool or equivalent to document lesions (included in Appendix 11).
Histology	Pathology report of the most recent biopsy required at enrollment.
Disease pattern	Bone, visceral, soft tissue, and lymph nodes
12-lead ECG	
Hematology	Refer to Section 6.3.1 for list of tests
Chemistry	Refer to Section 6.3.1 for list of tests
Urinalysis, macroscopic (microscopic when indicated)	Refer to Section 6.3.1 for list of tests
Serum/plasma testosterone	
PSA	Includes PSA results and dates of 2 previous measurements. Prior measurements are needed to assess PSA velocity/doubling time.
BPI-SF, EQ-5D-5L and FACT-P	Baseline pain score assessment (BPI-SF) and HRQoL (EQ-5D-5L, FACT-P) assessments. HRQoL assessments may be either self-completed by the subject or administered via face-to-face interview and completed by a caretaker/clinician.
Best supportive/best standard of care determination	To be decided prior to randomization, as part of screening.

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
PSMA PET/CT scan	To be done once all other eligibility requirements are confirmed. The metastatic lesion requirement may be confirmed at the same time as the baseline ^{68}Ga-PSMA-11 PET/CT[a] scan. Baseline ^{68}Ga-PSMA-11 PET/CT[a] scan must be done within 4 weeks (+ 2 weeks) of start of treatment but not within the 6 days prior to start of treatment. Study eligibility based on PSMA positivity will be determined by central readers.
Screening registration	Initial screening registration should take place after the patient has signed the Informed Consent Form. It should be completed once all screening assessments have been completed and results confirmed except for metastatic lesion requirement and PSMA positivity.
Study enrollment	Study enrollment should take place after screening registration is completed and once the metastatic lesion requirement is confirmed by the site and PSMA positivity has been confirmed by the central readers. Patients randomized to the investigational arm are to begin dosing with ^{177}Lu-PSMA-617 within 28 days after randomization.

[a] For background and additional details on ^{68}Ga-PSMA-11, refer to the ^{68}Ga-PSMA-11 Investigator's Brochure.

BPI-SF = Brief Pain Inventory – Short Form; CT= computed tomography; ECG = electrocardiography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; HRQoL = Health-related quality of life; IEC = Independent Ethics Committee; IRB = Institutional Review Board; MRI = magnetic resonance imaging; PCCTC = Prostate Cancer Clinical Trials Consortium; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; REB = Research Ethics Board; RECIST = Response Evaluation Criteria in Solid Tumors;

6.2 Efficacy assessments

For the timing of efficacy assessments, refer to the schedule of assessments provided in Appendix 1.

6.2.1 Radiographic imaging for tumor assessments

Radiologic assessment should follow PCWG3 guidelines. Periodic radiographic imaging will include both:

- CT with contrast/MRI imaging
- Bone scans with technetium-99m labeled diphosphonates

CT with contrast/MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis.

Disease progression by bone scan will be defined as at least 2 new bone lesions at the first post-treatment scan, with at least two additional lesions on the next (confirmatory) scan (2+2 PCWG3 criteria, Scher et al 2016). For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan (2+2 PCWG3 criteria).

If the second scan confirms the metastases, then the date of progression is the date of the scan when the first 2 new metastases were documented.

6.2.2 Additional Imaging Analyses

The baseline eligibility ^{68}Ga-PSMA-11 scan data will be used for additional exploratory analyses. The ^{68}Ga-PSMA-11 PET/CT and corresponding diagnostic CT/MRI scans will be used in a retrospective Independent Review assessing inter-reviewer variability. The Independent Review will serve to evaluate the reading procedure for ^{68}Ga-PSMA-11 PET/CT scans by assessing the variability and reproducibility of visual assessment. Visual assessment will be independently performed by three reviewers on ^{68}Ga-PSMA-11 PET/CT scans and corresponding diagnostic CT/MRI scans.

In addition, Quantitative Analysis will also be performed to assess tumor burden and tumor characteristics on ^{68}Ga-PSMA-11 PET/CT scans at the time of enrolment. The association of these baseline data with rPFS, OS, and other efficacy endpoints will be assessed in exploratory analyses.

An imaging charter will provide a detailed and expanded description of the planned analyses.

6.2.3 RECIST criteria

The responses of soft tissue, lymph node, and visceral lesions to treatment will be characterized using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations (see Appendix 6 and Appendix 7).

6.2.4 Symptomatic skeletal events

The time to the first SSE will measure the time to the 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.

6.2.5 Pain score

Pain will be assessed using the Brief Pain Inventory – Short Form (BPI-SF).

The Brief Pain Inventory- Short Form will be used as part of this study to assess the severity of pain and the impact of pain on daily functions. Full details regarding the BPI-SF, its validation and clinical application are available in the Brief Pain Inventory User Guide (Cleeland 2009).

A copy of the BPI-SF questionnaire is provided in Appendix 8.

6.2.6 Health-related quality of life

The ECOG Performance Status scale will be used to assess patients' ability to perform daily living tasks and their range of basic physical ability. A copy of the ECOG scale is provided in Appendix 4.

The EQ-5D-5L questionnaire will also be administered as a part of this study to assess HRQoL. EQ-5D is an international, validated, standardized, generic questionnaire for describing and valuing HRQoL (Rabin 2001). EQ-5D was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQoL Group 1990).

This instrument generates a preference-based health-state utility score (EQ-5D utility index) and an overall health-state score based on a visual analogue scale (EQ-5D VAS).

EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics and face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. The most recent version of EQ-5D is the EQ-5D-5L, which was developed to improve the instrument's sensitivity and to reduce ceiling effects. The number of dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) has not changed, however the new version includes five levels of severity in each of the existing dimensions in place of three (EuroQoL Group 2015). Full details regarding the EQ-5D-5L questionnaire, including references, are available at the EQ-5D website: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about.

A copy of the EQ-5D-5L questionnaire is provided in Appendix 9

The FACT-P questionnaire will also be administered as part of this study to specifically assess the HRQoL of prostate cancer patients. The FACT-P is made up of 2 parts: the FACT-G (general) questionnaire with 27 questions, and the Prostate Cancer Subscale (PCS) with an additional 12 questions. The FACT-G (Functional Assessment of Cancer Therapy – General) questionnaire is one of the most widely used HRQoL instruments and measures HRQoL in four different domains: Physical well-being, Functional well-being, Emotional well-being, and Social/Family well-being (Cella et al 1993). The PCS is designed specifically to measure prostate cancer-specific quality of life. Each item in both the FACT-G and PCS is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as global quality of life score with higher scores representing better QoL. The FACT system has a number of advantages as a method of measuring QoL:

- Questionnaires have been developed to reflect patients' concerns
- Measurements are reliable, reproducible, and have been validated in numerous studies (Cella et al 1993, Esper et al 1997)
- Available in over 45 different languages
- Designed for patient self-administration, but can also be administered by interview format (Webster et al 2003)

Full details regarding the FACT-P questionnaire, including references, are available at the FACIT website: http://www.facit.org/FACITOrg/Questionnaires.

A copy of the questionnaire (FACT-P version 4) is provided in Appendix 10.

HRQoL will be periodically assessed at baseline, prior to administration of each cycle of ^{177}Lu-PSMA-617, and through the End of Treatment visit.

6.2.7 Health Economics

A health economics (HE) sub-study will be performed.. Core health resource use information will be collected, using case report forms (CRFs) on days in hospital and any outpatient visits. Data collected on concomitant medication may also be used in the economic analysis.

For the economic modelling, costs will be imputed on the basis of representative country unit costs at the point of analysis using standard fee schedules. Health outcomes will be assessed in

terms of quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios. Quality adjustments will be based on patients' responses to the EQ-5D health status measure which will be administered at baseline, before each cycle of therapy, and each point of follow-up as part of the QoL questionnaire.

6.2.8 Clinical progression

Clinical progression will be assessed by the investigator. The following criteria should be used to determine when a patient has met the standard for unequivocal evidence of clinical progression:

- Marked escalation in cancer-related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical, or radiological intervention for complications due to tumor progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status to ≥ Grade 3 and a finding of the investigator that the deterioration indicates clinical progression
- In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

6.2.9 PSA levels

Local labs will measure PSA levels. Increases and decreases will be tracked to assess PSA responses as per PCWG3 (Appendix 7).

6.3 Safety assessments

6.3.1 Clinical laboratory evaluations

Local labs will perform hematology, chemistry, serum/plasma testosterone, and urinalysis testing.

Chemistry, urinalysis, and hematology testing will include the following:

Chemistry *total carbon dioxide or equivalent is acceptable ** urea is acceptable	• Sodium • potassium • total and direct bilirubin • ALP • AST • ALT	• LDH • blood urea nitrogen** • creatinine • uric acid • phosphorus • chloride	• bicarbonate* • calcium • glucose • total protein • albumin
Urinalysis	• urine pH • protein content • specific gravity • appearance and color	• glucose • ketones	
Hematology	• complete blood count (white blood cell count and differential) • red blood cell count • hemoglobin • hematocrit • platelet count		

6.3.2 Vital signs

Blood pressure, pulse and respiratory rate will be assessed.

6.3.3 Electrocardiograms

A 12-lead ECG will be done at screening.

6.3.4 Birth Control

It is recommended that male patients who are sexually active practice an effective barrier method of birth control (e.g, condom and spermicidal jelly). Effective birth control methods should be used from day of the ^{68}Ga-PSMA-11 dose, throughout study treatment and for at least 6 months following the last dose of ^{177}Lu-PSMA-617.

6.4 End of treatment visit procedures

The assessments and procedures to be done at the EOT visit are defined in the Schedule of Assessments tables, provided in Appendix 1.

6.5 Long-term follow-up procedures

A long-term follow-up period will collect, long term follow-up specific self-reported AE assessments, rPFS (if discontinuing for reasons other than radiographic progression), survival and treatment updates from patients every 3 months (± 1 month) via phone, email, or letter. Hematology and chemistry blood work results will also be collected. Patients who withdraw their consent to participate in the treatment portion of the study or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked for permission

to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

7. ADVERSE EVENTS

7.1 Adverse event definitions

The following definitions comply with the ICH E2A guidance, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and the safety definitions of the World Health Organization (WHO) International Drug Monitoring Center.

Term	Definitions[a]
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Progression of disease is not considered an AE or SAE for this study.
Adverse Drug Reaction	For an investigational medicinal product all noxious and unintended response to a medicinal product related to any dose should be considered adverse drug reactions. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
Serious Adverse Event (SAE) or Adverse Drug Reaction	A serious adverse event or reaction is any untoward medical occurrence that at any dose: • results in death; except for deaths due to progression of disease • is life-threatening; • requires inpatient hospitalization or prolongation of existing hospitalization; • results in persistent or significant disability/incapacity; or • is a congenital anomaly/birth defect. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Unexpected Adverse Drug Reaction[b]	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., Investigator's Brochure for an unapproved investigational medicinal product).

[a] ICH E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.
[b] Also referred to as a Suspected Unexpected Serious Adverse Reaction (SUSAR).
AE = adverse event; SAE = serious adverse event

7.2 Evaluating and recording adverse events

All AEs will be graded according to CTCAE v5.0. All AE monitoring and SAE recording and reporting will begin at the time of consent and will continue up to and including 30 days after the last dose of ^{177}Lu-PSMA-617 or the date of best supportive/best standard of care end of treatment decision, whichever is later. For patients that are not randomized, AE monitoring will continue up to and including 6 days after administration of ^{68}Ga-PSMA-11.

All AEs and abnormal test findings, regardless of suspected causal relationship to ^{68}Ga-PSMA-11, ^{177}Lu-PSMA-617, and/or best supportive/best standard of care, will be recorded in the patients' case histories. For all AEs sufficient information will be obtained to permit an adequate determination of the outcome of the event and an assessment of the casual relationship between the AE and ^{68}Ga-PSMA-11, ^{177}Lu-PSMA-617, and/or best supportive/best standard of care. AEs or abnormal test findings felt to be associated with ^{68}Ga-PSMA-11, ^{177}Lu-PSMA-617, and/or best supportive/best standard of care will be followed until the event or its sequelae or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

The investigator will promptly review AEs and abnormal test findings to determine if: 1) the abnormal test finding should be classified as an AE; 2) there is a reasonable possibility that the AE was caused by ^{68}Ga-PSMA-11, ^{177}Lu-PSMA-617, and/or best supportive/best standard of care; and 3) the AE meets the criteria for a serious adverse event (SAE). If the final determination of causality is "unknown and of questionable relationship to the study drug" the adverse event will be classified as associated with the use of the study drug for reporting purposes. If the final determination of causality is "unknown but not related to the study drug" the determination and rationale will be documented in the patient's case history.

7.3 Immediate Adverse Event Reporting

Endocyte will ensure that all relevant safety information as required by local and/or national laws, directives and/or regulations are reported to the appropriate Competent Authorities as well as the Principal Investigator and/or IRBs/Ethics Committees.

7.3.1 Serious Adverse Events

SAEs require expeditious handling and MUST IMMEDIATELY be reported upon discovery so the sponsor may comply with regulatory requirements.

Any SAE, regardless of causal relationship, must be reported to the Sponsor Contact listed in the Sponsor Contact section (Section 7.3.3) immediately (no later than 24 hours after the investigator becomes aware of the SAE) by emailing or faxing a completed SAE form to the number/email indicated and then confirming by telephone that the email/fax was received. Compliance with this time requirement is essential so that the sponsor may comply with its regulatory obligations.

Follow-up information relating to an SAE must be reported to the Sponsor Contact in Section 7.3.3 within 24 hours of receipt by the investigator by emailing or by faxing a completed SAE form to the number indicated and confirming by telephone that the fax was received. The patient should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified.

SAEs which are: 1) associated with ^{68}Ga-PSMA-11, ^{177}Lu-PSMA-617, and/or best supportive/best standard of care; 2) fatal or life-threatening; and 3) unexpected, will be reported to the principal investigator and/or IRBs/Ethics Committee/Research Ethics Boards (REBs) and the Regulatory Authorities within 7 days of awareness of the respective information. Other SAEs which are: 1) associated with the investigational drug or study treatment; 2) non-fatal or non-life-threatening; and 3) unexpected will be reported to the principal investigator and/or IRBs/Ethics Committee/REBs and Regulatory Authorities within 15 days of awareness of the respective information.

7.3.2 Serious adverse event subject follow-up

Follow-up information to a reported SAE will be submitted to the principal investigator and/or IRBs/Ethics Committees and Competent Authorities in accordance with local regulations and international guidelines. If the results of the follow-up investigation show that an SAE that was initially determined to not require reporting does, in fact, meet the requirements for reporting, the investigator will report the SAE to the principal investigator and/or IRBs/Ethics Committees/REBs in accordance with local regulations and international guidelines.

7.3.3 Sponsor Contact Information for Immediate Reporting

Serious adverse events and follow-up information should be reported on a completed serious adverse event report form to [redacted] by fax at [redacted] or emailed to [redacted] If reported by fax, please confirm receipt of fax via phone call to [redacted] at [redacted].

8. STATISTICS

This section outlines the general study design, study endpoints, and statistical analysis strategy for the study.

All statistical analyses will be carried out using SAS version 9.4 (or later). The SAP will be written and finalized prior to the first planned analysis and without knowledge of any by-treatment group accumulated data. The SAP will provide a detailed and expanded description of the statistical methods outlined in this protocol. Additional analyses, such as important subgroups, will be described.

8.1 Revision to the protocol and statistical analyses of rPFS and OS

The trial was originally designed to randomize 750 patients, targeting the primary analysis of rPFS with 457 events with a 1-sided alpha level of 0.001, an interim analysis of OS with a 1-sided alpha level of 0.001, to be conducted contemporaneously with the primary analysis of rPFS, and a final primary analysis of OS with 489 deaths with a 1-sided alpha of 0.023.

However, shortly after commencement of the trial, a high early dropout rate amongst those randomized to BS/BSC-only arm became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients which consequently could result in bias in the analysis of rPFS. Remedial measures to curtail this phenomenon were implemented and made effective on March 5th, 2019. As part of the plan to address the early withdrawal of consent in the BS/BSC-only arm, the primary analysis

of rPFS was altered to focus on patients prospectively randomized on or after March 5th, 2019; therefore, rPFS will be analyzed in these patients once 364 events have accrued with a 1-sided alpha level of 0.004. At time of this rPFS primary analysis, there will be an interim analysis of OS with a 1-sided alpha level of 0.001; this OS analysis will be on an ITT basis and will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final ITT primary analysis of OS will be performed when 508 deaths have accrued with a 1-sided alpha level of 0.020. To achieve these analyses, the total number of subjects randomized into the trial was increased from N=750 to N=814. The revisions described do not alter the hypothesized treatment effects for rPFS and OS upon which the study was originally powered.

8.2 Revisions to planned analyses

Subsequent to the protocol revision, if further changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be further amended (consistent with ICH Guideline E9). Any changes to exploratory or non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR). |Any post hoc exploratory analyses will be clearly identified in the CSR. Full details will be in the SAP. Any deviations from the statistical plan will be described and justified in a protocol amendment and/or in the CSR.

8.3 Sample size and power determination

The sample size was determined based on the alternate primary endpoints of rPFS and overall survival. Planned enrollment for this study is approximately 814 subjects.

Under the null hypothesis for survival, median survival is assumed to be 10 months on ^{177}Lu PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median overall survival on active is assumed to be 13.7 months for a HR of 0.7306.

Under the null hypothesis for rPFS, median rPFS is assumed to be 4 months on ^{177}Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median rPFS on active is assumed to be 6 months for a HR of 0.67.

Based on a non-linear patient accrual profile over 14 months, a total of 814 patients randomized and followed on an ITT basis for a minimum of 13 months is expected to yield 508 deaths. This number of events provides at least 90% power to test the hypothesis that the HR for OS is 0.7306 or better with a 1-sided alpha level of at least 0.020.

For rPFS, a total of approximately 557/814 patients are expected to be randomized on or after 5 March 2019, these being the patients to be included in the primary analysis of rPFS; with a minimum of approximately 6 months follow-up, these patients are expected to yield 364 rPFS events which will be sufficient to provide 84% power to test the hypothesis that the HR of rPFS is or 0.67 or better with a 1-sided alpha level if 0.004. At the time of this rPFS analysis, 341 deaths are expected amongst all randomized patients. These interim OS data will be analyzed with a 1-sided alpha level of 0.001. Central independent assessments will be used to determine rPFS events.

The alpha level applicable to OS in the final analysis will depend upon the earlier rPFS and interim OS results:

- if p<0.004 1-sided is achieved for rPFS and p<0.001 1-sided is achieved for interim OS, then the alpha level for the final analysis of OS will be raised to 0.025 1-sided.
- if p<0.004 1-sided is achieved for rPFS but p<0.001 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will be 0.024 1-sided.
- if p<0.004 1-sided is not achieved for rPFS but p<0.001 1-sided is achieved for interim OS, then the alpha level for the final analysis of OS will be raised to 0.021 1-sided.
- if p<0.004 1-sided is not achieved for rPFS and p<0.001 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will remain at 0.020 1- sided.

This design provides at least 90% power for OS and 84% power for rPFS; with an overall Type I error rate $\leq$0.025 1-sided.

The observed HRs that will meet p<0.004 for rPFS and the interim analysis of OS are 0.745 and 0.701 respectively; and the observed HR that will meet p<0.020 to p<0.025 in the final analysis of OS are 0.824 to 0.823.

8.4 Analysis populations

Analysis datasets are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients. OS will be assessed on an ITT basis and related data will be summarized by randomized treatment.
- **PFS Analysis Set (PFS-FAS)**: All patients randomized on or after March 5th, 2019. The primary analysis of rPFS will be based on this dataset on an ITT basis and related data will be summarized by randomized treatment.
- **Response Evaluable Analysis Set**: The subset of patients in the PFS-FAS with evaluable disease by RECIST at baseline. Soft tissue response as measured by RECIST will be assessed in this dataset.
- **Safety Analysis Dataset**: There will be two safety datasets
    - The subset of patients who received as least one dose of ^{68}Ga-PSMA-11.
    - The subset of patients in the FAS who received as least one dose of randomized therapy. Patient safety data in this dataset will be summarized by treatment received.

8.5 Demographics and baseline disease characteristics

Demographic and baseline disease characteristic data will be summarized in the FAS and PFS-FAS for each treatment with frequency distributions and/or descriptive statistics (mean, standard deviation, median, range, and/or relevant percentiles). Formal statistical tests comparing treatment groups will not be provided.

8.6 Patient disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. This will be done for the FAS and the PFS-FAS. If known, a reason for their discontinuation will be given. Reporting of patient disposition will include:

- A summary of data on patient discontinuation
- A summary of data on overall qualification status of all patients
- An account of all significant protocol deviations

All patients enrolled in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins, will be specified.

8.7 Efficacy analyses

8.7.1 Alternate primary endpoint efficacy analysis

8.7.1.1 rPFS

Radiographic progression-free survival (rPFS) is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. rPFS as determined by the independent central assessment will be used for this analysis. The primary analysis of rPFS will be based upon the PFS-FAS and will take place once 364 rPFS events have been reached. The allocated alpha level for the rPFS analysis is 0.004 1-sided.

Patients who are alive without radiographic progression at the analysis data cut-off or are lost to follow-up at the time of analysis will be censored for rPFS at the time of their last radiographic assessment or at the data cut-off date. rPFS data will be displayed using Kaplan Meier curves from which median rPFS times will be estimated for both treatment arms.

A stratified log-rank test model will be the primary statistical methodology used to analyze rPFS in the PFS-FAS dataset, stratified for the randomization stratification factors..

Supportive analyses of rPFS will be performed in terms of (i) a stratified Cox regression model on the PFS-FAS dataset with a single covariate for randomized treatment, and stratifying again for the randomization stratification factors; and (ii) the same as (i) but based upon the FAS dataset. The HR and CI from (i) will be used as an adjunct to the primary stratified log rank test p-value to provide the quantification of the treatment effect on rPFS.

8.7.1.2 OS

Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause and will be assessed in the FAS. A formal interim analysis of OS is planned to occur at the time of the rPFS analysis (with 364 rPFS events in PFS-FAS); it is anticipated that approximately 341 deaths will have accrued in the FAS at the time of the rPFS analysis in the PFS-FAS. The allocated alpha level for OS in this interim analysis is 0.001 1-sided. The final

analysis of OS is event driven and will take place once 508 deaths have occurred in the FAS. As described in Section 8.3, the allocated alpha level for the final OS analysis will be between 0.020 and 0.025 1-sided, depending on the results of the earlier primary rPFS analysis and interim OS analysis.

Patients who are lost to follow-up or are alive at the time of the OS analysis (for both interim and final analyses) will be censored at the time they were last known to be alive or at the date of event cut-off for the OS analysis. OS data will be displayed using Kaplan Meier curves from which median OS will be estimated for both treatment arms.

OS will be analyzed using the same statistical methodology as described for the primary analysis of rPFS. Supportive analyses of OS will be performed at the interim and final in terms of Cox regression model on the FAS dataset with a single covariate for randomized treatment, stratifying for the randomization stratification factors. The HR and CI from these analyses be used as an adjunct to the primary stratified log rank test p-values to provide the quantification of the treatment effect on OS.

8.7.1.3 Statistical Interpretation of Alternate Primary Endpoints

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either the primary analysis of rPFS **or** OS at the respective allocated alpha level; it is **not required** to meet both rPFS and OS to be declared a statistically positive study.

Note, this applies to OS assessed at either the interim or the final analysis, i.e. for the study to be declared statistically positive requires rPFS to meet its allocated alpha level **or** OS to meet its allocated alpha level at **either** (i) the formal OS interim analysis (conducted at the time of the rPFS analysis) **or** (ii) at the final OS analysis with 508 deaths.

Alpha allocation and recycling are used to ensure control of the overall Type I error rate as described in Section 8.3.

8.7.2 Secondary efficacy analyses

Key secondary endpoints

Key secondary endpoints will be subject to Type I error control. These endpoints are:

1. RECIST ORR and DCR
2. Time to SSE

The primary evaluation of these endpoints will be assessed in the PFS-FAS dataset. Time to SSE will be analyzed using a Cox regression model with a single covariate for randomized treatment, stratifying for the randomization stratification factors. ORR and DCR will be analyzed using logistic regression with a single covariate for randomized treatment and stratification for the randomization stratification factors. The odds ratio (active: control), its 95% confidence interval and associated 2-sided p-value will be presented. The DOR for binary response endpoint ORR will also be summarized and presented using Kaplan-Meier curves.

To control the overall Type I error rate, if either alternate primary endpoint is met, then the key secondary endpoints will be assessed using the Hochberg closed test procedure at the alpha level applicable to the successful alternate primary endpoint. This procedure is reasonable given the positive correlation between the two key secondary endpoints.

Supportive analyses of ORR, DCR and time to SSE will be performed in the FAS dataset using the same methods as described for the primary evaluation of these endpoints.

Additional Secondary Endpoints

Additional Secondary Endpoints will be assessed at the nominal 5% level, i.e. there will be no alpha control applied. These endpoints will be assessed in PFS-FAS with the exception of safety which will be assessed using the Safety analysis sets and are:

1. To evaluate the safety and tolerability of ^{177}Lu-PSMA-617
2. Aspects of HRQoL will be self-reported by patients (or via interview format) using the EQ-5D-5L and FACT-P questionnaires, and pain will be assessed by patients using the BPI-SF.
3. Health economics
4. PFS as defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
5. Biochemical response endpoints:

    d. Proportion of subjects who are PSA responders, defined as a patient who has achieved a ≥50% decrease from baseline that is confirmed by a second PSA measurement ≥4 weeks.

    e. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

Event-free survival endpoints (e.g., PFS, time to pain worsening) will be analyzed using a Cox regression model in the same manner as described for time to SSE except using a 2-sided p-value. DCR will be analyzed in the same manner as ORR and HRQoL will be analyzed in the same manner as pain score over time. Time to pain improvement response after initial pain worsening will be analyzed using mixture distribution methodology akin to that described by Ellis et al 2008.

8.8 Safety analyses

All safety evaluations will be based on the Safety Analysis Set.

8.8.1 Extent of exposure

The duration of exposure and dose intensity will be calculated. The relationship between dose intensity, duration of exposure, and frequency and severity of adverse events will be explored by data tabulation.

8.8.2 Analysis of adverse events

The frequency of treatment emergent adverse events (TEAEs) and SAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. The maximum NCI CTCAE grade and frequency of AEs will be summarized.

A ^{68}Ga-PSMA-11 TEAE is defined as an AE that was not present prior to dosing with ^{68}Ga-PSMA-11 but appeared following dosing or was present at time of initial dosing but worsened during or after dosing. The treatment-emergent period will be defined as the period from the date of ^{68}Ga-PSMA-11 dosing up to 6 days after the date of ^{68}Ga-PSMA-11 dosing as long as prior to the first dose of ^{177}Lu-PSMA-617 for the investigational arm and Cycle 1 Day 1 for the best supportive/best standard of care-only arm. Adverse events reported as "possibly", "probably", or "definitely" related to ^{68}Ga-PSMA-11 that occur beyond the 6-day reporting window but occur before the initiation of randomized treatment are also ^{68}Ga-PSMA-11 TEAEs. Unrelated ^{68}Ga-PSMA-11 adverse events that occur beyond 6 days will not be TEAEs.

A randomized treatment TEAE is defined as an AE that was not present prior to initiation of randomized treatment, defined as first dose of ^{177}Lu-PSMA-617 for the investigational arm and Cycle 1 Day 1 for the BS/BSC arm, but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated). The treatment-emergent period will be defined as the period from the initiation of randomized treatment up to 30 days after the date of the last dose or intervention of randomized treatment or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

Adverse events leading to permanent discontinuation of study drug and/or leading to death will be listed and tabulated.

8.8.3 Analysis of laboratory assessments

Laboratory values and change from baseline will be summarized by visit and treatment using descriptive statistics. Shift tables of the worst on-study laboratory toxicity based on CTCAE v5.0 grading relative to baseline will be presented by treatment group. Subject listings of laboratory toxicities ≥ Grade 3 will be provided.

8.8.4 Analysis of vital sign data

Vital sign data (observed and change from baseline) will be summarized using descriptive statistics by time point and treatment. Abnormal findings from physical examinations will be assessed for clinical significance which will be included in the AE listings and summaries.

8.9 IDMC and Interim Data Evaluation

8.9.1 IDMC

An IDMC will be convened to review accumulating safety and safeguard patient interest in the study. Safety data monitoring will be conducted quarterly by the IDMC. These safety reviews will commence following the completion of the first three months of study accrual.

In addition, a summary of efficacy data will also be provided to the IDMC at the time of routine safety data reviews; these efficacy data will be provided for information only, no statistical

analyses will be conducted. The only analyses of efficacy data are those formally planned for rPFS in the PFS-FAS at 364 events, interim OS (in the FAS) at the time of the rPFS analysis and final OS (in the FAS) with 508 deaths.

The IDMC will review these formal efficacy analyses. The IDMC may recommend early curtailment of trial on the basis of meeting one of the preplanned formal efficacy analyses or due to the emergence of an unforeseen safety concern placing patient safety at risk.

An IDMC Charter will be approved and finalized by the IDMC members prior to the initiation of any formal efficacy analysis.

The IDMC can recommend a course of action, but the sponsor will make the final decision regarding whether or not to continue or stop the trial, based on any analysis for reasons related to safety or efficacy.

8.9.2 Formal Interim Analysis of OS

As described above in Section 8.3, one formal interim analysis is planned for OS in the FAS to take place at the time of the primary rPFS analysis in the PFS-FAS. The allocated alpha level for the interim OS analysis is 0.001 1-sided. Regardless of whether a positive result is attained at this time, for either rPFS or interim OS, patient follow-up will continue until 508 OS events have accrued in the FAS at which time a final OS analysis will be performed.

9. ACCESS TO SOURCE DATA/DOCUMENTS

During the course of the study, a representative of Endocyte or its designee will be contacting and/or visiting the study sites to monitor the progress of the study. Contacts with the investigator and on-site visits for the purpose of data audits, including the comparison of source documents with case report forms (CRFs) and study agent accountability logs, will occur. The principal investigator or his/her representative will need to be available to the representative of Endocyte or its designee during these visits.

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, Endocyte, its designee, or responsible government agencies (as required by law) may review or copy source documents in order to verify case report form (CRF) data.

10. ETHICS

10.1 Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)

The investigator will obtain approval from the IRB/IEC/REB of the proposed clinical protocol and ICF for study recruitment and the approval will be provided to Endocyte or its designee prior to beginning the clinical trial. The only circumstance in which a deviation from the IRB/IEC/REB-approved clinical protocol/ICF may be initiated in the absence of prospective

IRB/IEC approval is to eliminate an apparent immediate hazard to the research participants. In such circumstances, the investigator will promptly notify the IRB/IEC/REB of the deviation.

The investigator will promptly notify Endocyte of any regulatory inspection relating to this study, including either the institution or the IRB/IEC/REB, and will promptly provide Endocyte with a copy of any inspection report.

10.2 Informed consent

The investigator will make certain that an appropriate informed consent process is in place to ensure that potential participants, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research participants. The investigator, or his/her authorized designee, will obtain the written, signed ICF of each participant, or the participant's authorized representative, prior to performing any protocol-specific procedures on the participant. The date and time that the participant, or the participant's authorized representative, signs the ICF and a narrative of the issues discussed during the informed consent process will be documented in the participant's case history. The investigator will retain the original copy of the signed ICF, and a copy will be provided to the participant, or to the participant's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled participants are adequately addressed and that the participants are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled participants for continued participation in the clinical study.

10.3 Health Insurance Portability and Accountability Act

Preparation of the Health Insurance Portability and Accountability Act (HIPAA) authorization form is the responsibility of the investigator and must include all elements required by the United States (US) Department of Health and Human Service's Privacy Rule. Prior to the beginning of the study, the investigator must have the IRB or the appropriate institution privacy board's written approval/favorable opinion of the HIPAA authorization form.

The HIPAA authorization must be signed and personally dated by the participant or their legally acceptable representative.

For sites located outside of the US, local regulations regarding protection of individually identifiable health information must be followed.

10.4 Confidentiality

All records will be kept confidential and the participant's name will not be released at any time. Participant records will not be released to anyone other than Endocyte or its designee(s) and responsible government agencies. Data sets for each participant will be identified by a unique number. If participant records are sent to Endocyte or its affiliates or designees, the participant's name or other identifying information will be masked and participant registration number or other unique identifier substituted.

11. COMPLIANCE AND QUALITY CONTROL

Independent auditing of the clinical study for protocol and GCP compliance may be conducted periodically at selected clinical sites by the Endocyte, Inc. Quality Assurance.

The purpose of the sponsor's audit is to evaluate trial conduct and compliance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements.

Site monitoring visits will be conducted periodically at each clinical site. During site monitoring visits the following but not exhaustive list of points will be reviewed: patient informed consent, patient recruitment and follow-up, AE reporting including SAE documentation, outcome events documentation and reporting, investigational drug allocation, storage and accountability, concomitant therapy use, and quality of data.

11.1 Compliance with Monitoring and Audits

Representatives of Endocyte or its designee must be allowed to visit (scheduled in advance) all study site locations periodically to assess the data, quality, and study integrity. On site, they will review study records and directly compare them with CRFs and discuss the conduct of the study with the investigator and verify that the facilities remain acceptable. It is the responsibility of the investigator (or designee) to be present or available for consultation during such monitoring visits.

In addition, the study may be evaluated by Endocyte (or designee's) internal auditors and government inspectors who must be allowed access to CRFs, source documents, investigational medication records, and other study files. The sponsor's (or designee's) audit reports will be kept confidential to the extent permitted by law. The investigator must notify Endocyte promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Endocyte. The investigator agrees to promptly take any reasonable steps that are requested by Endocyte as a result of monitoring or auditing activities to address deficiencies in study conduct or documentation. In the event that Endocyte is unable to secure compliance with the Statement of investigator or study protocol and prematurely terminates a trial site, Endocyte will notify the FDA (as required by 21 CFR § 312.56) the site's IRB/IEC/REB, and other regulatory authorities, as required.

12. DATA HANDLING, RECORD KEEPING, AND COMPLIANCE

12.1 Investigational medicinal product accountability

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug destroyed.

12.2 Breaking the blind

Not applicable.

12.3 Data collection forms and source document identification

All source data will be retained by the trial site to ensure that, if requested, a monitor, auditor, or regulatory agency has access to the source documents.

Source data are the clinical findings and observations, laboratory and test data, and other information contained in source documents. Source documents are the original records (and certified copies of original records) including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, biopsy reports, ultrasound reports, pharmacy records, or any other similar reports or records of any procedures performed in accordance with the protocol. Source documentation may also include any sponsor CRF when source data is recorded directly onto a CRF.

The health-related quality of life questionnaires will utilize electronic Clinical Outcome Assessments (eCOA) technology for direct entry of the patient's responses. The eCOA will serve as source data.

A CRF will be completed for each participant enrolled into the clinical study. Patients are to be identified by, year of birth, patient screening number and patient enrollment number. Information recorded on the CRF must match the source data recorded on the source documents.

The investigator will review, approve, and sign/date completed CRFs. Their signature serves as attestation ensuring that all clinical and laboratory data entered on the CRF are complete, accurate, and authentic. This review and sign-off may be delegated to a qualified physician appointed as a sub-investigator by the principal investigator. The transfer of duties must be recorded on the Delegation Log (kept on file at the site) and all sub-investigators must be listed on FDA Form 1572 or equivalent regulatory statement. The investigator must ensure that all sub-investigators are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study agent(s).

12.4 Record maintenance and retention

The investigator will maintain records in accordance with GCP guidelines including the following:

- IRB/IEC/REB correspondence (including approval notifications) related to the clinical protocol, including copies of adverse event reports and annual or interim reports
- All versions of the IRB/IEC/REB approved clinical protocol and corresponding ICFs and, if applicable, participant recruitment advertisements
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol and laboratory certification
- Instructions for on-site preparation and handling of the investigational drug, study treatment, and other study-related materials if not addressed in the clinical protocol;
- Participant screening and enrollment logs and signed ICFs
- Investigational drug accountability records, including documentation of drug return or destruction
- A summary of the final clinical study results

12.5 Archiving

Endocyte and the investigator will retain the records and reports associated with the clinical trial as required by local regulatory requirements after the marketing application is approved for the investigational drug. If a marketing application is not submitted or approved for the investigational drug the information will be retained until two years after investigations under the Investigational New Drug Application/Clinical Trial Application have been discontinued and the FDA/EMA/CA notified.

13. PUBLICATION POLICY

Endocyte and the investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Endocyte and the investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by the investigators or their personnel and associates resulting from or relating to this study must be submitted to Endocyte for review 60 days before submission for publication or presentation.

If the proposed publication or presentation contains patentable patient matter, which, at Endocyte's sole discretion, warrants intellectual property protection, Endocyte may delay any publication or presentation for up to 60 days after approval for the purpose of pursuing such protection.

14. REFERENCES

Ahmadzadehfar et al 2016
Ahmadzadehfar H, Eppard E, Kürpig S, Fimmers R, Yordanova A, Schlenkhoff CD, et al. Therapeutic response and side effects of repeated radioligand therapy with ^{177}Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. Oncotarget. 2016;7(11):12477-88.

Ahmadzadehfar et al 2015
Ahmadzadehfar H, Rahbar K, Kürpig S, Bögemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with ^{177}Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. EJNMMI Research. 2015;5:36.

Azad et al 2015
Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of Enzalutamide Following Abiraterone Acetate in Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer Patients. European Urology 2015, 67 23-29.

Badrising et al 2014
Badrising S, van der Noort V, van Oort IM, et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. Cancer 2014; 120:968-75.

Benešová et al 2015
Benešová M, Schäfer M, Bauder-Wüst U, Afshar-Oromieh A, Kratochwil C, Mier W, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. J Nucl Med. 2015;56(6):914–20.

Brasso et al 2015
Brasso K, Thomsen FB, Schrader AJ, Schmid SC, Lorente D, Retz M, Merseburger AS, von Klot CA, Boegemann M, de Bono J. Enzalutamide Antitumour Activity Against Metastatic Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis. European urology. 2015;68(2):317-24.

Bray et al 2012
Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013 Mar 1;132(5):1133-45. doi: 10.1002/ijc.27711. Epub 2012 Jul 26.

Bräuer et al 2017
Bräuer A, Grubert LS, Roll W, Schrader AJ, Schäfers M, Bögemann M, et al. ^{177}Lu-PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging*. 2017 Sep;44(10):1663-70.

Bostwick et al 1998
Bostwick DG, Pacelli A, Blute M, Roche P, and Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer. 1998;82:2256-61.

Cella et al 1993
Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993 Mar;11(3):570-9.

Cella et al 2009
Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy--Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. Value Health. 2009 Jan-Feb;12(1):124-9.

Cheng et al 2015
Cheng HH, Nadal R, Azad A, Gulati R, et al. Activity of enzalutamide in men with metastatic castration resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. Prostate Cancer Prostatic Dis. 2015; 18(2): 122–127. doi:10.1038/pcan.2014.53.

Cleeland 2009
Cleeland, CS. The Brief Pain Inventory User Guide. 2009. Available at: www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf.

Das et al 2016
Das T, Guleria M, Parab A, Kale C, Shah H, Sarma HD, et al. Clinical translation of (177)Lu-labeled PSMA-617: Initial experience in prostate cancer patients. Nucl Med Biol. 2016; 43(5): 296–302.

Delker et al 2016
Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2016;43(1):42-51.

Ellis et al 2008
Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. Contemp Clin Trials. 2008 Jul;29(4):456-65.

Emmett et al 2017
Emmett L, Willowson K, Violet J, Shin J, Blanksby A, and Lee J. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. J Med Radiat Sci. 2017 Mar; 64(1):52–60.

Esper et al 1997
Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology. 1997 Dec;50(6):920-8.

EuroQoL Group 1990
EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199-208.

EuroQoL Group 2015
EuroQol Group. EQ-5D-5L User Guide Basic information on how to use the EQ-5D-5L instrument. April 2015, Version 2.1. Retrieved from https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

Fendler et al 2017
Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S, Herrmann K. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017 Jun;44(6):1014-1024.

Ferdinandus et al 2017
Ferdinandus J, Eppard E, Gaertner FC, Kürpig S, Fimmers R, Yordanova A, et al. Predictors of Response to Radioligand Therapy of Metastatic Castrate-Resistant Prostate Cancer with ^{177}Lu-PSMA-617. J Nucl Med. 2017 Feb;58(2):312-319.

Ferlay et al 2013
Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on day/month/year.

Flaig et al 2016
Flaig TW, Potluri RC, Ng Y, Todd MB, and Mehra M. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. Cancer Med. 2016;5(2):182-91.

Ghosh and Heston 2004
Ghosh A and Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004;91:528–39.

Haberkorn et al 2016
Haberkorn U, Eder M, Kopka K, Babich JW, and Eisenhut M. New Strategies in Prostate Cancer: Prostate-Specific Membrane Antigen (PSMA) Ligands for Diagnosis and Therapy. Clin Cancer Res. 2016 Jan 1;22(1):9-15.

Haug et al 2016
Haug AR, Shariat S, Eidherr H, Vraka C, Wadsak W, Mitterhauser M, et al. Initial experience with aggressive treatment of metastastic prostate cancer using 3 cycles of 7.4 GBq [177Lu]-PSMA every 4 weeks. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S212 EPW11.

Hillier et al 2009
Hillier SM, Maresca KP, Femia FJ, Marquis JC, Foss CA, Nguyen N, et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. Cancer Res. 2009;69(17), 6932–40.

Hofman et al 2018
Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, Iravani A, Kong G, Ravi Kumar A, Murphy DG, Eu P, Jackson P, Scalzo M, Williams SG, Sandhu S. [177Lu]-PSMA-

617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol. 2018 Jun;19(6):825-833.

Hofman et al 2019
Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Iravani A, Kong G, Ravi Kumar A, Akhurst T, Mooi J, Guo C, Tran B, Jackson P, Scalzo m, Eu P, Williams S, Sandhu SK. Results of a 50 patient single-centre phase II prospective trial of Luteium-177 PSMA-617 theranostics in metastatic castrate-resistant prostate cancer. J Clin Oncol. 2019;37(suppl 7S): 228.

Kirby et al 2011
Kirby M, Hirst C, and Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract. 2011 Nov;65(11):1180-92.

Kulkarni et al 2016
Kulkarni HR, Singh A, Schuchardt C, Niepsch K, Sayeg M, Leshch Y, et al. PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. J Nucl Med. 2016 Oct;57(Suppl 3):97S-104S.

Kulkarni et al 2018
Kulkarni HR, Langbein T, Atay C, Singh A, Schuchardt C, Lehmann C, Pomper M, Pienta KJ, Baum RP. Safety and long-term efficacy of radioligand therapy using Lu-177 labeled PSMA ligands in metastatic prostate cancer: A single center experience over 5 years. Cancer Research. 2018 Jul;78(13):CT015.

Kratochwil et al 2015
Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benešová M, Mier W, et al. [^{177}Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42(6):987–88.

Kratochwil et al 2016
Kratochwil C, Giesel FL,Stefanova M, Benešová M, Bronzel M, Afshar-Oromieh A, Mier W, Eder M, Kopka K, Haberkorn U. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with ^{177}Lu-labeled PSMA-617. J Nucl Med. 2016;57(8):1170-1176.

Leuschner 2016
Leuschner J. Subchronis toxicity study of PSMA-617 by intravenous administration to male CD® rats. LPT Report No. 32508 2016, November 12, 2016.

Loriot et al 2013
Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, … and Massard C. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Annals of Oncology 2013 24: 1807–1812. doi:10.1093/annonc/mdt136

Mannweiler et al 2009
Mannweiler S, Amersdorfer P, Trajanoski S, Terrett JA, King D, and Mehes G. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. Pathol Oncol Res. 2009 June;15(2):167–72.

Noonan et al 2013
Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Annals of Oncology 2013 24: 1802–1807. doi:10.1093/annonc/mdt138

Rabin 2001
Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001 Jul;33(5):337-43.

Rahbar et al 2016a
Rahbar K, Bode A, Weckesser M, Avramovic N, Claesener M, Stegger L, et al. Radioligand Therapy With ^{177}Lu-PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer. Clin Nucl Med. 2016a;41(7):522-528.

Rahbar et al 2016b
Rahbar K, Schmidt M, Heinzel A, Eppard E, Bode A, Yordanova A, et al. Response and Tolerability of a Single Dose of ^{177}Lu-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis. J Nucl Med. 2016b;57(9):1334-38.

Rahbar et al 2017
Rahbar K, Ahmadzadehfar J, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German Multicenter Study Investigating ^{177}Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. J Nucl Med. 2017;58(1):85-90.

Rahbar et al 2018
Rahbar K, Boegemann M, Yordanova A, Eveslage M, Schäfers M, Essler M, Ahmadzadehfar H. PSMA targeted radioligand therapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. Eur J Nucl Med Mol Imaging. 2018 Jan;45(1):12-19.

Rajasekaran et al 2003
Rajasekaran SA, Anilkumar G, Oshima E, Bowie JU, Liu H, Heston WD, et al. A Novel Cytoplasmic Tail MXXXL Motif Mediates the Internalization of Prostate-specific Membrane Antigen. Mol Biol Cell. 2003;14(12):4835-4845.

Rathke et al 2017
Rathke H, Giesel FL, Flechsig P, Kopka K, Mier W, Hohenfellner M, Haberkorn U, Kratochwil C. Repeated Lu-177-PSMA-617 radioligand therapy using treatment activities up to 9.3 GBq. J Nucl Med. 2017 Aug 10. pii: jnumed.117.194209. doi: 10.2967/jnumed.117.194209. [Epub ahead of print]

Rathore et al 2016
Rathore H, Shah H, Aland P, Chaudhuri P, Bharadwaj T, Kale C, et al. Assessment of response, clinical evaluation and toxicity of radioligand therapy (RLT) with 177-Lutetium-DKFZ-617-labelled Prostate specific membrane antigen (177-Lu-DKFZ-617-PSMA) for metastatic castrate resistant prostate cancer (mCRPC): An initial experience in Jaslok. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S414 EP482.

Ross et al 2003
Ross JS, Sheehan CE, and Fisher H. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res. 2003;9:6357–62.

Saad et al 2004
Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone-Refractory Prostate Cancer. J Natl Cancer Inst. 2004;96(11):879–82.

Scher et al 2015
Scher HI, Solo K, Valant J, Todd MB, and Mehra M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. PLoS One. 2015 Oct 13;10(10):e0139440.

Scher et al 2016
Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Work Group 3. J Clin Oncol 2016;34(12):1402–18.

Siegel et al 2017
Siegel RL, Miller KD, and Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.

Smith et al 2016
Smith M, De Bono J, Sternberg C, Le Moulec S, Oudard S, De Giorgi U, et al. Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. J Clin Oncol. 2016;34:3005-13.

Soydal et al 2016
Soydal C, Ozkan E, Nak D, and Kucuk ON. The First Experience on Lutetium (lu)-177 Prostate Specific Antigen (PSMA) Treatment in Castration Resistant Prostate Cancer Patients. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S415 EP485.

Webster et al 2003
Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes. 2003 Dec 16;1:79.

Wegen et al 2016
Wegen S, Eppard E, Kürpig S, Essler M, Yordanova A, Hauser S, et al. Treatment response according to PSA changes in patients undergo more than one cycle of 177Lu-PSMA-617 therapy. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S213 EPW14.

Weinfurt et al 2005
Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, et al. The significance of skeletal-related events for the health related quality of life of patients with metastatic prostate cancer. Ann Oncol. 2005;16(4):579–84.

Yadav et al 2017
Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, et al. ^{177}Lu-DKFZ-PSMA-617 therapy with metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. Eur J Nucl Med Mol Imaging. 2017;44(1):81-91.

Yordanova et al 2017
Yordanova A, Becker A, Eppard E, et al. The impact of repeated cycles of radioligand therapy using [177Lu]Lu-PSMA-617 on renal function in patients with hormone refractory metastatic prostate cancer. *Eur J Nucl Med Mol Imaging*. 2017;DOI 10.1007/s00259-017-3681-9.

Zielinski et al 2014
Zielinski RR, Azad AA, Chi KN, Tyldesely S. Population-based impact on overall survival after the introduction of docetaxel as standard therapy for metastatic castration resistant prostate cancer. Can Urol Assoc J. 2014 Jul;8(7-8):E520-3.

Appendix 1 Schedules of Assessments

Table 3 Schedule of assessments: ^{177}Lu-PSMA-617 plus best supportive/best standard of care arm (Cycle 1)

Study Period:	**Cycle 1**					
Cycle Week:	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
Cycle Day:	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**
Concomitant medication review	X----------X					
AE monitoring[a]	X----------X					
Weight	X[b]					
ECOG	X[b]					
Directed physical exam	X[b]					
Vital signs[c]	X[b]					
EQ-5D-5L	X[d,f]					
FACT-P	X[d,f]					
BPI-SF	X[d,f]					
Administer ^{177}Lu-PSMA-617	X					
Best supportive/best standard of care	As per physician's orders					
Hematology[e]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Chemistry[e]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Serum/plasma testosterone	X[b]					
PSA	X[b]					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (± 4 days) after first dose of ^{177}Lu-PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days)					

[a] Adverse event monitoring will commence at time of consent.
[b] Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 8, 15, 22, 29, and 36.
[c] Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1) and at 15(+/-5) minutes before, 30 (+/-5) minutes post, and 60 (+/-5) minutes post ^{177}Lu-PSMA-617 administration.
[d] To be completed prior to drug administration on Day 1. Can be completed up to 3 days prior to Day 1.
[e] Hematology and chemistry to be done every week for Cycle 1 only.
[f] HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

Table 4 Schedule of assessments: ^{177}Lu-PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Study Period:	**Cycles 2-6***						**After Cycle 6****	**End of Treatment[g]**	**Long-term follow-up**
Cycle Week:	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Every 12 weeks (± 4 days)**		**Every 3 months (± 1 month)**

Cycle Day:	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**			**Collect:**
									• Hematology
									• Chemistry
									• Survival
									• New treatment:
									  • Start/stop dates
									  • Best response
									  • Type of response
									• AE assessment
									• Radiographic imaging (only if pt came off the active part of the study for any reason other than radiographic disease progression)

Concomitant medication review	X----------X[a]							X	
AE monitoring[b]	X----------X[a]							X	
Weight	X[c]						X[c]	X	
ECOG	X[c]						X[c]	X	
Directed physical exam	X[c]						X[c]	X	
Vital signs[d]	X[c]						X[c]	X	
EQ-5D-5L	X[e,h]						X[e,h]	X[h]	
FACT-P	X[e,h]						X[e,h]	X[h]	
BPI-SF	X[e,h]						X[e,h]	X[h]	
Administer ^{177}Lu-PSMA-617	X								
Best supportive/ best standard of care	As per physician's orders								
Hematology[f]	X[c]		X[c]		X[c]		X[c]	X	
Chemistry[f]	X[c]		X[c]		X[c]		X[c]	X	
Serum/plasma testosterone	X[c]						X[c]	X	
PSA	X[c]						X[c]	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (± 4 days) after first dose of ^{177}Lu-PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days)								

[*] After the Cycle 4 dose of ^{177}Lu-PSMA-617 and prior to Cycle 5 Day 1, the investigator should determine if:
- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- has shown good tolerance to the ^{177}Lu-PSMA-617 treatment.

If the patient meets the criteria above, and agrees to continue with additional treatment of ^{177}Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu-PSMA-617 treatment, then no additional doses of ^{177}Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ^{177}Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

[**] Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards.

[a] Phone evaluations are allowed, but are not required for visits after Day 1 of each cycle.

[b] Adverse event monitoring will commence at time of consent.

[c] Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 15, and 29.

[d] Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1) and at 15(+/-5) minutes before, 30(+/-5) minutes post, and 60(+/-5) minutes post ^{177}Lu-PSMA-617 administration.

[e] To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.

[f] For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done on Cycle 7 Day 1 and then every 12 weeks (± 4 days).

[g] To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose of ^{177}Lu-PSMA-617 or last dose or intervention of best supportive/best standard of care end of treatment decision, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study

[h] HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.

AE = adverse event; ANC= absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; WBC = white blood cell

Table 5 Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)

Study Period:	Cycle 1					
Cycle Week:	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
Cycle Day:	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**
Concomitant medication review	X----------X					
AE monitoring[b]	X----------X					
Weight	X[a]					
ECOG	X[a]					
Directed physical exam	X[a]					
Vital signs[c]	X[a]					
EQ-5D-5L	X[d,f]					
FACT-P	X[d,f]					
BPI-SF	X[d,f]					
Best supportive/ best standard of care	As per physician's orders					
Hematology[e]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Chemistry[e]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Serum/plasma testosterone	X[a]					
PSA	X[a]					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (± 4 days) after Cycle 1 Day 1[g] for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days) through the End of Treatment visit					

[a] Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 8, 15, 22, 29, and 36.
[b] Adverse event monitoring will commence at time of consent.
[c] Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).
[d] To be completed prior to any drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.
[e] Hematology and chemistry to be done every week for Cycle 1 only.
[f] HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.
[g] Cycle 1 Day 1 for patients on the Best supportive/best standard of care only arm is considered as the day that the majority of the day 1 assessments are conducted

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

Table 6 Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6**						After Cycle 6**	End of Treatment[g]	Long-term follow-up
Cycle Week:	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Every 12 weeks (± 4 days)**		**Every 3 months (± 1 month)**

Cycle Day:	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**			**Collect:**
									• Hematology
									• Chemistry
									• Survival
									• New treatment:
									  • Start/stop dates
									  • Best response
									  • Type of response
									• AE assessment
									• Radiographic imaging (only if pt came off the active part of the study for any reason other than radiographic disease progression)

Concomitant medication review	X----------X[a]							X	
AE monitoring[b]	X----------X[a]							X	
Weight	X[c]						X[c]	X	
ECOG	X[c]						X[c]	X	
Directed physical exam	X[c]						X[c]	X	
Vital signs[d]	X[c]						X[c]	X	
EQ-5D-5L	X[e,h]						X[e,h]	X[h]	
FACT-P	X[e,h]						X[e,h]	X[h]	
BPI-SF	X[e,h]						X[e,h]	X[h]	
Best supportive/best standard of care	As per physician's orders								
Hematology[f]	X[c]		X[c]		X[c]		X[b]	X	
Chemistry[f]	X[c]		X[c]		X[c]		X[b]	X	
Serum/plasma testosterone	X[c]						X[b]	X	
PSA	X[c]						X[b]	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (± 4 days) after Cycle 1 Day 1 for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days)								

** Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards.

[a] Phone evaluations are allowed, but are not required for visits after Day 1 of each cycle.
[b] Adverse event monitoring will commence at time of consent.
[c] Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 15, and 29.
[d] Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).
[e] To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.
[f] For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every12 weeks (± 4 days).
[g] To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the date of the last dose or intervention of best supportive/best standard of care end of treatment decision, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study.
[h] HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; WBC = white blood cell count

Appendix 2 Suggested treatment guidelines

The following are suggested guidelines for clinical support during ^{177}Lu-PSMA-617 administration. They are to be used at the discretion of the investigator.

- Cooling the salivary glands from 30 min. before and up to 4 hours after the ^{177}Lu-PSMA-617 injection for reducing the risk of salivary glands radiation injuries is optional and depends on center practice.
- 500 mL of 0.9% (i.e., normal) saline may be infused at a rate of 125 mL/hour to begin after administration of ^{177}Lu-PSMA-617. Additionally, fluid intake should be encouraged on the day of treatment.
- In patients with high tumor burden or gout allopurinol may be started within 7 days and up to 10 days following ^{177}Lu-PSMA-617 therapy

Appendix 3 Principal Investigator Signature

I have read this clinical protocol, no. PSMA-617-01, in its entirety and:

- I agree to implement and conduct this clinical study diligently and in strict compliance with the protocol, good clinical practices, and all applicable national, federal, and local laws and/or regulations.
- I agree that this clinical protocol will not be modified by me or any member of my staff without the written consent of Endocyte, Inc. and, if required, I will receive approval of these modifications by my institution's IRB/REB/Independent Ethics Committee (IEC).
- I certify that neither I nor any member of my staff has been disqualified or debarred by the Food and Drug Administration (FDA), European or any other regulatory bodies for clinical investigations or any other purpose.
- I understand that this clinical protocol and the accompanying clinical Investigator's Brochure contains trade secrets and/or commercial information that are privileged and/or confidential and may not be disclosed unless such disclosure is required by national, federal, or local laws and/or regulations.

Pursuant to 21 CFR § 312.53(c), each US investigator will complete and sign FDA Form 1572, Statement of Investigator, prior to participating in the study. The completed form, along with a curriculum vitae, will be returned to Endocyte and maintained on record.

Form FDA 1572, Statement of Investigator, which must be completed, is available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf

Principal Investigator Signature	Date
Name (Printed)	
Title (Printed)	

Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

Eastern Cooperative Oncology Group Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.
**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *Journal of Chronic Diseases*; 1960:11:7-33.

Appendix 5 Common Terminology Criteria for Adverse Events

The complete NCI CTCAE (version 5.0) can be found at the following site:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

Appendix 6 Response Evaluation Criteria in Solid Tumors

The latest RECIST guidelines (version 1.1) can be found at the following site:
http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf

Appendix 7 Prostate Cancer Working Group 3 Recommendations

The sections that apply to this trial are the criteria for prostate-specific antigen (PSA) response and progression, and the criteria for bone lesion "prevent/delay end points" (progression). It is based on the PCWG3 recommendations. Please note that not all the recommendations listed below are applicable to this patient population or to the specifics of this study.

Variable	PCWG3 (2016)
PSA	• Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drug • Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression • Ignore early rises (prior to 12 weeks) in determining PSA response **For control/relieve/eliminate endpoints:** • Describe absolute changes in PSA over time from baseline to best response **For delay/prevent endpoints: Decline from baseline:** • Record time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend) **No decline from baseline:** • PSA progression ≥25% and ≥2 ng/mL after 12 weeks
Soft-tissue lesions	**For control/relieve/eliminate end points:** Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats: • Record up to 5 lesions per site of disease • Record changes in nodal, lung, liver adrenal and central nervous system (CNS) sites separately • Only report changes in lymph nodes that were ≥1.5 cm in diameter in short axis at baseline • Record changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separately • Only report changes in visceral lesions (liver, lung, adrenal, CNS) that were ≥1.0 cm in the longest dimension • Record complete elimination of disease at any site separately • Confirm favorable change with second scan • Record changes using waterfall plot **For delay/prevent end points:** • Record changes in nodal and visceral disease separately • Record up to 5 lesions per site of spread • Use RECIST 1.1 criteria for progression, but clearly record type of progression (growth of existing lesions vs development of new lesions) separately by site. With additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. (Particularly important when anticipated effect on PSA is delayed or for biologic therapies) • Previously normal (<1.0 cm) lymph nodes must have grown by ≥5 mm in the short axis from baseline or nadir and be ≥1.0 cm in the short axis to be considered to have progressed. Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable. For existing pathologic adenopathy (≥1.5 cm), progression is defined per RECIST 1.1

Bone	For control/relieve eliminate end points: • Record outcome as new lesions, no new lesions or resolved lesion • First scheduled reassessment: o No new lesions: continue therapy o New lesions: perform a confirmatory scan 6 or more weeks later • Confirmatory scan: o No new lesions: continue therapy o Additional new lesions: progression • Subsequent scheduled reassessments: o No new lesions: continue o New lesions: progression • Changes in intensity or uptake do not constitute regression or progression For prevent/delay end points (progression): • Exclude pseudoprogression in the absence of symptoms or other signs of progression • At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule) • If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented • For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan • Date of progression is the date of the scan that first documents the second lesion • Changes in intensity of uptake alone do not constitute either progression or regression • Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
Symptoms	Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use). **For control/relieve eliminate end points:** • Serial (eg, daily x 7 days) assessments at each time point can improve the stability of values Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement. **For delay/prevent end points:** Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use). Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later). Time to deterioration of physical function and/or health-related quality of life (HRQoL) scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire.

Refer to Scher et al 2016 for more details.

CNS = central nervous system; HRQoL = health-related quality of life; PCWG3 = Prostate Cancer Working Group 3; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

Appendix 8 BPI-SF (*sample only, not for patient use)*

Brief Pain Inventory (Short Form)

Time: ____ : ____ ☐ AM ☐ PM

Today's Date (day, month, year):

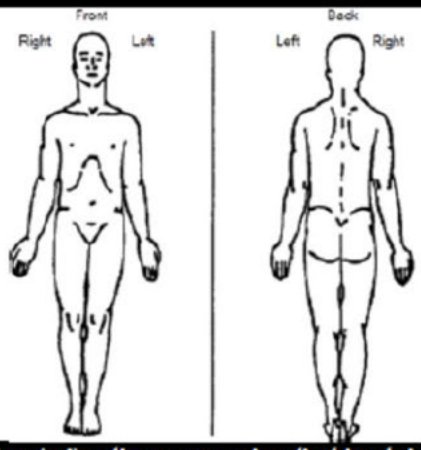
☐ JAN ☐ FEB ☐ MAR ☐ APR ☐ MAY ☐ JUN ☐ JUL ☐ AUG ☐ SEP ☐ OCT ☐ NOV ☐ DEC

Day ____ - Year ____

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that best describes how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Page 1 of 2

Today's Date (Day, Month, Year): ____-____-____ (Example: 08-FEB-2016) DAY MONTH YEAR

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (inculdes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Please place an "X" in the appropriate box to indicate who completed the form:

☐ Patient

☐ Another person read the patient the questions and marked the form with the patient's answers

Appendix 9 EQ-5D-5L (European Quality of Life (EuroQol) – 5 Domain 5 Level scale) (*sample only, not for patient use)*

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

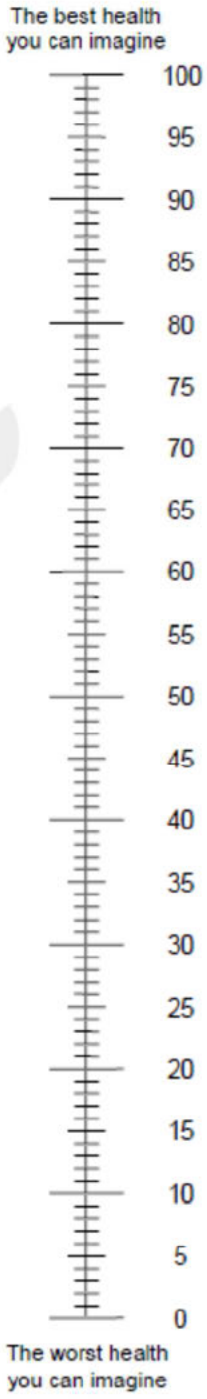
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 10 FACT-P (Functional Assessment of Cancer Therapy – Prostate) *(sample only, not for patient use)*

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

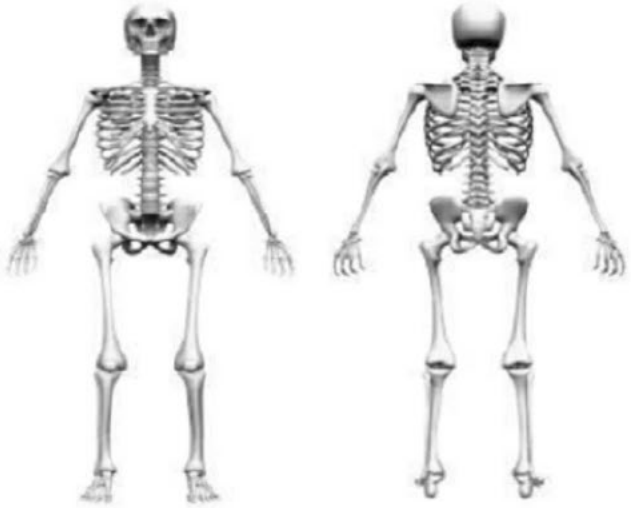
	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Appendix 11 PCCTC Bone Scan Assessment Tool

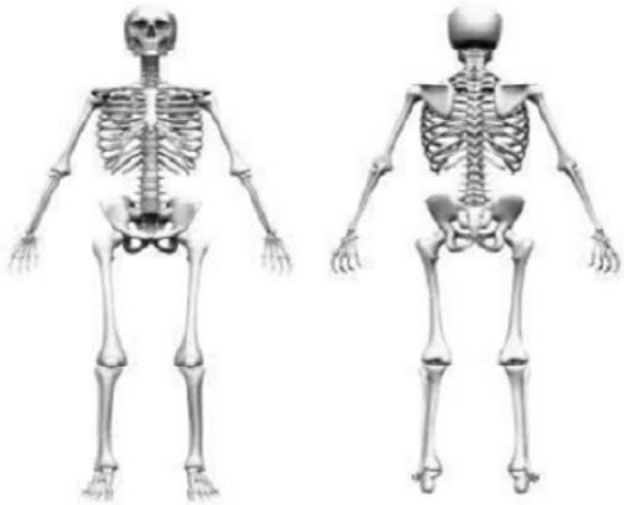
Screening Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	☐ Yes ☐ No [do not fill out the rest of the form]
If yes, indicate total number of lesions related to metastatic disease at Screening: ☐ 1 ☐ 2-4 ☐ 5-9 ☐ 10-20 ☐ >20	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

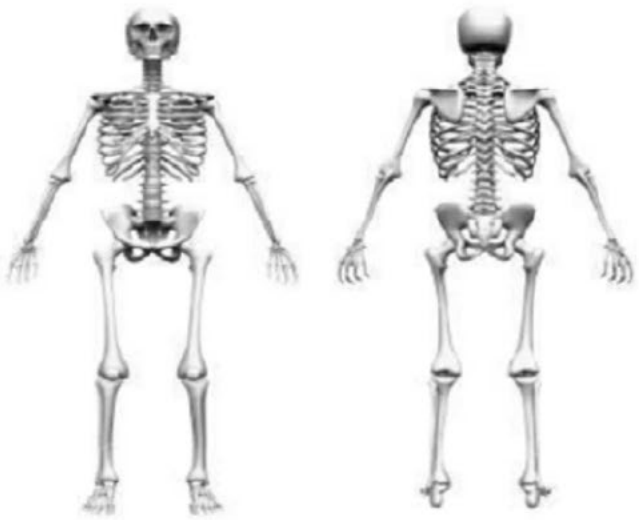
Week 8 BASELINE Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	☐ Yes ☐ No [do not fill out the rest of the form]
If yes, indicate total number of NEW lesions compared to Screening Bone Scan: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ >5	
Check Region(s) of NEW Disease Post-Screening: ☐ Skull ☐ Thorax ☐ Spine ☐ Pelvis ☐ Extremities	**Draw site(s) of NEW lesion(s) on skeleton:** 
Are there 2 or more NEW lesions at this Week 8 Bone Scan compared to the Screening Bone Scan?	☐ Yes* ☐ No
** Presence of new lesions at this time does not confirm progression*	
Clinical Impression: ☐ Improved ☐ Stable ☐ Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

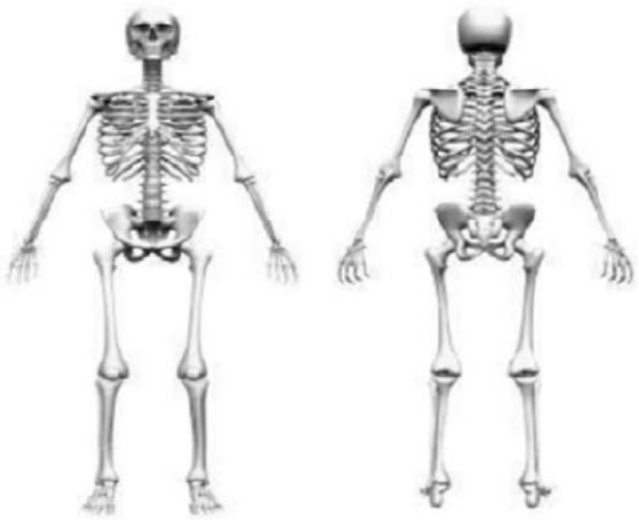
Week 16 Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	☐ Yes ☐ No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ >5	
Check Region(s) of NEW Disease Post-Screening: ☐ Skull ☐ Thorax ☐ Spine ☐ Pelvis ☐ Extremities	**Draw site(s) of NEW lesion(s) on skeleton:** 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?	☐ Yes ☐ No [Not PD]
Were there 2 or more NEW lesions at the Week 8 Bone Scan compared to the Screening Bone Scan *AND* were there 2 or more NEW lesions compared to the Week 8 Bone Scan?	☐ Yes [PD] ☐ No [Not PD]
Clinical Impression: ☐ Improved ☐ Stable ☐ Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Week ☐ 24 ☐ 36 ☐ 48 ☐ 60 ☐ 72 ☐ 84 ☐ ___ **Scan**

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	☐ Yes ☐ No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ >5	
Check Region(s) of NEW Disease Post-Screening: ☐ Skull ☐ Thorax ☐ Spine ☐ Pelvis ☐ Extremities	**Draw site(s) of NEW lesion(s) on skeleton:** 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?	☐ Yes ☐ No [Not PD]
Does this bone scan confirm (2+2) the presence of 2 or more new lesions seen since the Week 8 Bone Scan?	☐ Yes [PD] ☐ No [Not PD]
Clinical Impression: ☐ Improved ☐ Stable ☐ Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Week ☐ 24 ☐ 36 ☐ 48 ☐ 60 ☐ 72 ☐ 84 ☐ ___ **Scan**

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	☐ Yes ☐ No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ >5	
Check Region(s) of NEW Disease Post-Screening: ☐ Skull ☐ Thorax ☐ Spine ☐ Pelvis ☐ Extremities	**Draw site(s) of NEW lesion(s) on skeleton:** 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?	☐ Yes ☐ No [Not PD]
Does this bone scan confirm (2+2) the presence of 2 or more new lesions seen since the Week 8 Bone Scan?	☐ Yes [PD] ☐ No [Not PD]
Clinical Impression: ☐ Improved ☐ Stable ☐ Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

ENDOCYTE

Statistical Analysis Plan

Sponsor:	Endocyte, Inc.
Protocol Title:	VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF ^{177}LU-PSMA-617 IN THE TREATMENT OF PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)
Protocol Number:	PSMA-617-01
SAP Version, Date:	Version 1.0, 08 June 2018

The undersigned certify that they have read, reviewed and approved this document:

[redacted] – Author, [redacted]
Electronically signed in MasterControl

[redacted] –
Electronically signed in MasterControl

[redacted]
Electronically signed in MasterControl

[redacted] –
Electronically signed in MasterControl

[redacted] ([redacted]) –
Signature, Date:

[redacted] –
Signature, Date:

ENDOCYTE

Statistical Analysis Plan

Sponsor:	Endocyte, Inc.
Protocol Title:	VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF ^{177}LU-PSMA-617 IN THE TREATMENT OF PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)
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The undersigned certify that they have read, reviewed and approved this document:

[redacted] – Author, [redacted]
Electronically signed in MasterControl

[redacted]
Electronically signed in MasterControl

[redacted]
Electronically signed in MasterControl

[redacted]
Electronically signed in MasterControl

[redacted]
Signature, Date:

[redacted] 8th June 2018

[redacted]
Signature, Date:

[redacted] 08Jun2018

Table of Contents

1. LIST OF ABBREVIATIONS AND DEFINITION of TERMS

Abbreviation	Term/Definition
ANC	Absolute neutrophil count
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
BPI-SF	Brief Pain Inventory – Short Form
BSC	Best supportive care
BSoC	Best standard of care
C1D1	Cycle 1 Day 1
CFR	United States Code of Federal Regulations
CR	Complete response
CRO	Contract Research Organization
CRF	Case Report Form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EQ-5D-5L	European Quality of Life (EuroQol) – 5 Domain 5 Level scale
EudraCT	European Union Drug Regulating Authorities Clinical Trial
FACT-P	Functional Assessment of Cancer Therapy - Prostate
GCSF	Granulocyte colony-stimulating factors
FDA	Food and Drug Administration
FAS	Full Analysis Set
^{68}Ga	Gallium-68
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

Abbreviation	Term/Definition
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
^{177}Lu	Lutetium-177
LTFU	Long term follow up
mCRPC	Metastatic castration-resistant prostate cancer
NAAD	Novel androgen axis drug (such as abiraterone, enzalutamide, or apalutamide)
OAU	Opioid analgesic use
ORR	Overall response rate
OS	Overall survival
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PRO	Patient reported outcome
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
PT	Preferred term
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
SSE	Symptomatic Skeletal Event
SOD	Sum of the diameter
TDRP	Time to disease-related pain
TEAE	Treatment-emergent adverse event
TFOA	Time to first use opioid analgesic
ULN	Upper limit of normal
US	United States
WBC	White blood cell
^{90}Y	Yttrium-90

2. Introduction

This Statistical Analysis Plan (SAP) was written for the clinical trial PSMA-617-01 based on the protocol version 1.0 dated 22 March 2018. The ICH guideline E3 "Structure and Content of Clinical Study Reports" was used as a guide to the writing of the plan.

2.1 Changes from the Protocol

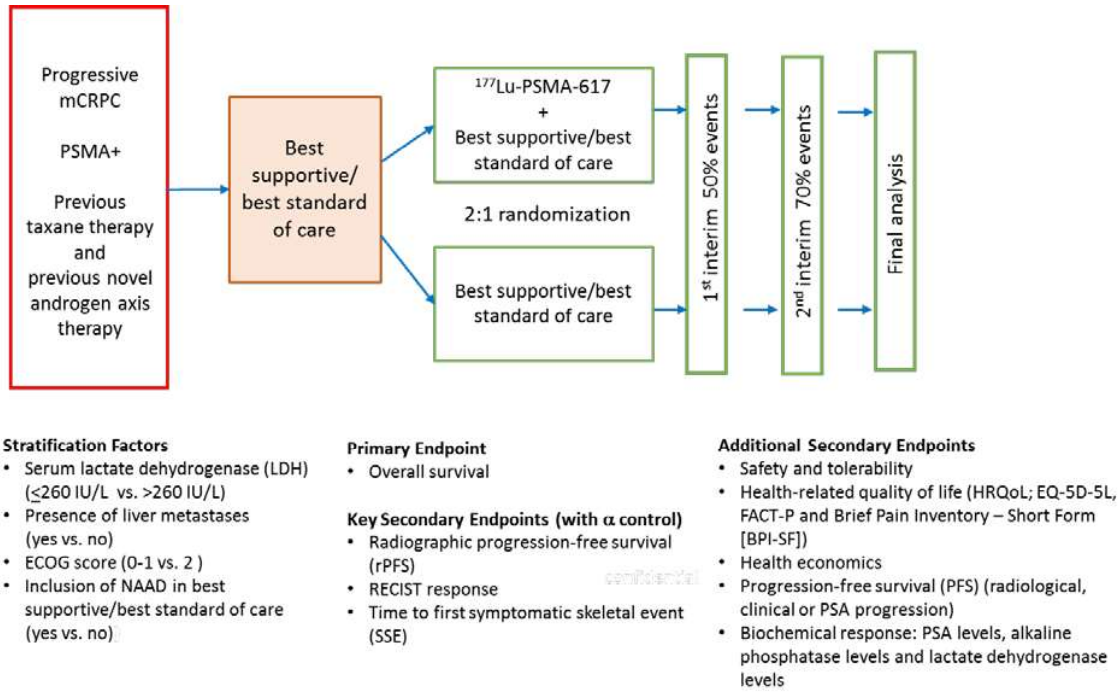
Death is included as an event in analysis of time to first symptomatic skeletal event in this SAP.

3. Study Design and Objectives

3.1 Study Design

This is a Phase 3, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in addition to best supportive/best standard of care as compared to best supportive/best standard of care alone (Figure 1).

Figure 1 Diagram of trial design



ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

Best supportive/best standard of care includes available care for the eligible patient according to best institutional practice and at the discretion of the investigator. Novel androgen axis drugs [NAADs] (i.e., enzalutamide or abiraterone) are allowed.

Investigational agents, cytotoxic chemotherapy, other systemic radio isotopes (e.g. radium-223) or hemi-body radiotherapy treatment may not be administered on study.

At screening, potential subjects will be assessed for eligibility and will undergo a ^{68}Ga-PSMA-11 PET/computed tomography (CT) scan to evaluate PSMA positivity. Only patients with PSMA-positive cancer will be randomized in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 plus best supportive/best standard of care (investigational arm) or to receive best supportive/best standard of care alone (BS/BSC-only arm). Randomization will be stratified by 4 factors (Section 3.2).

Patients randomized to the investigational arm must begin ^{177}Lu-PSMA-617 dosing within 28 days of randomization. These patients will receive best supportive/best standard of care and 7.4 GBq (±10%) ^{177}Lu-PSMA-617 once every 6 weeks (±1 week) for a maximum of 6 cycles.

After the Cycle 4 dose of ^{177}Lu-PSMA-617 and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, Prostate-specific antigen (PSA), clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- Has shown good tolerance to the ^{177}Lu-PSMA-617 treatment.

If the patient meets all of the criteria above, and agrees to continue with additional treatment of ^{177}Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet any of the criteria or does not agree to additional ^{177}Lu-PSMA-617 treatment, then no additional doses of ^{177}Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ^{177}Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

Best supportive/best standard of care for each patient will be selected at the discretion of the patient's physician, prior to randomization and will be administered per the physician's orders and continued until the patient comes off the treatment part of the study and enters the long-term follow-up stage.

A patient may choose to discontinue the treatment part of the study at any time. If a patient withdraws consent for the treatment part of the study, the patient will continue to be followed for long term follow up unless they specifically withdraw for the long term follow up of the study.

An End of Treatment (EOT) visit should occur once a patient is to enter the long-term follow-up part of the study. This visit should occur approximately 30 days from the last dose of ^{177}Lu PSMA-617 or best supportive/best standard of care, but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

After the EOT visit, patients will enter the long-term follow-up period. The long-term follow-up period will include the collection of survival and treatment updates, adverse events assessment, as well as blood for hematology and chemistry testing. During follow-up, patients will be contacted every 3 months (±1 month) via phone, email, or letter for up to 24 months.

This study will enroll approximately 750 patients involving about 80 sites worldwide.

Treatment Discontinuation

Patients may continue treatment until radiographic progressive disease, withdrawal of consent, the occurrence of unacceptable toxicity, or a determination by the investigator

the patient is not clinically benefiting (further details are in the protocol Section 5.5). As per the patient's physician, when the patient requires care that is not allowed on study, the patient will discontinue treatment and enter the long-term follow-up period.

Duration of Trial

Total duration of the trial is event driven, with a total of 489 deaths required as per the prespecified power calculation. A total trial duration of 28 months, consisting of a 13 month recruitment period and a 15 month minimum follow-up period, is expected to deliver the required number of events. Further patient follow-up after the required 489 events may be undertaken to provide additional data on ^{177}Lu-PSMA-617 and long term follow up may last up to 24 months.

3.2 Randomization and Blinding

Patients will be randomized by an interactive response system in a 2:1 ratio to the investigational treatment arm or the best supportive/best standard of care-only arm using a permuted block scheme. Randomization will be stratified by the following factors:

- LDH (≤ 260 IU/L vs. > 260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0 or 1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care (yes vs. no)

The study is open-label. However, access to subject treatment allocation will be limited to those individuals whose roles require access to perform their study responsibilities. Details of what roles and which individuals have access to unblinded data will be documented in a separate Data Access Plan maintained by the sponsor. Dates of access and reason for accesses will be recorded. Regarding data analysis, sponsor statisticians will be blinded. At the contract research organization (CRO) there will be separate blinded and unblinded statisticians. Prior to database lock and data unblinding at the end of the study, programmers will work with blinded data, and then when analyses are needed, the unblinded statistician will unblind the data and run the analyses.

3.3 Study Objectives

Primary objective

The primary objective of this study is to compare overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ^{177}Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone.

Key secondary objectives

Key secondary objectives are an arm-to-arm comparison of the following:

1. Radiographic progression-free survival (rPFS)
2. RECIST response to include:
    a. Overall Response Rate (ORR) as measured by RECIST v1.1 criteria
    b. Disease Control Rate as measured by RECIST v1.1 criteria
3. Time to a first symptomatic skeletal event (SSE)

Additional secondary objectives

1. Safety and tolerability of ^{177}Lu-PSMA-617
2. Periodic assessment of health-related quality of life to evaluate impact of intervention on patient well-being (HRQoL; EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF])
3. Health Economics
4. Progression-free survival (PFS) (radiographic, clinical, or PSA progression-free survival)
5. Biochemical response as measured by PSA. Alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) levels will also be collected.

3.4 Sample Size Justification

The sample size was determined based on the primary endpoint of overall survival. Planned enrollment for this study is approximately 750 subjects.

Under the null hypothesis, median survival is assumed to be 10 months on ^{177}Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median overall survival on active is assumed to be 13.7 months for a HR of 0.7306. This trial has 90% overall power and an overall Type I error rate of 0.025 1-sided.

Based on a non-linear patient accrual profile over 13 months and a follow up of 15 months, a total of 750 patients randomized will yield 489 events. Follow up will be extended for up to 24 months for additional monitoring.

4. Interim Analysis

4.1 Interim Efficacy Analyses

Two interim analyses (IAs) are planned at 50% and 70% events. The purpose of these interim analyses is to allow early stopping for efficacy should sufficient statistical evidence be found to reject the null hypothesis of no survival effect. There will be no assessment for futility.

Interim analysis is based on the primary outcome Overall Survival and will be analyzed as described in Section 8.2.1.

A supportive unadjusted analysis will also be conducted as sparse sample sizes and events may be observed in some strata.

Statistical significance will be determined under the assumptions and criteria below in Table 1 using the stratified Cox proportional hazards regression model results.

Table 1. Overall Survival Interim and Final Analyses

Analysis	Statistic	Efficacy criteria
IA 1 at 50% events (243/489)	1-sided p-value	0.00153
Assumptions:	Expected timing	~16.5 mo after FPR
	Observed HR required to reach $p \leq 0.00153$	0.669
	Corresponding observed increase in Median OS to reach $p \leq 0.00153$*	4.9 months
	P(stop|Ha: True HR=0.7306)	35.4%
IA 2 at 70% events (344/489)	1-sided p-value	0.00690
Assumptions:	Expected timing	~20.5 mo after FPR
	Observed HR required to reach $p \leq 0.00690$	0.754
	Corresponding observed increase in Median OS to reach $p \leq 0.00690$*	3.3 months
	P(stop|Ha: True HR=0.7306)	61.3% cumulative
Final analysis at 489 events	1-sided p-value	0.02266
Assumptions:	Expected timing	~28 months after FPR
	Observed HR required to reach $p \leq 0.02266$	0.825
	Corresponding observed increase in Median OS to reach $p \leq 0.02266$*	2.1 months
	P(stop|Ha: True HR=0.7306)	90% cumulative**

IA=Interim analysis; HR=Hazard ratio (intervention/control); FPR= First patient randomized; Ha=alternate hypothesis; P(stop|Ha)=probability of stopping given Ha.
*Assuming median OS in control group of 10 months
**90% power of concluding statistical significance at either 1st IA, 2nd IA, or final analysis

These interim analyses will be overseen by a fully Independent Data Monitoring Committee (IDMC) who may recommend stopping the study for superior efficacy at the first or second interim if the corresponding pre-specified 1-sided p-value threshold is met. An IDMC Charter will be approved and finalized by the IDMC members prior to the initiation of any interim analysis.

The IDMC can recommend a course of action, but the sponsor will make the final decision to continue or stop the trial based on either interim analysis.

4.2 Interim Safety Analyses

Safety monitoring will be conducted quarterly by the IDMC. These analyses will commence following the completion of the first three months of study accrual. Specifics of the safety analyses to be conducted are outlined in the IDMC charter.

5. General Analysis Definitions

Data will be analyzed using SAS version 9.4 or higher.

No tests of significance will be carried out to compare treatment arms on baseline data because any observed differences between them must be attributed to chance.

Descriptive statistics will be presented in tables as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages.
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, minimum, and maximum values.

Unless otherwise indicated, for frequency tables, patients with missing data will be excluded from the denominator of percentage calculations. All treatment arm comparisons other than the one-sided analysis described for OS will be based on two-sided tests.

Tables will be created by treatment arm or for all patients combined as described at the beginning of sections 7, 8, and 9.

Individual patient listings will include all study-related data. The sort order of the listings will be by treatment, patient ID (center number-patient number), and date of assessment (if available).

Reference date is the date of first dose unless otherwise noted. In the intervention arm, first dose is date of first ^{177}Lu-PSMA-617 administration. In the control arm, first dose is date of first dose for BSC/BSoC and occurs on or after date of randomization and up to Cycle 1 Day 1 (C1D1; see definition below). If a patient's BSC/BSoC does not involve receiving any treatment, date of first dose will be imputed as date of C1D1 visit.

The number of days until a study assessment or procedure is calculated as:

- Study Day= Assessment date – Reference date +1 if assessment date is after or on the reference date
- Study Day= Assessment date – Reference date if assessment date is before the reference date

Baseline for a given variable will be defined as the last value for that variable obtained prior to or on the reference date but before the first treatment dose, unless otherwise noted.

Cycle 1 Day 1 (C1D1) is date of first study procedures and assessments and typically occurs on, but can be soon after, the reference date.

Date of randomization is used for the start date of "time to" endpoints for efficacy analyses.

5.1 Study Periods and Visit Window Definitions

5.1.1 Study Periods

The study consists of 3 periods: screening, treatment (with no maximum number of cycles defined), and a follow-up period (end of treatment, long-term follow-up). Results will be presented by time point and not by period. However, the naming of the time points will reflect the period. In the experimental arm, a patient will be treated with ^{177}Lu-PSMA-617 + BSC/BSoC up to a maximum of 6 cycles, and then BSC/BSoC only for the duration of the on-treatment period. Note that for cycles 1-6, cycle duration is 6 weeks, and for cycles 7 and beyond, cycle duration is 8 weeks.

5.1.2 Visit Windows

For data collected at multiple time points, the scheduled collection date/time will be used to summarize the data. Visits are scheduled from time of previous cycle's Day 1 Cycle 1. A listing of the visit dates will be created with a flag indicating visits outside the pre-specified time window.

Scan assessments are scheduled from the reference date (date of first dose). Scan dates are not associated with a visit number. Dates are used for analyses and patient listings.

Unscheduled assessments will not be taken into account in summary variable calculations, except for unscheduled RECIST and bone scan evaluations. All measurements will be presented in the listings, flagging the results not used for the summary tables.

Unless otherwise indicated, if more than one measurement (a lab result for example) exists for a patient on a particular time point/visit, the last value obtained at that time point/visit will be used when summarizing the data.

Refer to Appendix A for schedules of study assessments during each study period.

5.2 Partial/Missing Dates

In general, the database requires a valid date, including dates used for the primary endpoint. However, for missing day and month for time since cancer diagnosis, prior therapies, and concomitant medication start dates, the rules shown below will be applied. (Concomitant medication stop dates and start and end dates for adverse events, (concurrent) radiotherapy, and concurrent surgical/therapeutic procedures are full date required fields.)

The imputed dates will only be used for the assignment to prior and/or concomitant medication or concurrent therapy and will not be used in any other calculation and will not be listed.

For the calculation of the time since initial cancer diagnosis, the following imputation rules will be applied when the date of initial diagnosis is incomplete:

- If the day is missing: first day of the month.
- If the day and month are missing: first day of January.

For the assignment of medication and therapy to prior or concomitant/concurrent, the following rules will be applied in case of incomplete dates:

- If start date is incomplete:
    - if end date is before the date of first study drug administration, the start date will remain missing (i.e. prior);
    - if end date is on or after date of first study drug administration or the medication is ongoing,
        - if the day is missing: the start date will be imputed with the first day of the month;
        - if the day and month are missing: the start date will be imputed with 01 January of the year.

5.3 Definition of Populations

5.3.1 Efficacy Populations

- **Full Analysis Set (FAS)**: All randomized patients. Patients will be included in the treatment arm to which they were randomized regardless of actual treatment received. This is an intent to treat analysis set.

- **Response Evaluable Analysis Set**: The subset of patients in the FAS with evaluable disease by RECIST at baseline. Patients will be included in the treatment arm to which they were randomized. Soft tissue response as measured by RECIST will be assessed in this dataset.

5.3.2 Safety Populations

- **PSMA-11 Safety Analysis Set:** All patients who received a dose of ^{68}Ga-PSMA-11. This includes some screened patients that aren't enrolled.

- **FAS Safety Analysis Set:** The subset of patients in the FAS who received at least one dose of randomized therapy. Patients will be included in the treatment arm corresponding to the actual treatment received.

5.4 Subgroup Definitions

Two sets of subgroup analyses will be performed.

1. Treatment arm subgroups will be defined by patients with and without novel androgen axis drugs (NAADs; i.e., enzalutamide, abiraterone, or apalutamide) as part of assigned BSC/BSoC treatment at start of study as follows:
   - Lu-PSMA-617+BSC (no NAAD): ^{177}Lu-PSMA-617 + Best supportive care
   - Lu-PSMA-617+BSoC (with NAAD): ^{177}Lu-PSMA-617 + Best standard of care
   - BSC (no NAAD): Best supportive care
   - BSoC (with NAAD): Best standard of care

2. Subgroup analyses will also be performed for the following intervention arm subsets of patients:
   - Patients that received 4 cycles of ^{177}Lu-PSMA-617 + BSC/BSoC
   - Patients that received 6 cycles of ^{177}Lu-PSMA-617 + BSC/BSoC

5.4.1 Analyses on subgroups

All subgroup analyses are to be considered exploratory and descriptive; p-values presented with efficacy results will be treated as nominal.

For the subgroup analyses, descriptive statistics at baseline will be presented for the following:

Stratification Information

As described in Section 6.4.

Demographic and Baseline Assessments

- Age (years)
- Race
- Ethnicity

Baseline Disease Characteristics

- Site of disease (lung (yes/no), liver (yes/no), lymph node (yes/no), bone (yes/no) using target and non-target lesions)
- PSA % increase prior to baseline (within a 6 month period, over more than 6 months)
- Baseline PSA doubling time
- Baseline PSA
- Baseline ALP
- Baseline LDH

Prior Cancer Related Therapy

- Docetaxel (yes/no)
- Cabazitaxel (yes/no)
- Abiraterone (yes/no)
- Enzalutamide (yes/no)
- Apalutamide (yes/no)
- Radium 223 (yes/no)
- Palliative radiotherapy (yes/no)

Efficacy analyses will be performed as described in Section 8 on the subset of patients in each of the subgroups, except Quality of Life (QoL) analyses will be abbreviated as described below and Health Economics analyses will be excluded. Both main and supportive and sensitivity analyses will be presented, except supportive analysis of rPFS from date of first dose will be excluded.

Abbreviated QoL analyses will include the following:

- EQ-5D-5L: descriptive analyses in Section 8.2.3.3.1 of the 5 dimensional scales and EQ-VAS
- FACT-P: descriptive analyses in Section 8.2.3.3.2 of the FACT-P Total and PCS (Prostate Cancer Subscale) scores
- BPI-SF: descriptive analyses in Section 8.2.3.3.3 of the Pain Intensity Scale and Pain Interference Scale

Additionally, forest plots will be used to depict efficacy results of subgroups.

Safety analyses will be performed as described in Section 9, except Vital Signs and ECG will be excluded.

Results (tables and figures) of subgroups above will be presented separately from study arm results.

Separate listings will not be created for subgroups. However, patient listings for the study analyses will be sorted by subgroups within the treatment arms and indicated in page headers.

5.5 Treatment Arms

The following treatment arm labels will be used in the analysis:

- Lu-PSMA-617+BSC/BSoC: ^{177}Lu-PSMA-617 + Best supportive/best standard of care (intervention arm)
- BSC/BSoC only: Best supportive/best standard of care only (control arm)

5.6 General Variable Definitions

- Age (years): year of informed consent - year of birth; calculated within clinical database.
- Time since initial cancer diagnosis (years): (Date of informed consent - Date of initial cancer diagnosis)/(365.25). For incomplete dates, see Section 5.2.
- Weight (kg) = weight (lb) * 0.45359237
- Height (cm) = height (in) * 2.54
- Last taxane therapy treatment-free interval (months): reference date - last taxane therapy end date)/(30.4375). For incomplete dates, the see Section 5.2.
- Baseline PSA doubling time (months): PSA is collected at screening visit and for the most recent 2 PSA measurements available prior to screening. PSA doubling time will be calculated using a linear regression model of the normal logarithm of PSA and time. Calculations will be performed only for subjects with (1) all 3 PSA values with each value ≥ 0.2 ng/dL and (2) for which the interval between the first and last PSA values are ≥8 weeks but ≤ 12 months (Prostate Cancer Clinical Trials Working Group 3 (PCWG3) as stated in Scher et al., 2016).

  For interpretation of PSA doubling time it should be noted that PCWG3 guidelines state the calculation should be based on the most recent PSA values during androgen deprivation therapy, and that 3 PSA values ≥ 0.2 ng/dL should be consecutive. These additional criteria will not be applied since the information is not available.

- Lu-PSMA-617 Exposure Variables:

  Average duration of treatment cycles (months) = mean across cycles of (date of dosing for cycle n – date of dosing for cycle n-1)/30.4375, where n=2 to total number of cycles.

  Duration of exposure (months) = (Date of last study drug administration – Reference date + 1)/30.4375

  Dose intensity per month

  Dose intensity for each month/overall (GBq/month) = (actual total dose during the cycle/study) / (actual duration of the cycle/study (months))

Planned dose intensity for each month/overall (GBq/month) = (planned total dose during the cycle/study) / (planned duration of the cycle/study (months))

Relative dose intensity per month/overall (%) = (dose intensity by month/overall) / (planned dose intensity by month/overall)

Dose intensity per cycle

Dose intensity for each cycle/overall (GBq/cycle) = (actual total dose during the cycle/study) / (1 or actual # of cycles)

Planned dose intensity for each cycle/overall (GBq/cycle) = (planned total dose during the cycle) / (1 or planned # of cycles)

Relative dose intensity per cycle/overall (%) = (dose intensity by cycle/overall) / (planned dose intensity by cycle/overall)

6. Study Patients

6.1 Patient Disposition

Sample size flow will be displayed in a consort diagram with content shown in Appendix B, and the following patient data will be summarized in tables.

Patient disposition for all patients:

- Number of patients who signed informed consent
- Number of patients screened
- Number of patients administered ^{68}Ga-PSMA-11 (PSMA-11 Safety Analysis Set)

  By treatment arm and combined:
- Number of randomized patients – Full Analysis Set
  - Number (%) of patients in Response Evaluable Analysis Set
- Number of randomized patients administered study treatment (FAS Safety Analysis Set)

End of treatment status for all randomized patients, by treatment arm and combined:

- Number (%) of patients discontinued from all study treatments
- Number (%) for each primary reason for discontinuation

6.2 Protocol Deviations

For the FAS, major protocol deviations will be summarized for each treatment arm and overall. The details will be listed by treatment and patient ID. All Protocol deviations (major and minor) will be recorded as part of the Trial Master File (TMF).

6.3 Inclusion and Exclusion Criteria

For all screened patients, a listing of all inclusion criteria not met and exclusion criteria met will be provided, including the protocol version the patient was consented under and a flag for the FAS population.

6.4 Stratification Information

For the FAS, the number of patients will be presented by treatment arm and overall of each stratification arm: LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in best supportive/standard of care (yes vs no).

7. Baseline Characteristics and Prior and Concurrent Therapies and Medications

All tables in Section 7 will be presented by treatment and for all patients combined for the FAS, the Response Evaluable Analysis Set, and the FAS Safety Analysis Set (defined in Section 5.3).

7.1 Demographic and baseline assessments

Descriptive statistics of patient characteristics at baseline will be presented for the following variables:

- Age (years)
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- ECOG performance status (0, 1, 2)

7.2 Baseline Disease Characteristics

Descriptive statistics of patient disease characteristics at baseline will be presented for the following variables:

- Time since initial cancer diagnosis (years)
- Initial Histopathological Classification
- Initial Histopathological Grade
- Initial Gleason score
  - Categorical: 2-3,4-7,8-10, unknown
  - Continuous
- Stage at Initial Diagnosis
- RECIST Sum of Diameters
- Site of disease (lung (yes/no), liver (yes/no), lymph node (yes/no), bone (yes/no) using target and non-target lesions; sponsor to provide categorization)
- Baseline PSA doubling time
- Baseline PSA
- Baseline ALP
- Baseline LDH

7.3 Medical History

Relevant medical condition, other than the study disease, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 21.0 or later (may use newer version if available at end of study)).

The relevant medical conditions will be tabulated separately for active (ongoing) and not-active conditions by system organ class and preferred term. Medical history events will be marked as ongoing if still active at time of PSMA-11 dosing.

7.4 Prior Cancer Related Therapy

Descriptive statistics with respect to prior therapy will be displayed. A listing of all data recorded on the Prior Cancer Related Surgery, Prior Radiotherapy and Prior Cancer Systemic Therapy CRF pages will also be provided.

The variables to be summarized in tables are:

- Prostate Cancer-related Surgery
  - Number of patients with at least one prostate cancer-related Surgery (including biopsies)
  - Prior number of prostate cancer-related surgeries/biopsies
- Prostate Cancer-related Radiotherapy
  - Number of patients with at least one Prostate Cancer-related Radiotherapy
  - Prior number of radiotherapies
  - Site
- Prostate Cancer-related Systemic Therapy: All Therapies
  - Prior number of regimens
  - Prior number of taxane-containing regimens
  - Reason for therapy
  - Number of unique agents
  - Type of prior therapy (by WHO Drug preferred name)
- Prostate Cancer-related Systemic Therapy: Last Taxane Therapy
  - Reason for Therapy
  - Number of cycles
  - Duration of therapy (months)
  - Progression
    - PSA progression (yes, no, not applicable, unknown)
    - Bone progression (yes, no, not applicable, unknown)
    - Soft tissue progression (yes, no, not applicable, unknown)
    - Type(s) of progression (New lesions, existing lesions, new and existing lesions, not applicable, unknown)
  - Treatment-free interval (months, defined in Section 5.6)
  - Best overall response (BOR) to last taxane-therapy (Complete response (CR), Partial response (PR), Stable disease (SD), Progressive Disease (PD), Not Available, Unknown)
  - Duration of historic BOR of Response (CR or PR)
  - Reason last taxane therapy ended
- Prostate Cancer-related Systemic Therapy: Last Therapy
  - Reason for Therapy
  - Type of prior therapy (by WHO Drug preferred name)
  - Number of cycles
  - Duration of therapy (months)
  - Progression
    - PSA progression (yes, no, not applicable, unknown)
    - Bone progression (yes, no, not applicable, unknown)
    - Soft tissue progression (yes, no, not applicable, unknown)
    - Type(s) of progression (New lesions, existing lesions, new and existing lesions, not applicable, unknown)
  - Best Response (CR, PR, SD, PD, Not Available, Unknown)
  - Duration of historic BOR of Response (CR or PR)
  - Reason therapy ended

8. Efficacy Evaluation

8.1 Efficacy Variable Definitions

In general, Time to event and duration, in number of days is, is calculated as:
Days = Date 2 – Date 1 +1. If a patient has no assessment after first dose, censoring is at date of randomization.

8.1.1 Primary Efficacy Definition

Overall Survival (OS) (months): (Date of death/censor - Date of randomization + 1)/30.4375. The censoring date is date of the last study visit, last contact, or date patient was last known to be alive, whichever is latest.

8.1.2 Key Secondary Efficacy Definitions

- Radiographic progression-free survival (rPFS) (PCWG3, Scher et al. 2016; protocol Appendix 7, RECIST 1.1; FDA guidance, 2007; EMA guideline, 2012)
    - Radiographic progression-free survival (rPFS) (months): (Date of radiographic PD/death/censor – date of randomization + 1) / 30.4375. PD and censoring definitions for main analysis of rPFS follow.
        - Note:
            - No study scans are scheduled during the long-term follow-up period.
            - In the investigational treatment arm, a patient continues to be in the treatment period of the study on BSC/BSoC after receiving their final dose of ^{177}Lu-PSMA-617.
            - Patients are at risk of the different types of rPFS events for different lengths of time:
              - RECIST (Soft tissue) PD can occur up through EOT visit.
              - Bone PD can occur up to scan prior to EOT (confirmation must occur by EOT)
              - Death can occur up through 24 weeks past the last study scan, or if no post treatment scans, up to 24 weeks after the first randomized treatment dose (based on the 2 missed visits censoring rule)
    - Date of radiographic progressive disease (radiographic PD) event: date of the first of CT/MRI/bone scan PD/death occurs with no more than 1 immediately prior missing assessment.
        - RECIST PD
            - Assessment in which Overall RECIST Response is PD
            - Date of PD is date of first appearance of the new lesion(s), if applicable.
        - Bone scan PD must be confirmed as follows (treats first post treatment scan as a baseline):
            - If there are at least two new lesions on the first post-treatment scan, they must be confirmed with at least two additional lesions on the next scan (2+2 rule)
            - For scans after the first post-treatment scan, there must be at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan
            - Date of PD is date of first appearance of the two new lesions.

- Date of Censoring for rPFS:
    - The censoring date is the date when the last radiographic assessment (CT/MRI/bone scan) up through the EOT visit determined a lack of progression.
    - If there were no evaluable assessments while on treatment (up through EOT visit) whether scans were evaluable or not, censoring occurs at the date of randomization.
    - Patients who have 2 or more consecutive missed tumor assessments immediately prior to progressive disease (PD) or death will be censored at the date of the last tumor assessment prior to those missing tumor assessments. Study scans are every 8 weeks +/- 4 days for the first 24 weeks, then every 12 weeks +/- 4 days up through EOT, and scans are scheduled relative to date of randomization. Thus, subjects are considered as having 2 missed assessments if:

        • day 117 $\leq$ study day of event scan $\leq$ day 229 and time since last evaluable assessment $\geq$ 118 days

        (2 missed visits, 117 = 16 weeks + 4 days + 1; 229 = 24 weeks + 8 weeks + 4 days + 1)

        • day 230 $\leq$ study day of event scan $\leq$ day 313 and time since last evaluable assessment $\geq$ 146 days

        (2 missed visits, 145 = 20 weeks + 4 days + 1; 313 = 24 weeks 20 weeks + 4 days +1)

        • study day of event scan $\geq$ day 314 and time since last evaluable assessment $\geq$ 174 days

        (2 missed visits, 173 = 24 weeks + 4 days + 1)

- Sensitivity and supportive analyses for rPFS:
    - The first sensitivity analysis is the same as the main rPFS analysis except with additional rPFS events as follows:
        - Includes events regardless of intervening missed assessments.
        - Bone PDs are indicated by one of the following (treating first post treatment scan as baseline):
            - If there are at least two new lesions on the first post-treatment scan, they must be confirmed on the next scan. Date of PD is date of first post-treatment scan (no longer 2+2).
            - For scans after the first post-treatment scan, there must be at least two new lesions relative to the first post-treatment scan (no longer confirmed).
        - Includes radiographic PD and deaths captured during long term follow up (LTFU).
    - The second sensitivity analysis is the same as the main analysis except with additional censoring as follows:
        - Deaths occurring after start of a new anti-cancer therapy will be censored at start date of new therapy.

- A supportive analysis of rPFS will be defined from date of first dose, C1D1, and otherwise defined the same as the main analysis for rPFS. No sensitivity analyses and no subgroup analyses will be performed using C1D1.

- RECIST responses for patients with measurable disease at baseline (RECIST guidelines v1.1, Eisenhauer et al., 2009)
  - Overall Response = Best Overall Response of Complete Response (CR) or Partial Response (PR).

    Patients with no RECIST evaluations after baseline will be considered non-responders.

    Soft tissue CR or PR needs to be confirmed with a second scan at least 4 weeks later or at the next scheduled scan. If soft tissue CR or PR is not confirmed the following rules will be taken into account to define the BOR:

    - No scan after CR or PR or the confirmatory scan is done before 4 weeks: BOR will be SD
    - Confirmatory result is PR after CR: BOR will be PR
    - Confirmatory result is SD or PD: BOR will be SD
  - Disease Control (DC) = BOR of Complete Response (CR) or Partial Response (PR) or Stable disease (SD).
    - Same rules for no post baseline evaluations and for confirmation of CR and PR
    - Also, best response of SD must be at least 6 weeks after randomization. Scans prior contribute to BOR only if they are CR, PR, or PD.
  - Duration of response (DOR) (months) (only for patients with a tumor response): (Date of RECIST PD/death/censor – Date of Overall Response + 1)/30.4375. Date of Overall Response is the date of the first RECIST response of CR or PR of the confirmed response endpoint Overall Response. Censoring rules are the same as for rPFS, except using only soft tissue scan dates (excluding bone scan dates).
  - Sensitivity Analysis for RECIST ORR and DC Rate
    - The sensitivity analysis is the same as the main analysis described above except using the FAS analysis population (defined in Section 5.4.1). Patients with no evaluable disease by RECIST at baseline will be included in the denominator.
    - Only ORR and DC rate will be presented (duration of response would not be affected).

- Time to first symptomatic skeletal event (SSE, months): (Date of SSE/censor – Date of randomization + 1)/30.4375. SSE date is date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopaedic surgical intervention, requirement for radiation therapy to relieve bone pain, or death, whichever occurs first. SSE data for this endpoint is collected up through EOT visit.

  Censoring date is date of the last study visit (on or before EOT).

8.1.3 Additional Secondary Efficacy Definitions

Progression-free survival (PFS) (months): (Date of first radiographic progression/clinical progression/PSA progression/death/censor – Date of randomization + 1)/30.4375.

- Date of radiographic progression: defined in Section 8.1.2.
- Date of clinical progression: earliest date of assessment for when the investigator indicates clinical progression has occurred.
- Date of PSA progression: date that a ≥ 25% increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance; thus for PFS calculations, ignore PSA rises within the first 12 weeks; if PSA progression as an endpoint by itself is needed, "other disease progression" includes radiographic and clinical progression). Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.
- Date of censoring for PFS: Censoring date is the same as defined for rPFS.

PSA doubling time (months): PSA doubling time is time (months) from randomization to PSA doubling. Doubling time will be calculated using a linear regression model of the normal logarithm of PSA and time. The calculation will be based on (1) latest pre-randomization study PSA measurement ≥ 0.2 ng/dL, (2) at least three consecutive PSA values with each value ≥ 0.2 ng/dL, and (3) interval between first and last PSA values of ≥8 weeks but ≤ 12 months (PCWG3 as stated in Scher et al., 2016).

If all pre-treatment PSA values are missing or < 0.2 ng/dL, PSA doubling time will be missing. If PSA values up to time of randomization are all missing or <0.2 ng/dL, the earliest PSA measurement post-randomization prior to first study dose (such as on D1C1) that is ≥ 0.2 ng/dL will be used if available.

For interpretation of PSA doubling time it should be noted that PCWG3 guidelines state the calculation should be based on the most recent PSA values during androgen deprivation therapy. These additional criteria will not be applied.

PSA response: ≥50% decrease from baseline that is confirmed by a second PSA measurement ≥4 weeks later.

PSA ≥ 80% decrease: ≥80% decrease from baseline that is confirmed by a second PSA measurement ≥4 weeks later.

Duration of PSA response (only for patients with response) (months): (date of PSA progression/censor – Date of PSA response + 1)/30.4375. The censoring date is the date of last PSA assessment.

8.2 Efficacy Analyses

For both primary and secondary efficacy endpoints, efficacy analyses will be performed on the FAS efficacy population, defined in Section 5.3, except for soft tissue response as measured by RECIST, for which main analysis will be performed on the Response Evaluable efficacy population and a supportive analysis will be performed on the FAS efficacy population.

A supportive unadjusted analysis will also be conducted for all efficacy analyses as sparse sample sizes and events may be observed in some strata. In survival analyses and logistic regression analyses, this consists of performing an unstratified analysis. In mixed effects models, this consists of removing stratification variable fixed effects from the model.

All data summaries will be presented by treatment arm.

8.2.1 Primary Efficacy Analysis

The primary efficacy endpoint is overall survival (defined in Section 8.1.1). Median follow-up will be reported by treatment arm as follows:

- Median follow-up with 95% CI, censoring for deaths, and range

OS data will be displayed using Kaplan-Meier estimates by treatment arm as follows:

- Median follow-up (months) with 95% CI, censoring for deaths, and range
- Kaplan-Meier curves
- Kaplan-Meier median, 25th percentile, and 75th percentile with 95% CIs
- Survival rates at 6 months, 12 months, and 18 months with 95% CIs

To analyze OS, a stratified Cox proportional hazards regression model will be used. The model will include a single covariate for randomized treatment and will be stratified for the randomization stratification factors: LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in best supportive/standard of care (yes vs no). To control type one error with interim and final analyses, level of significance is described in Section 4.1. Tables will include:

- Cox regression HR (active: control) with 95% CI
- The associated 1-sided p-value

A supportive analysis will be provided via a stratified log-rank test of treatment arm differences in Kaplan-Meier curves, stratifying again for the randomization stratification factors. Include in Tables:

- Log-rank test 1-sided p-value

8.2.2 Key Secondary Efficacy Analyses

Refer to Section 8.2 for analysis sets and presentation of summary statistics. To control the overall Type I error rate, if the primary endpoint is met, then the key secondary endpoints will be assessed using the Hochberg closed test procedure. This procedure is reasonable given the positive correlation between the 3 key secondary endpoints.

Key secondary endpoints subject to Type I error control:

1. rPFS
2. RECIST response: ORR and DOR
3. Time to SSE

Radiographic Progression-free Survival and Time to Symptomatic Skeletal Event

rPFS and time to SSE (defined in Section 8.1.2) will be summarized and analyzed in the same manner as described for the primary endpoint (both main and supportive analyses), except using 2-sided p-values.

For rPFS, sensitivity analyses will be done according to censoring and event definitions in Section 8.1.2. Sensitivity analyses will be performed on both the FAS and Response Evaluable Analysis Set. Both main analysis and supportive analysis models will be presented, a total of 4 models for each analysis set for sensitivity analyses.

Additionally, for rPFS, the following will be reported:

- Number and % of deaths and progression censored due to at least 2 missed visits immediately prior.

Overall Response and Disease Control Rate

Percent change of sum of diameters of target lesions (in mm) from baseline will be summarized as follows:

- Summaries of baseline, maximum % change from baseline with 95% CIs

Overall response and disease control rate (defined in Section 8.1.2) will be analyzed using logistic regression with a single covariate for randomized treatment and stratification for the randomization stratification factors. The following will be reported:

- Odds ratio (active: control) with 95% CI
- The associated 2-sided p-value
- DOR for ORR will be displayed using Kaplan-Meier curves and will be analyzed using mixture distribution methodology described by Ellis et al. 2008 outlined below.

As mentioned in Section 5.3.1, main analysis of RECIST ORR and DC rate outcomes will be on the Response Evaluable Analysis Set and additional analysis will be done on the FAS Efficacy Analysis population, including all randomized patients in the denominator for overall response rate (ORR).

Mixture distribution analysis for duration of response

Duration of ORR will be analyzed using mixture distribution methodology described by Ellis et al. 2008. To avoid an inflated estimate of duration of response that occurs when estimating only in the subset of patients that have a response, the following methods, paraphrasing from Ellis et al., will be used. Treatment arm differences in duration of response will be analyzed using a mixture distribution to test the hypothesis that the expected duration of response (EDoR) is equal for the experimental treatment, E, and the control treatment, C, that is:

$$\text{Ho: } R = \text{EDoR}_E/\text{EDoR}_C = 1 \quad \text{versus} \quad \text{Ha: } R = \text{EDoR}_E/\text{EDoR}_C \neq 1 \qquad (1)$$

The test will be performed as follows.

(i) Estimate the proportions of patients with RECIST response as

$$p_E = r_E/N_E \quad \text{and} \quad p_C = r_C/N_C \qquad (2)$$

Where r_E and r_C are the number of patients responding to treatment arms E and C;

N_E and N_C are the number of all patients in each treatment arm.

(ii) Estimate the mean duration of response in each treatment arm, M_E and M_C, and their standard errors, using a time to event probability distribution, stratified for the randomization stratification factors, censoring subjects that do not have a RECIST response. This can be done using SAS PROC LIFEREG for distributions such as the exponential, the Weibull, the gamma, the Normal, and the log Normal.

(iii) Combine the estimates from step (i) and (ii) to calculate estimates of R and Var[ln(R)]. Then assess the difference between treatment arms E and C using the test statistic:

$$z = \frac{\ln\left(\hat{R}\right)}{\sqrt{\widehat{\mathrm{Var}}\left[\ln\left(\hat{R}\right)\right]}}$$

8.2.3 Additional Secondary Efficacy Analyses

Refer to Section 8.2 for analysis sets and presentation of summary statistics. The Additional Secondary Endpoints will be assessed at the nominal 5% level, i.e., there will be no alpha control applied. These endpoints are PFS, Biochemical Response (PSA response endpoints, LDH and ALP assessments), Health-related QoL, and Health Economics. Analysis will be performed on the FAS efficacy population.

8.2.3.1 Progression-free Survival Analysis

For PFS (defined in Section 8.1.3), descriptive presentation of data and main and supportive analyses will be the same as those described for the primary endpoint, OS (Cox regression and Log-Rank test). No sensitivity analyses will be performed for PFS. Additionally, the following will be presented:

- Number and % of PFS events that are due to death, radiographic progression, clinical progression, and PSA progression

8.2.3.2 Biochemical Response Analysis

PSA, ALP, and LDH values will be summarized descriptively as follows:

- Continuous variable summary statistics for baseline, each time, and % change from baseline for each treatment arm
- Plots of the mean (±standard deviation) values over time for PSA, ALP, and LDH.
- Summary statistics of PSA doubling time with 95% CI
- Summary statistics of maximum % decrease from baseline
- Categorical variable summary statistics and 95% CIs of PSA response (≥50% decrease) and PSA $\geq$ 80% decrease
- Duration of PSA response (≥50% decrease) will be presented descriptively the same as OS (Section 8.2.1).

Unscheduled labs will not be included in tables but will be provided in listings.

Treatment arm differences of % change from baseline in PSA, ALP, and LDH across all time points will be analyzed using mixed effects general linear models for repeated measures, under the assumption of Missing at Random (MAR). The fixed effects will include treatment arm, time (as a categorical variable), treatment by time interaction, and randomization stratification factors. An unstructured variance-covariance matrix for the repeated measures for a single patient will be used. In case of problems with fitting the model, as an alternative, a heterogeneous Toeplitz and AR(1) structures will be considered to reduce the number of parameters of the model. If necessary for the model fit, the outcome variables might be transformed. Details of any transformations used will be provided in the CSR.

For PSA response, analyses will be the same as those described for binary outcome ORR (Section 8.2.2).

Duration of PSA response will be analyzed using a mixture distribution analysis, as described for duration of ORR (Section 8.2.2).

8.2.3.3 Quality of Life (QoL) Analysis

For QoL analyses, patient reported outcomes (PROs) will be assessed using the questionnaires EQ-5D-5L, FACT-P, and BPI-SF.

Analyses will be done on the FAS, and all results will be reported by treatment arm. QoL measures are collected on Day 1 of each treatment cycle and at the EOT visit. Analyses over time will include time up through EOT visit.

For analysis of each outcome, only patients with a baseline value and at least one post baseline time point will be included. As with all efficacy analyses, main models will be adjusted for randomization stratification factors and supportive analyses will be done without stratification factors. Type I error is not controlled in the multiple health related QoL analyses. Thus, all p-values presented will be unadjusted and are nominal and descriptive.

8.2.3.3.1 EQ-5 Dimension-5 Level (EQ-5D-5L) Questionnaire

The EQ-5D-5L is shown in protocol Appendix 9. The higher the EQ-VAS score, the better the QoL. The higher the EQ-5D items, the worse the QoL.

Description and Scoring

The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-VAS records the respondent's self-rated health on a vertical, visual analogue scale.

Each of the five dimension-scales contain five levels, with level 1 indicating no problems, level 2 indicating slight problems, level 3 indicating moderate problems, level 4 indicating severe problems, and level 5 indicating unable to/extreme problems.

The EQ-VAS is scored by assigning an integer value, ranging from 0 (Worst imaginable health state) to 100 (Best imaginable health state), corresponding to the mark placed by the patient on the VAS. Ambiguous answers (e.g., two marks placed on the scale by a patient) should be treated as missing values.

Scale name	Number of items	Item range*
Descriptive System Dimension		
Mobility	1	1-5
Self-Care	1	1-5
Usual Activities	1	1-5
Pain/Discomfort	1	1-5
Anxiety/Depression	1	1-5
Health State Evaluation		
EQ-VAS*	1	0-100

* EQ-VAS is a continuous visual analog scale, with integer scores ranging from 0 to 100.

A utility score will be obtained by using a weighted combination of the levels of the five dimension-scales. The weights are based on value sets which are country-specific. The country specific code for the U.K. will be used for all sites in this study since the health economics modeling will target the U.K. population. Each patient's 5 digit health states code (response to question 1,2,3,4, and 5 concatenated (ex., 41325 results in a utility score of 0.193)) is converted to a utility score using the EQ-5D-5L value set, available in the cross-walk index value calculator which can be downloaded from the web site https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation/crosswalk-index-value-calculator/ . (Scroll to the bottom of the web page and download the Excel file. Use the sheet labelled 'EQ-5D-5L Value Sets.')

Since utility score depends on the combination of all items' responses, any missing response results in a missing utility score. If a patient dies, for analysis he will be assigned a score of 0 on the date of death. In the U.K. value set, utility scores ranges from the lowest possible score for a living patient of -0.594 (when all responses are '5') to 1 (when all responses are '1').

Analysis

Descriptive analyses:
For each of the five dimension-scales, frequency count and percentage of each reporting level (1 to 5) over time will be presented.

For utility score and EQ-VAS, continuous variable summaries will be presented for each time point. For EQ-VAS, a plot of the mean values with standard deviations by treatment group at each time point (showing number of subjects at each visit), will be constructed.

Dichotomous endpoints:
Proportion of patients with 95% CI who experience any improvement relative to baseline in utility score (an increase of .001 or more) at any time up through EOT will be summarized for each treatment.

Similarly, the proportion of patients with worsening relative to baseline, indicated by no change or any decrease in score, will be summarized.

Survival analysis:
Time to worsening for utility score is defined as time from randomization to the first occurrence of worsening in score relative to baseline (no change or any decrease), clinical disease progression, or death. If no event is experienced, the censoring date will be time of the last QoL assessment.

Survival curves for the time to worsening (months) for each treatment arm will be computed by using the Kaplan-Meier method. The two treatment arms will be compared by using a log-rank test stratified for study stratification factors (LDH $\leq$ 260 UI/L vs $>$, liver metastases (yes vs no), ECOG (0-1 vs 2), Inclusion of NAAD in BSC/BSoC (yes vs no)). 25^{th} percentile of and median time to worsening will be presented, in case less than 50% of subjects experienced worsening for some variables. Cox's proportional hazard models will be used to estimate hazard ratios (intervention/control) stratifying for study stratification factors, including two-sided 95% CIs and p-values.

Repeated measures analysis:
Change from baseline in utility score will also be analyzed using general linear models for repeated measures. Baseline value (as a continuous variable), treatment arm, time (as visit number), treatment by time interaction, baseline by time interactions, and randomization stratification factors as main effects will be the fixed factors. A general (unstructured) variance-covariance matrix for the repeated measures for a single patient will be used. In case of problems with fitting the model, as an alternative, a heterogeneous Toeplitz and AR(1) structures will be considered to reduce the number of the parameters of the model.

Forest plots for overall treatment difference (average effect across visits) in mean utility change scores (Lu-PSMA-617+BSC/BSoC - BSC/BSoC), calculated from contrasts of the repeated measures models, will be provided plotted for all patients combined and by stratification factors.

8.2.3.3.2 FACT-P

The Functional Assessment of Cancer Therapy – Prostate (FACT-P) is shown in protocol Appendix 10. The higher the FACT-P score (for all subscales and total scales), the better the QoL.

Description

Scale/Sub-scale Name	Number of Items	Scale Range	FACT-P Item numbers	Threshold for worsening*
Subscale				
Physical Well-Being (PWB)	7 items	0-28	GP1-GP7	3
Social/Family Well-Being (SFWB)	7 items	0-28	GS1-GS7	3
Emotional Well-Being (EWB)	6 items	0-24	GE1-GE6	3
Functional Well-Being (FWB)	7 items	0-28	GF1-GF7	3
Prostate Cancer Subscale (PCS)	12 items	0-48	All items in "Additional	3

			Concerns" section	
PCS pain-related subscale (PRS)	4 items	0-16	P1, P2, P3, GP4	2
FACT Advanced Prostate Symptom Index-8 (FAPSI-8)**	8 items	0-32	GP1, GP4, GE6, C2, P2, P3, P7, P8	3
Total Scale				
Trial Outcomes Index (TOI) score	3 subscales	0-104	PWB, FWB, PCS	9
FACT-G (General)	4 subscales	0-108	PWB, SFWB, EWB, FWB	9
FACT-P Total	39 items	0-156	All	10

*Minimally important difference for both 1) decrease from baseline for within subject change and 2) between group differences for treatment comparisons.

** Symptom index of important clinician-rated symptoms/concerns to monitor when assessing value of treatment for advanced prostate cancer (FAPSI-8; Yount et al. 2003)

Scoring

Scoring of FACT-P subscales and total scores (Trial Outcome Index (TOI), FACT-G Total Score (G for general), and FACT-P Total Score (P for prostate)) are shown below. These are from the FACT-P Scoring Guidelines (Version 4). Item codes in scoring guidelines are shown on the FACT-P form in Appendix 10 of the protocol.

FACT-P Instructions:

1) Record answers in "item response" column. If missing, mark with an X
2) Perform reversals as indicated, and sum individual items to obtain a score.
3) Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4) Add subscale scores to derive total scores (TOI, FACT-G, FACT-P).
5) Handling missing items. The FACT scale is considered to be an acceptable indicator of patient quality of life as long as **overall item response rate** is greater than 80% (e.g., at least 32 of 39 FACT-P items completed). In addition, a total score should only be calculated if ALL of the component subscales have valid scores. For subscales, as long as **more than** 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc), prorate the subscale score by following the scoring instructions below, producing an observed sum weighted by the inverse of the proportion of observed items.

Subscale	Item Code	Reverse item?		Item response		Item Score
Physical Well-Being (PWB)	GP1	4	-		=	
	GP2	4	-		=	
	GP3	4	-		=	
Score range: 0-28	GP4	4	-		=	
	GP5	4	-		=	
	GP6	4	-		=	
	GP7	4	-		=	
				Sum individual item scores:		
				Multiply by 7:		
				Divide by number of items answered:		= PWB subscale score

Social/Family Well-Being (SFWB)	GS1	0	+	=	
	GS2	0	+	=	
	GS3	0	+	=	
	GS4	0	+	=	
Score range: 0-28	GS5	0	+	=	
	GS6	0	+	=	
	GS7	0	+	=	
		Sum individual item scores:			
		Multiply by 7:			
		Divide by number of items answered:			= SFWB subscale score
Emotional Well-Being (EWB)	GE1	4	-	=	
	GE2	0	+	=	
	GE3	4	-	=	
Score range: 0-24	GE4	4	-	=	
	GE5	4	-	=	
	GE6	4	-	=	
		Sum individual item scores:			
		Multiply by 6:			
		Divide by number of items answered:			= EWB subscale score
Functional Well-Being (FWB)	GF1	0	+	=	
	GF2	0	+	=	
	GF3	0	+	=	
Score range: 0-28	GF4	0	+	=	
	GF5	0	+	=	
	GF6	0	+	=	
	GF7	0	+	=	
		Sum individual item scores:			
		Multiply by 7:			
		Divide by number of items answered:			= FWB subscale score

Subscale	Item Code	Reverse item?		Item response	Item Score
Prostate Cancer Subscale (PCS)	C2	4	-	=	
	C6	0	+	=	
	P1	4	-	=	
Score range: 0-48	P2	4	-	=	
	P3	4	-	=	
	P4	0	+	=	
	P5	0	+	=	
	P6	4	-	=	
	P7	4	-	=	
	BL2	4	-	=	
	P8	4	-	=	
	BL5	0	+		
		Sum individual item scores:			
		Multiply by 12:			
		Divide by number of items answered:			= PC Subscale score

To derive a FACT-P Trial Outcome Index (TOI):
Score range: 0-104

_____ + _____ + _____ = _____ = FACT-P TOI
(PWB score) *(FWB score)* *(PCS score)*

To derive a FACT-G Total score:
Score range: 0-108

_____	+	_____	+	_____	=	_____ = FACT-G Total score
(PWB score)		*(SFWB score)*		*(EWB score)*		*(FWB score)*

To derive a FACT-P Total score:
Score range: 0-156

_____	+	_____	+	_____	+	_____	+	_____	= __ = FACT-P Total score
(PWB score)		*(SFWB score)*		*(EWB score)*		(FWB *score*)		(PCS *score*)	

To derive Pain-related subscale (PRS):

Subscale	Item Code	Reverse item?		Item response		Item Score
Pain-related subscale	P1	4	-		=	
	P2	4	-		=	
	P3	4	-		=	
Score range: 0-16	GP4	4	-		=	
				Sum individual item scores:		
				Multiply by 4:		
				Divide by number of items answered:		= PR Subscale score

To derive FACT Advanced Prostate Symptom Index-8 (FAPSI-8):

Using the 8 items GP1, GP4, GE6, C2, P2, P3, P7, P8, do the following:
Reverse code individual items as needed following guidelines in scores above.

Sum individual item scores.

Multiply by 8.

Divide by the number of items answered.

Analysis

Descriptive analysis:
For each FACT-P related total scale and subscale in the table in the Description section above, continuous variable summaries will be presented for each time point.

Subscale analysis criteria:
For dichotomous endpoints, survival analysis, and repeated measures analysis, when treatment differences result in a $p < 0.05$ for FACT-P total score, subscales defined above (PWB, SFWB, EWB, FWB, PCS) will be analyzed to determine which are associated with the differences.

Dichotomous endpoints:
Whether patients experience improvement relative to baseline in FACT-P total score indicated by a $\geq$10 point increase at any time up through EOT will be summarized as

described in Section 8.2.3.3.1 for EQ-5D-5L utility score, and subsequently for the subscales when the .05 criteria described above is met.

Whether patients experience worsening relative to baseline in FACT-P total score indicated by a $\geq$10 point decrease will be summarized similarly.

Survival analysis:
Time to worsening for FACT-P total score is defined as time from randomization to the first occurring of a $\geq$10 point decrease in FACT-P compared to baseline, clinical disease progression, or death. If no event is experienced, the censoring date will be time of the last QoL assessment.

Survival analyses will be conducted as described in Section 8.2.3.3.1 for EQ-5D-5L utility score, and subsequently for the subscales when the .05 criteria described above is met.

Repeated measures analysis:
Change from baseline in FACT-P total score will also be analyzed using general linear models for repeated measures and forest plots produced as described in Section 8.2.3.3.1 for EQ-5D-5L utility score, and subsequently for the subscales (PWB, SFWB, EWB, FWB, PCS) when the .05 criteria described above is met.

8.2.3.3.3 BPI-SF

The Brief Pain Inventory - Short Form (BPI-SF) is shown in protocol Appendix 8. The higher the BPI-SF score, the worse the pain.

Description and Scoring

The BPI-SF consists of 4 questions regarding pain intensity, 2 questions on the use of analgesics, and 7 questions on how the level pain has interfered with the subject's life. Intensity items consist of an 11-response rating scale scored from 0 ("No Pain") to 10 ("Pain As Bad As You Can Imagine"). Interference items consist of scores from 0 ("Does Not Interfere") to 10 ("Completely Interferes").

Scale Name	Number of Items	Scale Range	BPI-SF Item numbers	Threshold for worsening*
Individual Item Scales				
Worst pain intensity	1	0-11	3	Either of ≥30% of baseline or ≥2-point increase**
Least pain intensity	1	0-11	4	
Average pain intensity	1	0-11	5	
Pain intensity right now	1	0-11	6	
Summary Scales				

Pain Intensity Scale	4	0-11	3-6	≥30% of baseline
Pain Interference Scale	7	0-11	9a-9g	≥30% of baseline

*Minimally important difference for both 1) increase from baseline for within subject change and 2) between group differences for treatment comparisons.

**Analysis of worst pain intensity is included in Section 8.2.3.4 Health Economics Analysis as time to disease related pain (TDRP).

BPI-SF Intensity is the mean of non-missing items of the 4 items in the table above, if there are 3 or more items not missing; otherwise this scale is set to missing.

BPI-SF Interference scale is the mean of non-missing items of the 7 items in the table above, if there are 4 or more items not missing; otherwise this scale is set to missing.

Analysis

Descriptive analysis:
For Pain Intensity Scale and Pain Interference Scale, and the four individual pain intensity items in the table above, continuous variable summaries will be presented for each time point.

Survival analysis:
Time to worsening of Worst Pain Intensity (item 3), Pain Intensity Scale, and Pain Interference Scale are defined as time from randomization to the first occurring of 1) an increase of worsening threshold (in the table above) compared to baseline, 2) clinical disease progression, or 3) death. If no event is experienced, the censoring date will be time of the last BPI-SF assessment.

Survival analyses of time to worsening of Worst Pain Intensity, Pain Intensity Scale, and Pain Interference Scale will be conducted as described in Section 8.2.3.3.1 for EQ-5D-5L utility score.

Repeated measures analysis:
Change from baseline in Worst Pain Intensity, Pain Intensity Scale, and Pain Interference Scale will also be analyzed using general linear models for repeated measures and forest plots produced as described in Section 8.2.3.3.1 for EQ-5D-5L utility score.

8.2.3.4 Heath Economics Analysis

The health economics analysis will be done by a separate vendor and is not a part of this SAP; however, data feeding into the health economics analysis will be summarized and analyzed as noted in this section.

Health resource utilization data will be used for health economics analysis. As with all efficacy analyses, models will be stratified or adjusted for randomization stratification factors and supportive analyses will be done in which models are not adjusted for stratification factors.

Variables below will be summarized as described in Section 5 for categorical and continuous variables on a per treatment cycle basis (6-8 week period) where applicable, or across entire length of trial (up through EOT).

Hospitalizations (yes/no) and clinic visits outside of trial (yes/no) will be analyzed using the probit model (Mihaylova et al., 2011). The explanatory variable will be treatment arm, and the model will be stratified for randomization stratification factors.

For censored resource use data variable hospital length of stay (LOS), the fully non-parametric method from Lin et al. (1997) will be used. The explanatory variable will be treatment arm, and the model will be stratified for randomization stratification factors.

1. Hospital admissions
    - Number of hospitalizations both as a categorical variable and a continuous variable
    - Hospitalizations (yes/no) (admitted as in-patient)
    - LOS per hospitalization episode
    - Number of symptomatic skeletal events (SSEs; includes symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain; captured in 3 CRFs: Adverse Events, Concurrent Surgical/Therapeutic Procedures, and Radiotherapy)
    - Number of hospitalizations for SSEs
2. Concomitant drug category use (frequency of administration, dose; total number of days administered)
    (1) Bisphosphonates (including but not limited to denosumab, zoledronic acid, alendronic acid, etc.)
    (2) Corticosteroids
    (3) Antifungals (i.e. ketoconazole)
    (4) ESA (erythropoietin stimulating agents, i.e. epoetin alfa)
    (5) Granulocyte macrophage colony-stimulating factor (GM-CSF)
    (6) Novel androgen axis drugs (NAADs; i.e. enzalutamide, abiraterone)
    (7) Antiemetics
    (8) Opioid analgesics use for cancer-related pain
        1. Time to disease-related pain (TDRP, defined below)
        2. Time to first use of opioid analgesics (TFOA, defined below)
3. Therapeutic interventions (frequency; total number of days administered)
    - Local external beam radiotherapy, including palliative external radiation
    - Blood transfusion
4. Monitoring activities (number of procedures, percent of all procedures done of all kinds; a chemistry panel, for example, including multiple items counts as one procedure in the total sum)
    - Abdominal computed tomography, total body bone scintigraphy, prostate-specific antigen level, testosterone level, renal function, liver function, blood test, lactate dehydrogenase, alkaline phosphatase

Variable definitions:

Time to disease-related pain (TDRP) – TDRP is defined as days from randomization to the first occurrence of a ≥2-point increase in worst-pain intensity from baseline as indicated on the BPI-SF (question 3), clinical disease progression, or death. If no event is experienced, the censoring date will be time of the last BPI-SF assessment.

Time to first use of opioid analgesic (TFOA) – TFOA is defined as days from randomization to the first occurrence of first need of pain and opioid analgesic use (OAU) as indicated in concurrent medications), clinical disease progression, or death. If no event is experienced, censoring date is the later of date of last visit and last concomitant medication recorded.

9. Safety Evaluation

Safety analyses will be presented for both the PSMA-11 Safety Analysis Set and the FAS Safety Analysis Set, except for study drug exposure (specifics in Section 9.1) and AE interactions with drug exposure (summarized for FAS Safety Analysis Set only).

For both safety analysis sets, tables will show results by treatment arm and for all patients combined. For the PSMA-11 Safety Analysis Set, an additional column will be included for patients not randomized.

Listings will be created by treatment arm.

9.1 Extent of Exposure

^{68}GA-PSMA-11 Exposure

For both the PSMA-11 Safety Analysis Set and the FAS Safety Analysis Set, the variables to be summarized for ^{68}GA-PSMA-11 exposure are:

- ^{68}GA-PSMA-11 activity injected-decay corrected dose (MBq)
- ^{68}GA-PSMA-11 activity injected-decay corrected dose (MBq/kg)

Randomized Treatment Exposure, Summary of Cycles

For the FAS Safety Analysis Set, summary of treatment cycles variables to be included are:

Randomized treatment exposure, for both treatment arms:

- Duration of study treatment (months) (definition in Section 5.6)
- Number of cycles started per patient (both as categorical and continuous variable)
- Average duration of treatment cycles (months) (definition in Section 5.6)
- Number of patients with at least one cycle delayed with the reasons for delay
- Number of cycles delayed with reasons for delay

^{177}Lu-PSMA-617 exposure, for the Lu-PSMA-617 + BSC/BSoC arm:

- Number of patients with at least one dose interrupted (omitted) with the reasons for interruption
- Number of cycles with at least one dose interrupted (omitted) with the reasons for interruption

- Number of patients with at least one dose reduced with the reasons for dose reduction
- Number of cycles with at least one dose reduced with the reasons for dose reduction

Randomized Treatment Exposure, By Cycle and Across Cycles Combined

^{177}Lu-PSMA-167 exposure, for the Lu-PSMA-617 + BSC/BSoC arm

For the FAS Safety Analysis Set intervention arm, ^{177}Lu-PSMA-167 exposure variables to be summarized for the entire study and for each cycle (definitions in Section 5.6) are:

- Cumulative dose (GBq) of patient
- Dose intensity (GBq/cycle)
- Dose intensity (GBq/month)
- Relative cycle dose intensity (%)
- Relative monthly dose intensity (%)

BSC/BSoC exposure, for both treatment arms

For the FAS Safety Analysis Set (both treatment arms), variables to be tabulated for BSC/BSoC for the entire study and for each treatment cycle are:

- Concomitant medications indicated as study BSC/BSoC, coded using WHODrug Global version 2018 Mar 1 dictionary.
- Concurrent procedures other than radiotherapy indicated as study BSC/BSoC, coded using MedDRA V21.0.
- Concurrent radiotherapy indicated as study BSC/BSoC

9.2 Adverse Events and Deaths

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 21.0) preferred term (PT) and system organ class (SOC) and will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE criteria [v5.0]).

9.2.1 Definition of Treatment Emergent Adverse Events (TEAEs)

^{68}GA-PSMA-11

A ^{68}Ga-PSMA-11 TEAE is defined as an AE that was not present prior to dosing with ^{68}Ga-PSMA-11 but appeared following dosing, or was present at time of dosing but worsened during or after dosing.

The treatment-emergent period will be defined as the period from the date of ^{68}Ga-PSMA-11 dosing up to 6 days after the date of ^{68}Ga-PSMA-11 dosing as long as prior to the first dose of ^{177}Lu-PSMA-617 for the investigational arm and prior to Cycle 1 Day 1 for the BSC/BSoC arm.

Randomized treatments

A randomized treatment TEAE is defined as an AE that was not present prior to first dose of randomized treatment (prior to first dose of ^{177}Lu-PSMA-617 for the investigational arm and prior to Cycle 1 Day 1 for the BSC/BSoC arm) but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated).

The treatment-emergent period will be defined as the period from the date of the first dose of randomized treatment up to 30 days after the date of the last dose of treatment or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

9.2.2 General Convention

Any event that is considered study drug-related (at least possible relationship to study treatment, or missing assessment of relatedness), regardless of the start date of the event, or any event that worsens in toxicity grade while on treatment or is subsequently considered study drug-related by the investigator is also defined as a treatment-emergent adverse event.

In case a patient experienced the same event more than once, the maximum toxicity grade will be presented.

In all AE tables except the ones presented by Cycles, multiple occurrences of the same adverse events occurring in one individual are counted only once.

In all AE tables presented by cycle of onset, multiple occurrences of the same adverse events occurring in one individual within one cycle are counted only once.

9.2.3 ^{68}Ga-PSMA-11 Adverse Events

A summary table including the number of patients with at least one event, and the total number of events will be presented for the following variables:

- TEAE[1]
- serious TEAE[1]
- grade 3/4/5 TEAE[2]
- drug-related TEAE[1]
- serious drug-related TEAE[1]
- drug-related grade 3/4/5 TEAE[2]
- fatal TEAE[2]
- Deaths, including the primary cause of death. [2] The details of the 'other cause' will be included in the listing.

[1]AE variables to be tabulated by system organ class (SOC) and preferred term (PT) by grade including a total across all grades and all grades 3/4/5.

[2]AE variables to be tabulated by system organ class (SOC) and preferred term (PT).

A listing will include the participant identifier, age, race, verbatim, preferred term, duration of the event, toxicity grade, seriousness, action taken regarding ^{68}Ga-PSMA-11, outcome, relationship to study drug, and start and end date. Non-treatment-emergent adverse events will be flagged.

There will be a separate listing of all deaths.

9.2.4 Randomized Treatment Adverse Events

A summary table including the number of patients with at least one event, and the total number of events will be presented for the AE variables below.

- TEAE[1]
- Serious TEAE[1]
- Grade 3/4/5 TEAE[2]
- Drug-related TEAE[1]
- Serious drug-related TEAE[1]
- Drug-related grade 3/4/5 TEAE[2]
- TEAE leading to reduction of ^{177}Lu-PSMA-617 dose[1] or of BSC/BSoC
- TEAE leading to interruption of ^{177}Lu-PSMA-617 treatment[1] or of BSC/BSoC
- TEAE leading to permanent discontinuation of ^{177}Lu-PSMA-617 treatment[1] or of BSC/BSoC
- Fatal TEAE[2]
- All deaths, including the primary cause of death.[2] The details of the 'other cause' will be included in the listing.

[1]AE variables to be tabulated by system organ class (SOC) and preferred term (PT) by grade including a total across all grades and all grades 3/4/5.

[2]AE variables to be tabulated by system organ class (SOC) and preferred term (PT).

A summary table will also be presented for each AE variable by cycle of onset and percent of cycles for these AE variables.

A listing for each patient will include the same variables as mentioned above in Section 9.2.3 except will include action taken regarding ^{177}Lu-PSMA-617 and action taken regarding Best supportive/Best standard of care.

There will be a separate listing for all deaths.

9.2.5 Adverse Event Interactions with Drug Exposure

AE interaction with drug exposure will be presented for the FAS Safety Analysis Set only. The relationship between dose intensity, duration of exposure, and frequency and severity of AEs will be explored by data tabulation as follows:

- Dose intensity vs TEAEs by SOC and PT by grade
- Duration of exposure summary vs TEAEs by SOC and PT by grade

9.2.6 Long-term Follow up Adverse Events

During LTFU, new and existing TEAEs in the randomized treatment arms will continue to be followed, capturing only AE term and grade.

A summary table including the number of patients with at least one event, and the total number of events will be presented for the AE variables below.

- TEAE[1]
- Grade 3/4 TEAE[2]

- Fatal TEAE[2]
- All deaths, including the primary cause of death.[2] The details of the 'other cause' will be included in the listing.

[1]AE variables to be tabulated by system organ class (SOC) and preferred term (PT) by grade including a total across all grades and all grades 3/4/5.

[2]AE variables to be tabulated by system organ class (SOC) and preferred term (PT).

A listing will include the participant identifier, age, race, verbatim, preferred term, and toxicity grade.

9.3 Clinical Laboratory Determination

Local labs will perform hematology, chemistry, serum testosterone, and urinalysis testing. The following laboratory parameters are to be summarized:

- Testosterone
- Chemistry
  - sodium
  - potassium
  - total and direct bilirubin
  - ALP
  - AST
  - ALT
  - LDH
  - blood urea nitrogen
  - creatinine
  - uric acid
  - phosphorus
  - chloride
  - bicarbonate
  - calcium
  - glucose
  - total protein
  - albumin
- Urinalysis
  - urine pH
  - protein content
  - specific gravity
  - appearance and color
  - glucose
  - ketones
- Hematology
  - complete blood count (white blood cell count and differential)
  - red blood cell count
  - hemoglobin
  - hematocrit
  - platelet count

Laboratory values and change from baseline will be summarized by visit. Shift tables of the worst on-study laboratory toxicity based on CTCAE v5.0 grading relative to baseline will be presented as well as the frequency of grade 3/4 toxicities. Frequency statistics for qualitative laboratory parameters will also be presented by visit.

The mean (±standard deviation) values over time will be plotted for hemoglobin, hematocrit, platelets, WBC, absolute neutrophil count, AST, ALT, BUN, and creatinine by treatment arm.

Patient listings of laboratory toxicities ≥ Grade 3 will be provided. Values outside of the laboratory's reference range will be flagged. The patient listings will indicate the CTCAE grade.

During long-term follow up, hematology and chemistry are collected every 3 months. These will be displayed in similar tables, listings, and figures separately for LTFU.

9.4 Vital Signs, Physical Findings, and ECG

Vital signs (blood pressure, pulse, and respiratory rate) and weight, will be summarized by visit (observed and change from baseline).

ECOG performance status will be summarized as a categorical variable.

ECG will be done at screening only. Overall ECG interpretation will be summarized. QTc, PR, RR, and QRS Intervals and heart rate will be summarized as continuous variables.

Abnormal findings from physical examinations will be assessed for clinical significance and will be presented in the AE listings and tables.

9.5 Concurrent Surgical and Therapeutic Procedures

Concurrent surgical and therapeutic procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 21.0).

Procedures will be classified as prior and/or concurrent. Prior procedures are all procedures occurring before the date of the first randomized drug administration (prior to first dose of ^{177}Lu-PSMA-617 for the investigational arm and prior to Cycle 1 Day 1 for the BSC/BSoC arm). Concurrent procedures are all procedures continued or started on or after the date of the first randomized study drug administration. Assignment will be done after applying the imputation rules as specified in Section 5.2 for partial start and end dates.

Concurrent surgical and therapeutic procedures will be tabulated separately for active (ongoing) and not-active procedures by system organ class and preferred term.

All procedures will be listed including all details from the concurrent surgical and therapeutic procedures CRF page.

9.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHODrug Global version 2018 Mar 1 dictionary.

The medications will be classified as prior and/or concomitant. Prior medications are all medications taken before the date of the first randomized drug administration (prior to first dose of ^{177}Lu-PSMA-617 for the investigational arm and prior to Cycle 1 Day 1 for the BSC/BSoC arm). Concomitant medications are all medications continued or started on or after the date of the first randomized study drug administration. Assignment will be done after applying the imputation rules as specified in Section 5.2 for partial start and end dates.

The number and percentage of patients will be tabulated by ATC level 4 and Preferred Term, by prior or concomitant medications.

A listing of all medications recorded on the concomitant medications CRF page will provide details including flag for Best Supportive/Best Standard of Care, indication, dose, route, frequency, and start and stop dates.

9.7 Post-Study Cancer-related Therapy

Drug or other non-radiation therapies will be classified according to WHODrug Global version 2018 Mar 1 dictionary.

The number and percentage of participants receiving a post-study prostate cancer-related therapy will be displayed by preferred term within each ATC. Therapy summaries will be sorted alphabetically by preferred term within ATC class.

Best response to post therapy prostate cancer therapy and type of response will be summarized.

A listing of all data recorded on the post-treatment disease assessment, post-treatment radiotherapy, post-treatment anti-cancer therapies, and long-term follow-up contact CRFs will be provided.

10. REFERENCES

- Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating Clinically Meaningful Changes for the Functional Assessment of Cancer Therapy—Prostate: Results from a Clinical Trial of Patients with Metastatic Hormone-Refractory Prostate Cancer. Value in Health 12(1): 124-129, 2009.
- Cella D, Zagari MJ, Vandoros C, Gagnon DD, Hurtz HJ, and Nortier JWR. Epoetin Alfa Treatment Results in Clinically Significant Improvements in Quality of Life in Anemic Cancer Patients When Referenced to the General Population. JCO 21(2): 366-373, 2003
- Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, dd. June 14, 2010 - National Cancer Institute.
- Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer 2009;45:228-247.
- Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. Contemp Clin Trials. Jul 2008;29(4):456-65.
- European Medicines Agency. Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man. Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials. Science Medicines Health. 13 Dec 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137126.pdf
- EQ-5D-5L User Guide: https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf
- Fitzmaurice G, Laird N, Ware J. Applied Longitudinal Analysis, 2004; https://content.sph.harvard.edu/fitzmaur/ala/
- Lin DY, Feuer EJ, Etzioni R, Way Y. Estimating medical costs from incomplete follow-up data. Biometrics. Jun 1997; 53(2):419-434. http://dlin.web.unc.edu/files/2013/04/LinEA97.pdf
- Mihaylova B, Briggs A, O'Hagan A, Thompson SG. Review of statistical methods for analyzing healthcare resources and costs. Health Economics. 2011; 20:897-916. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3470917/pdf/hec0020-0897.pdf
- Newcombe RG. Interval estimation for the difference between independent proportions: Comparison of eleven methods. Statistics in Medicine 1998;17:873–90.
- Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Work Group 3. J Clin Oncol 2016;34(12):1402–18.
- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research. Guidance for industry. Clinical trial endpoints for the approval of cancer drugs and biologics. May 2007. https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf
- Yount S, Cella D, Banik D, Ashraf T, Shevrin D. Brief assessment of priority symptoms in hormone refractory prostate cancer: The FACT advanced prostate symptom index (FAPSI). Health and Quality of Life Outcomes. 21 Nov 2003;

1:69
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC305353/pdf/1477-7525-1-69.pdf

Appendix A: Schedules of Study Assessments

Screening procedures and baseline assessments will be performed within 4 weeks of randomization except for baseline imaging. Baseline medical imaging (CT with contrast/ MRI, and bone scan) is to be performed within 28 days of start of treatment. Any medical imaging done within this time frame may be accepted as the baseline imaging. The screening procedures are detailed in Table 2.

Table 2. Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Informed consent	As per local/central IRB/IEC/REB timing requirements but prior to the performance of any study specific procedures.
Inclusion/exclusion criteria	Refer to protocol Section 4.1 and Section 4.2 for additional details.
Medical history	Collect medical history, including the following details about prior prostate cancer treatment(s): • Date of initial diagnosis • Approximate start and stop date of each therapy • Date and type of progression (e.g. PSA, radiological, bone, or no clinical benefit) • Site of progression (new lesions, existing lesions, or both) when available
Prior/concomitant medication review	
Full physical examination	Should be performed by a qualified medical practitioner.
Height	
Weight	
ECOG performance score	Refer to protocol Appendix 4 for the ECOG performance score scale.
Vital signs	Includes: blood pressure, pulse, and respiratory rate
CT with contrast /MRI	CT with contrast/MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations The radiological technique used for measurement of the baseline images should also be the radiological technique used for each reassessment.
^{99m}Tc diphosphonate bone scan	Baseline and follow up radiological disease assessments must include bone scans performed with technetium-99m labeled diphosphonates as per the local standard of care for patients with prostate cancer. Use the PCCTC bone scan assessment tool to document lesions (included in protocol Appendix 11).
Histology	Pathology report of the most recent biopsy required at enrollment.
Disease pattern	Bone, visceral, soft tissue, and lymph nodes
12-lead ECG	

Table 2. Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Hematology	Refer to protocol Section 6.3.1 for list of tests
Chemistry	Refer to protocol Section 6.3.1 for list of tests
Urinalysis, macroscopic (microscopic when indicated)	Refer to protocol Section 6.3.1 for list of tests
Serum testosterone	
PSA	Includes PSA results and dates of 2 previous measurements. Prior measurements are needed to assess PSA velocity/doubling time.
BPI-SF, EQ-5D-5L and FACT-P	Baseline pain score assessment (BPI-SF) and HRQoL (EQ-5D-5L, FACT-P) assessments. HRQoL assessments may be either self-completed by the subject, or administered via face-to-face interview and completed by a caretaker/clinician.
Best supportive/best standard of care determination	To be decided prior to randomization, as part of screening.
PSMA PET/CT scan	To be done once all other eligibility requirements are confirmed. The metastatic lesion requirement may be confirmed at the same time as the baseline ^{68}Ga-PSMA-11 PET/CT[a] scan. Baseline ^{68}Ga-PSMA-11 PET/CT[a] scan must be done within 4 weeks of start of treatment but not within the 6 days prior to start of treatment. PSMA eligibility will be determined by central readers.
Screening registration	Initial screening registration should take place after the patient has signed the Informed Consent Form. It should be completed once all screening assessments have been completed and results confirmed except for metastatic lesion requirement and PSMA positivity.
Study enrollment	Study enrollment should take place after screening registration is completed and once the metastatic lesion requirement is confirmed by the site and PSMA positivity has been confirmed by the central readers. Patients randomized to the investigational arm are to begin dosing with ^{177}Lu-PSMA-617 within 28 days after randomization.

[a] For background and additional details on ^{68}Ga-PSMA-11, refer to the ^{68}Ga-PSMA-11 Investigator's Brochure.

BPI-SF = Brief Pain Inventory – Short Form; CT= computed tomography; ECG = electrocardiography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; HRQoL = Health-related quality of life; IEC = Independent Ethics Committee; IRB = Institutional Review Board; MRI = magnetic resonance imaging; PCCTC = Prostate Cancer Clinical Trials Consortium; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; REB = Research Ethics Board; RECIST = Response Evaluation Criteria in Solid Tumors;

Table 3. Schedule of assessments: ^{177}Lu-PSMA-617 plus best supportive/best standard of care arm (Cycle 1)

Study Period:	Cycle 1					
Cycle Week:	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
Cycle Day:	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**
Concomitant medication review	X----------					----------X
AE monitoring[a]	X----------					----------X
Weight	X[b]					
ECOG	X[b]					
Directed physical exam	X[b]					
Vital signs[c]	X[b]					
EQ-5D-5L	X[d,f]					
FACT-P	X[d,f]					
BPI-SF	X[d,f]					
Administer ^{177}Lu-PSMA-617	X					
Best supportive/best standard of care	As per physician's orders					
Hematology[e]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Chemistry[e]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Serum testosterone	X[b]					
PSA	X[b]					
Radiographic imaging (CT with contrast /MRI and bone scan)	Every 8 weeks (± 4 days) after first dose of ^{177}Lu-PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days) through the End of Treatment visit.					

[a] Adverse event monitoring for treatment-emergent ^{177}Lu-PSMA-617 events will commence with initial dosing of ^{177}Lu-PSMA-617
[b] Within 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 8, 15, 22, 29, and 36.
[c] Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1) and at 15 minutes before, 30 minutes post, and 60 minutes post ^{177}Lu-PSMA-617 administration.
[d] To be completed prior to drug administration on Day 1.
[e] Hematology and chemistry to be done every week for Cycle 1 only.
[f] HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

[redacted]

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

[redacted]

Table 4. Schedule of assessments: ^{177}Lu-PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6*						After Cycle 6*	End of Treatment[g]	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 8 weeks (± 1 week)		Every 3 months (± 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			Collect: • Hematology • Chemistry • Survival • New treatment: • Start/stop dates • Best response • Type of response • AE assessment
Concomitant medication review	X----------X[a]						X[a]	X	
AE monitoring[b]	X----------X[a]						X[a]	X	
Weight	X[c]						X[c]	X	
ECOG	X[c]						X[c]	X	
Directed physical exam	X[c]						X[c]	X	
Vital signs[d]	X[c]						X[c]	X	
EQ-5D-5L	X[e,h]						X[e,h]	X[h]	
FACT-P	X[e,h]						X[e,h]	X[h]	
BPI-SF	X[e,h]						X[e,h]	X[h]	
Administer ^{177}Lu-PSMA-617	X								
Best supportive/ best standard of care	As per physician's orders						As per physician's orders		
Hematology[f]	X[c]		X[c]		X[c]		X[c]	X	
Chemistry[f]	X[c]		X[c]		X[c]		X[c]	X	
Serum testosterone	X[c]						X[c]	X	
PSA	X[c]						X[c]	X	
Radiographic imaging (CT with contrast /MRI and bone scan)	To be conducted every 8 weeks (± 4 days) after first dose of ^{177}Lu-PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days) through the end of treatment visit								

[redacted]

* After the Cycle 4 dose of ^{177}Lu-PSMA-617 and prior to Cycle 5 Day 1, the investigator should determine if:
- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast /MRI or bone scan and
- has shown good tolerance to the ^{177}Lu-PSMA-617 treatment.

If the patient meets the criteria above, and agrees to continue with additional treatment of ^{177}Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu-PSMA-617 treatment, then no additional doses of ^{177}Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ^{177}Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

[a] Phone evaluation is allowed during Weeks 2, 4, and 6.

[b] Adverse event monitoring for treatment-emergent ^{177}Lu-PSMA-617 events will commence with initial dosing of ^{177}Lu-PSMA-617 and continue up to and including 30 days after the last dose of ^{177}Lu-PSMA-617.

[c] Within 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 15, and 28.

[d] Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1) and at 15 minutes before, 30 minutes post, and 60 minutes post ^{177}Lu-PSMA-617 administration.

[e] To be completed prior to drug administration (if applicable) on Day 1.

[f] For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every 8 weeks (±1 week). If at any time, WBC count $<3.0 \times 10^9$/L, ANC is $<1.5 \times 10^9$/L, platelet count is $<100 \times 10^9$/L or hemoglobin level is <9 g/dL, hematologic parameters (i.e., CBC with differential analysis) should be done no less frequently than once each week until resolution to Grade 1 or baseline. If at any time there is a ≥ Grade 2 related chemistry lab result, chemistry should be done no less frequently than once each week until resolution to Grade 1 or baseline.

[g] To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose of ^{177}Lu-PSMA-617 or best supportive/best standard of care, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study

[h] HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

AE = adverse event; ANC= absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; WBC = white blood cell

[redacted]

Table 5. Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)

Study Period:	Cycle 1					
Cycle Week:	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
Cycle Day:	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**
Concomitant medication review	X----------X					
AE monitoring[b]	X----------X					
Weight	X[a]					
ECOG	X[a]					
Directed physical exam	X[a]					
Vital signs[c]	X[a]					
EQ-5D-5L	X[d,f]					
FACT-P	X[d,f]					
BPI-SF	X[d,f]					
Best supportive/ best standard of care	As per physician's orders					
Hematology[e]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Chemistry[e]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Serum testosterone	X[a]					
PSA	X[a]					
Radiographic imaging (CT with contrast /MRI and bone scan)	Every 8 weeks (± 4 days) after first dose of best supportive/best standard of care for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days) through the End of Treatment visit					

[a] Within 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 8, 15, 22, 29, and 36.
[b] Adverse event monitoring will begin Cycle 1 Day 1
[c] Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1).
[d] To be completed prior to any drug administration (if applicable) on Day 1.
[e] Hematology and chemistry to be done every week for Cycle 1 only.
[f] HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

Table 6. Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6						After Cycle 6	End of Treatment[f]	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 8 weeks (± 1 week)		Every 3 months (± 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			Collect: • Hematology • Chemistry • Survival • New treatment: • Start/stop dates • Best response • Type of response • AE assessment
Concomitant medication review	X----------X[a]						X[a]	X	
AE monitoring	X----------X[a]						X[a]	X	
Weight	X[b]						X[b]	X	
ECOG	X[b]						X[b]	X	
Directed physical exam	X[b]						X[b]	X	
Vital signs[c]	X[b]						X[b]	X	
EQ-5D-5L	X[d,g]						X[d,g]	X[d,g]	
FACT-P	X[d,g]						X[d,g]	X[d,g]	
BPI-SF	X[d,g]						X[d,g]	X	
Best supportive/best standard of care	As per physician's orders						As per physician's orders		
Hematology[e]	X[b]		X[b]		X[b]		X[b]	X	
Chemistry[e]	X[b]		X[b]		X[b]		X[b]	X	
Serum testosterone	X[b]						X[b]	X	
PSA	X[b]						X[b]	X	
Radiographic imaging (CT with contrast /MRI and bone scan)	To be conducted every 8 weeks (± 4 days) after first dose of best supportive/best standard of care for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days) through the end of treatment visit								

[a] Phone evaluation is allowed during Weeks 2, 4, and 6.
[b] Within 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 15, and 29.
[c] Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1).
[d] To be completed prior to drug administration (if applicable) on Day 1.

[e] For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every 8 weeks (± 1 week). If at any time, WBC <3.0 x 10^9/L, ANC is <1.5 x 10^9/L, platelet count is <100 x 10^9/L or hemoglobin level is <9 g/dL, hematologic parameters (i.e., CBC with differential analysis) should be done no less frequently than once each week until resolution to Grade 1 or baseline. If at any time there is a Grade 2 related chemistry lab result, chemistry should be done no less frequently than once each week until resolution to Grade 1 or baseline.

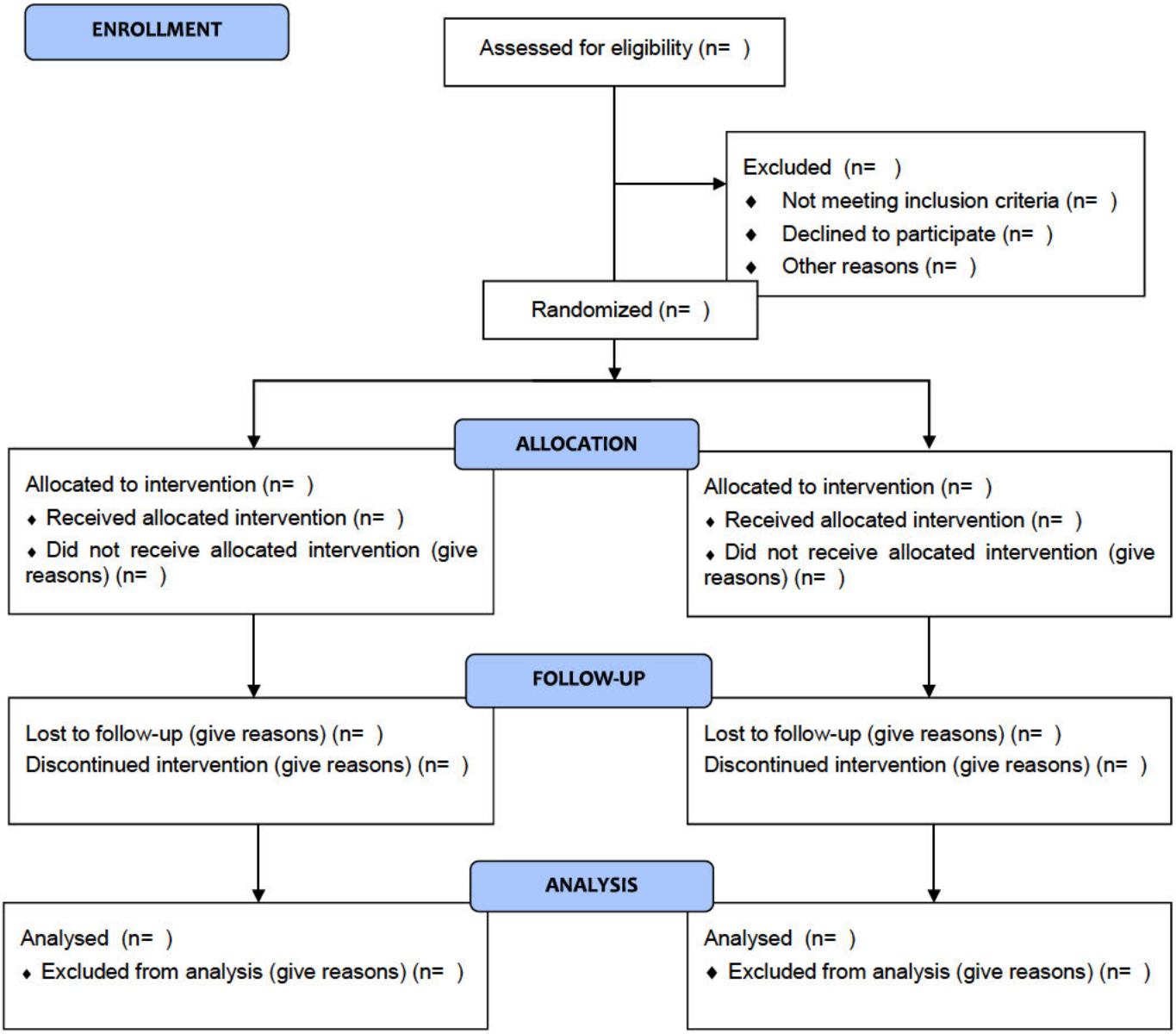
[f] To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose of best supportive/best standard of care, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study.

[g] HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; WBC = white blood cell count

Appendix B: Consort Flow Diagram

Consort Diagram of Full Analysis Set



Appendix C: Quality of Life Questionnaire References

References regarding EQ-5D-5L

Full scoring details for the EQ-5D-5L are described at the site https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

The derivation and performance of the value set for conversion of questionnaire responses to a utility score is described in the manuscript http://eprints.whiterose.ac.uk/121473/1/Devlin_et_al-2017-Health_Economics.pdf

Repeated measures analysis of PROs: Fistzmaurce G, et al., 2004. (full reference in Section 10)

References regarding the FACT-P

Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System, version 4.0 (November 1997) is located on-line at www.facit.org

Minimally important differences in FACT-P related scales

Score type	Source	Total possible score	Range of MID	MID used in analyses
Physical well-being (PWB)	Cella et al. Qual Life Res 2002; 11: 207-221; Yost et al. Eval Health Prof 2005; 28: 172-191	28	2-3	3
Social/family well-being (SFWB)	Yost et al. Eval Health Prof 2005; 28: 172-191	28	2-3	3
Emotional well-being (EMB)	Yost et al. Eval Health Prof 2005; 28: 172-191	24	2-3	3
Functional well-being (FWB)	Cella et al. Qual Life Res 2002; 11: 207-221; Yost et al. Eval Health Prof 2005; 28: 172-191	28	2-3	3
FACT-G total score[a]	Cella et al. Value Health 2009; 12: 124-129	108		9
Prostate cancer subscale (PCS) score	Cella et al. Value Health 2009; 12: 124-129	48	2-3	3
FACT-P total score[b]	Cella et al. Value Health 2009; 12: 124-129	156	6-10	10
Pain-related subscale (PRS)[c]	Cella et al. Value Health 2009; 12: 124-129	16	1-2	2
TOI score	Yost et al. Eval Health Prof 2005; 28: 172-191	104	5-9	9
FAPSI-8	Cella et al. Value Health 2009; 12: 124-129	32	2-3	3
Notes: (a) Composite of the scores on the PWB+SFWB+EWB+FWB (b) Composite of the scores PWB+SFWB+EWB+FWB+PCS. Impaired QoL has been defined arbitrarilty in published literature as a FACT-P score of ≤122-128, of the 156 maximum score (c) Calculated using the 4 questions on pain in the FACT-P, but the scores are reversed such that higher score indicates better health and less pain. A decrease in score signifies pain progression				

Change thresholds for deterioration on the FACT-P PCS, TOI, and FACT-P Total scales are based upon Cella et al. 2009, which provided clinically meaningful change estimates in a prostate cancer sample based upon an anchoring methodology. The FACT-G scales (PWB, SFWB, EWB, FWB, and the FACT-G) were not addressed in that article, and so the clinically meaningful change estimates for those scales are derived from an earlier reference, which reports normative values from a large sample from the general population for the FACT-G scales. Standard deviations (once normalized back to their original scales from the zero to 100 scale reported in the article) for the PWB, SFWB, EWB, FWB, and the FACT-G were 5.35, 6.80, 4.78, 6.83, and 18.04, respectively. Taking one half the standard deviation is equivalent to finding a 0.5 effect size. Using this distributional technique to find the clinically meaningful change estimates produced values of about 3 points for PWB, SFWB, EWB, and FWB and about 9 points for the FACT-G.

Revision History

Version	Date	Revised by:	Changes
1.0	08 Jun 2018	[redacted]	Original version

ENDOCYTE

Statistical Analysis Plan

Sponsor:	Endocyte, Inc.
Protocol Title:	VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF ^{177}LU-PSMA-617 IN THE TREATMENT OF PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)
Protocol Number:	PSMA-617-01
SAP Version, Date:	Version 1.0, 08 June 2018 Version 2.0, 24 October 2019 Version 3.0, 18 January 2021

The undersigned certify that they have read, reviewed and approved this document:

[redacted] – Author,

Signature, Date: [redacted] Date: 2021.01.18 06:54:43 -05'00'

[redacted]

Signature, Date: [redacted] Digitally signed by [redacted] DN: dc=com, dc=novartis, ou=people, ou=GD, serialNumber=[redacted] cn=[redacted] Reason: I am approving this document Date: 2021.01.19 07:25:56 -05'00'

[redacted]

Signature, Date: [redacted] Digitally signed by [redacted] DN: dc=com, dc=novartis, [redacted] Date: 2021.01.18 22:29:33 -05'00'

[redacted]

Signature, Date: [redacted] signed by [redacted] DN: dc=com, [redacted] ou=GD, serialNumber=[redacted] cn=[redacted] Reason: I am approving this document Date: 2021.01.18 07:51:52 -05'00'

[redacted]

Signature, Date: [redacted] Digitally signed by [redacted] DN: dc=com, [redacted] ou=GD, serialNumber=[redacted] cn=[redacted] Reason: I am approving this document Date: 2021.01.18 15:18:17 -05'00'

Table of Contents

1. LIST OF ABBREVIATIONS AND DEFINITION of TERMS

Abbreviation	Term/Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic classification
BOR	Best overall response
BPI-SF	Brief Pain Inventory – Short Form
BSC	Best supportive care
BSoC	Best standard of care
C1D1	Cycle 1 Day 1
CI	Confidence interval
CR	Complete response
CRO	Contract Research Organization
CRF	Case Report Form
CRS	Case Retrieval Strategy
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease control rate
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDoR	Expected duration of response
EMA	European Medical Agency
EOT	End of Treatment
ESA	Erythropoietin stimulating agents
EuroQoL	European Quality of Life
EQ-5D-5L	European Quality of Life (EuroQol) – 5 Domain 5 Level scale
EQ-VAS	European Quality of Life – Visual Analogue Scale
EWB	Emotional Well-Being
FACT-P	Functional Assessment of Cancer Therapy - Prostate
FACT-G	Functional Assessment of Cancer Therapy - General
FAPSI-8	Functional Assessment of Cancer Therapy Advance Prostate Symptom Index-8
FDA	Food and Drug Administration

Abbreviation	Term/Definition
FAS	Full Analysis Set
FWB	Functional Well-Being
^{68}Ga	Gallium-68
GM-CSF	Granulocyte macrophage colony-stimulating factor
HLGT	High level group terms
HLT	High level terms
HR	Hazard ratio
HRQoL	Health-related quality of life
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IRT	Interactive response technology
ITT	Intent to treat
LDH	Lactate dehydrogenase
LOS	Length of stay
^{177}Lu	Lutetium-177
LTFU	Long term follow up
MAR	Missing at random
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NAAD	Novel androgen axis drug (such as abiraterone, enzalutamide, or apalutamide)
NCI	National Cancer Institute
NMQ	Novartis Medical Dictionary for Regulatory Activities (MedDRA) queries
OAU	Opioid analgesic use
ORR	Overall response rate
OS	Overall survival
PCS	Prostate Cancer Subscale
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PK	Pharmacokinetics
PET	Positron emission tomography
PFS	Progression-free survival
PR	Partial response
PRO	Patient reported outcome
PRS	Prostate Cancer Subscale Pain-Related Subscale
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
PT	Preferred term

Abbreviation	Term/Definition
PWB	Physical Well-Being
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic progression-free survival
SAP	Statistical analysis plan
SD	Stable disease
SFWB	Social/Family Well-Being
SMQ	Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries
SOC	System organ class
SSE	Symptomatic Skeletal Event
TDRP	Time to disease-related pain
TEAE	Treatment-emergent adverse event
TFOA	Time to first use opioid analgesic
TOI	Trial Outcomes Index
TMF	Trial Master File
VAS	Visual analogue scale
WBC	White blood cell
WHO	World Health Organization

2. Introduction

This Statistical Analysis Plan (SAP) was written for the clinical trial PSMA-617-01 and is based on the current protocol version 4.0 dated 08 July 2019 and current country specific protocol version 4.4 DE dated 22 July 2020 that supports the sub-study conducted at sites in Germany. All decisions regarding the analyses, as defined in the SAP, have been made prior to database lock. The ICH guideline E3 "Structure and Content of Clinical Study Reports" was used as a guide to the writing of this SAP.

2.1 Changes from the Protocol

In protocol section 8.7.2, it states that the primary evaluation of the key secondary endpoints will be assessed in the PFS-FAS. While this is the case for the key secondary endpoint of time to first symptomatic skeletal event (SSE), the other key secondary endpoints, Overall Response Rate (ORR) and Disease Control Rate (DCR) per RECIST 1.1, will be assessed in the Response Evaluable Analysis Set defined as the subset of patients in the PFS-FAS with evaluable disease by RECIST 1.1 at baseline. In addition, the supportive analyses of ORR and DCR will not be performed in the FAS as the FAS would have included patients without RECIST evaluable disease and may result in bias due to the early dropout in the BSC/BSoC arm (see Section 3.1). Furthermore , the protocol specified that the time to first SSE will be analyzed using a Cox regression model, stratifying for the randomization factors however, the primary analysis of this endpoint will compare the treatment arms using the stratified log-rank test. The specific analyses that are planned for the key secondary endpoints are described in Section 8.2.2.

The analysis population PFS Analysis Set (PFS-FAS) as stated in protocol section 8.4, will be referred in the SAP and tables, listings and figures as PFS Full Analysis Set (PFS-FAS) as shown in Section 5.3.1.

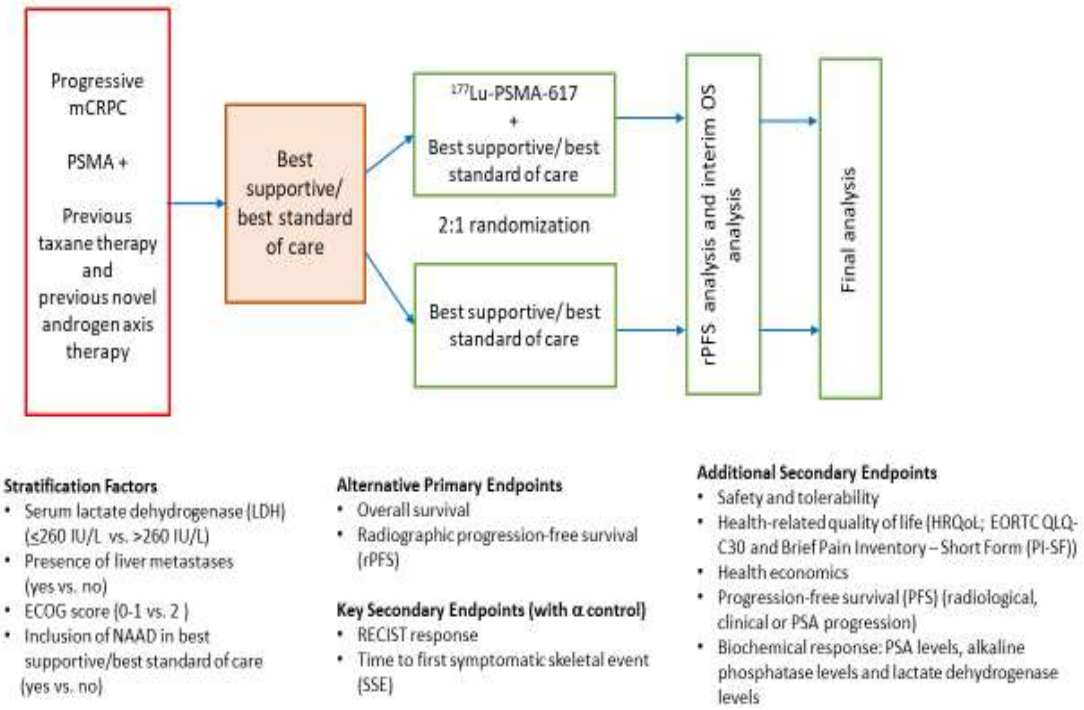
As stated in section 8.3 of the protocol, the alpha level applicable to overall survival (OS) in the final analysis will depend upon the earlier radiographic progression-free survival (rPFS) and interim OS results. This implies that regardless of the interim analysis result of OS, final OS will be re-tested at the applicable alpha level. However, if the interim OS results are met at the pre-specified alpha level, the final OS will be presented descriptively without statistical inference and at the same nominal alpha level as specified in Section 3.4. In the event the formal interim OS analysis is not performed, the alpha level applicable to the final OS analysis will only depend on the final rPFS results. The details are further described in Section 4 and Section 8.2.1.

3. Study Design and Objectives

3.1 Study Design

This is a Phase 3, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}LuPSMA-617 in patients with progressive PSMA positive mCRPC, when administered in addition to best supportive/best standard of care (BSC/BSoC) as compared to BSC/BSoC alone (Figure 1).

Figure 1 Diagram of trial design



ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

BSC/BSoC includes available care for the eligible patient according to best institutional practice and at the discretion of the investigator. Novel androgen axis drugs [NAADs] (i.e., enzalutamide, abiraterone, or apalutamide) are allowed.

Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223) or hemi-body radiotherapy treatment may not be administered on study.

At screening, potential subjects will be assessed for eligibility and will undergo a ^{68}Ga-PSMA-11 PET/computed tomography (CT) scan to evaluate PSMA positivity. Only patients with PSMA-positive cancer will be randomized in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 plus BSC/BSoC (investigational arm) or to receive BSC/BSoC only (BSC/BSoC-only arm). Randomization will be stratified by 4 factors (Section 3.2).

Patients randomized to the investigational arm must begin ^{177}Lu-PSMA-617 dosing within 28 days of randomization. These patients will receive BSC/BSoC and 7.4 GBq (±10%) ^{177}Lu-PSMA-617 once every 6 weeks (±1 week) for a maximum of 6 cycles.

After the Cycle 4 dose of ^{177}Lu-PSMA-617 and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, Prostate-specific antigen (PSA), clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- Has shown good tolerance to the ^{177}Lu-PSMA-617 treatment.

If the patient meets all of the criteria above, and agrees to continue with additional treatment of ^{177}Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet any of the criteria or does not agree to additional ^{177}Lu-PSMA-617 treatment, then no additional doses of ^{177}Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ^{177}Lu-PSMA-617, patients can continue BSC/BSoC alone.

BSC/BSoC for each patient will be selected at the discretion of the patient's physician, prior to randomization and will be administered per the physician's orders and continued until the patient comes off the treatment part of the study and enters the long-term follow-up stage.

A patient may choose to discontinue the randomized treatment part of the study at any time. If a patient chooses only to discontinue from the randomized treatment in the study for a reason other than radiographic progression, the patient will be asked to confirm if they consent to continue to be followed for long term safety, radiographic Progression-Free Survival (rPFS), and survival follow up. The patient will continue to be followed for long term follow up unless they specifically withdraw consent from long term follow-up of the study. Crossover to ^{177}Lu-PSMA-617 treatment is not allowed.

An End of Treatment (EOT) visit should occur once a patient discontinues randomized treatment for any reason (patient or investigator decision, going on to long term follow up, etc.). The EOT visit should occur approximately 30 days from the last dose of ^{177}Lu PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever is later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

After the EOT visit, patients will enter the long-term follow-up period. The long-term follow-up period will include the collection of rPFS (if discontinuing for reasons other than radiographic progression), survival and information about new treatments, along with the patient's response to these treatments, adverse events assessment, and results of hematology and chemistry testing. During follow-up, patients will be followed for safety and survival. They will be contacted every 3 months (±1 month) via phone, email, or letter for up to 24 months or until 508 deaths have occurred, whichever is sooner.

Patients who withdraw their consent to participate in the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

This study will enroll approximately 814 patients involving about 110 sites worldwide.

<u>Study design update:</u>

The trial was originally designed to randomize 750 patients, targeting the primary analysis of rPFS with 457 events, an interim analysis of Overall Survival (OS), to be

conducted contemporaneously with the primary analysis of rPFS, and a final analysis of OS with 489 deaths.

However, shortly after commencement of the trial, a high, early dropout rate amongst those randomized to BSC/BSoC only became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients which consequently could result in bias in the analysis of rPFS. Remedial measures to curtail this phenomenon were implemented and made effective on 5-Mar-2019. As part of the plan to address the early withdrawal of consent in the BSC/BSoC-only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after 5-Mar-2019; therefore, rPFS will be analyzed in these patients once 364 events have accrued. At time of the rPFS primary analysis, there will also be an interim analysis of OS; this OS analysis will be on an intent to treat (ITT) basis and will include all randomized patients (i.e., including those randomized before 5-Mar-2019). Following the analysis of rPFS and the interim analysis of OS, a final ITT analysis of the OS primary objective will be performed when 508 deaths have accrued. To achieve these analyses, the total number of subjects randomized into the trial was increased from N=750 to N=814. The revisions described do not alter the hypothesized treatment effects for rPFS and OS upon which the study was originally powered.

Dosimetry, Pharmacokinetics and ECG Sub-study:

A dosimetry, pharmacokinetics (PK) and ECG sub-study will be conducted in a single arm, non-randomized cohort of approximately 30 patients at sites in Germany. These patients will receive the investigational treatment arm only (i.e., ^{177}Lu-PSMA-617 plus best supportive/best standard of care) and will provide a complete assessment of the safety aspects of ^{177}Lu-PSMA-617. To prevent biasing the results obtained from patients randomized in the main study, the patients enrolled in the sub-study will not be included in the in the analyses of the randomized main study but will be described separately from the main study. The data analysis of dosimetry, PK and ECG from the sub-study will be described in stand-alone analysis plan documents.

3.2 Randomization and Blinding

Eligible patients will be randomized by an interactive response technology (IRT) system in a 2:1 ratio to the investigational treatment arm or the BSC/BSoC -only arm using a permuted block scheme. The approximate 30 eligible patients included in the sub-study will not undergo randomization as all patients will receive the investigational treatment arm. Randomization will be stratified by the following factors:

- LDH (≤ 260 IU/L vs. > 260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0 or 1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care at time of randomization (yes vs. no)

The study is open-label. However, access to subject treatment allocation will be limited to those individuals whose roles require access to perform their study responsibilities. Details of what roles and which individuals have access to unblinded data will be documented in a separate Data Access Plan maintained by the sponsor. Dates of access and reason for accesses will be recorded. Sponsor statisticians will be blinded and contract research organization (CRO) statisticians assigned to the study will be unblinded.

3.3 Study Objectives

Primary objective

The primary objective of this study is to compare the two alternate endpoints of radiographic progression free survival (rPFS) per Prostate Cancer Clinical Trials Working Group 3 (PCWG3) guidelines (Scher et al 2016) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ^{177}Lu-PSMA-617 in addition to BSC/BSoC versus patients treated by BSC/BSoC alone.

Key secondary objectives

Key secondary objectives are an arm-to-arm comparison of the following:

1. RECIST response to include:
    a. Overall Response Rate (ORR) as measured by RECIST v1.1 criteria
    b. Disease Control Rate (DCR) as measured by RECIST v1.1 criteria
2. Time to the first symptomatic skeletal event (SSE)

Additional secondary objectives

1. Safety and tolerability of ^{177}Lu-PSMA-617
2. Periodic assessment of health-related quality of life to evaluate impact of intervention on patient well-being (HRQoL; EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF])
3. Health Economics
4. Progression-free survival (PFS) (radiographic, clinical, or PSA progression-free survival)
5. Biochemical response as measured by PSA. Alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) levels will also be collected.
6. Dosimetry, PK and ECG (sub-study of approximately 30 patients)

3.4 Sample Size Justification

The sample size was determined based on the alternate primary endpoints of rPFS and overall survival. Planned enrollment for this study is approximately 814 subjects.

Under the null hypothesis for survival, median overall survival is assumed to be 10 months on ^{177}Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median overall survival on active is assumed to be 13.7 months for a HR of 0.7306.

Under the null hypothesis for rPFS, median rPFS is assumed to be 4 months on ^{177}Lu-PSMA-617 and best supportive/best standard of care (active) for a HR of 1.00. Under the alternative hypothesis, median rPFS on active is assumed to be 6 months for a HR of 0.67.

Based on a non-linear patient accrual profile over 14 months, a total of 814 patients randomized and followed on an ITT basis for a minimum of 13 months is expected to yield

508 deaths. This number of events provides at least 90% power to test the hypothesis that the HR for OS is 0.7306 or better with a 1-sided alpha level of at least 0.020.

For rPFS, a total of approximately 557/814 patients are expected to be randomized on or after 5 March 2019, these being the patients to be included in the primary analysis of rPFS; with a minimum of approximately 6 months follow-up, these patients are expected to yield 364 rPFS events which will be sufficient to provide 84% power to test the hypothesis that the HR of rPFS is 0.67 or better with a 1-sided alpha level of 0.004. At the time of this rPFS analysis, 341 deaths are expected amongst all randomized patients. These interim OS data will be analyzed with a 1-sided alpha level of 0.001. Central independent assessments will be used to determine rPFS events.

The alpha level applicable to OS in the final analysis will depend upon the earlier rPFS and interim OS results:

- if $p<0.004$ 1-sided is achieved for rPFS and $p<0.001$ 1-sided is achieved for interim OS, then the alpha level for the final analysis of OS will be raised to 0.025 1-sided.
- if $p<0.004$ 1-sided is achieved for rPFS but $p<0.001$ 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will be 0.024 1-sided.
- if $p<0.004$ 1-sided is not achieved for rPFS but $p<0.001$ 1-sided is achieved for interim OS, then the alpha level for the final analysis of OS will be raised to 0.021 1-sided.
- if $p<0.004$ 1-sided is not achieved for rPFS and $p<0.001$ 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will remain at 0.020 1- sided.

This design provides at least 90% power for OS and 84% power for rPFS; with an overall Type I error rate ≤0.025 1-sided.

The observed HRs that will meet $p<0.004$ for rPFS and the interim analysis of OS are 0.745 and 0.701 respectively; and the observed HR that will meet $p<0.020$ to $p<0.025$ in the final analysis of OS are 0.824 to 0.823.

4. Planned Analyses

The analyses of the alternate primary endpoints, rPFS and OS, are event driven. The formal planned analysis of rPFS is when 364 rPFS events have been observed in patients randomized on or after 5 March 2019 with an interim analysis of OS at the time of the rPFS analysis using all patients randomized since trial commencement (see Section 5.3.1 for Efficacy Populations). A final analysis of OS, using all patients randomized, will take place when 508 deaths have been observed.

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either the primary analysis of rPFS or OS at the respective allocated alpha level; it is not required to meet both rPFS and OS to be declared a statistically positive study.

Note, this applies to OS assessed at either the interim or the final analysis, i.e. for the study to be declared statistically positive requires rPFS to meet its allocated alpha level or OS to meet its allocated alpha level at either (i) the formal OS interim analysis (conducted at the time of the rPFS analysis) or (ii) at the final OS analysis with 508 deaths.

The alpha level applicable to OS in the final analysis will depend upon the earlier rPFS and interim OS results as described in Section 3.4. If the formal interim OS analysis is met at the pre-specified alpha level, the final OS will only be presented descriptively without statistical inference at the nominal alpha level. However, if the formal interim OS analysis is not performed, the alpha level applicable to the OS analysis will depend on the final rPFS results as follows:

- if p<0.004 1-sided is achieved for rPFS, then the alpha level for the final analysis of OS will be raised to 0.025 1-sided.
- if p<0.004 1-sided is not achieved for rPFS, then the alpha level for the final analysis of OS will be 0.021 1-sided.

4.1 Interim Analyses and IDMC Oversight

Safety data monitoring will be conducted quarterly by the Independent Data Monitoring Committee (IDMC). Safety reviews will commence following the completion of the first three months of study accrual. Safety analyses to be conducted are outlined in the IDMC charter. The specific responsibilities and composition of the IDMC are outlined in the IDMC Charter. The IDMC Charter will be approved and finalized by the IDMC members prior to the initiation of any formal efficacy analysis. A summary of efficacy data will also be provided to the IDMC at the time of routine safety data reviews; these efficacy data will be provided for information only; no statistical hypothesis testing will be conducted.

The planned analysis of rPFS and the interim analysis of OS will be overseen by the IDMC who may recommend stopping the study for superior efficacy at the first interim analysis for efficacy if the corresponding pre-specified 1-sided p-value threshold is met. The IDMC can recommend a course of action including early cessation if one of the alternate primary endpoints is met, but the sponsor will make the final decision regarding whether or not to continue or stop the trial, based on any analysis for reasons related to safety or efficacy.

4.2 Sub-study Analyses

The analyses of dosimetry, PK and ECG from the sub-study are described in separate analysis plans and are outside the scope of this SAP. All other analyses as described in this SAP will be performed, at the earliest, when all patients have completed study treatment (i.e. ^{177}Lu-PSMA-617+BSC/BSoC) or discontinued study treatment for any reason. Separate TFL shells will detail the planned outputs for the sub-study analyses.

5. General Analysis Definitions

Data will be analyzed using SAS version 9.4 or higher.

No tests of significance will be carried out to compare treatment arms on baseline data because any observed differences between them must be attributed to chance.

Descriptive statistics will be presented in tables as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages.
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, minimum, and maximum values.

Unless otherwise indicated, for frequency tables, patients with missing data will be excluded from the denominator of percentage calculations. All treatment arm comparisons other than the one-sided analyses described for the alternate primary endpoints, rPFS and OS, will be based on two-sided tests.

Tables will be created by treatment arm and for all patients combined as described at the beginning of sections 7, 8, and 9.

Individual patient listings will include all study-related data. The sort order of the listings will be by treatment, patient ID (center number-patient number), and date of assessment (if available).

Randomized treatment throughout this document will refer to ^{177}Lu-PSMA-617+BSC/BSoC and BSC/BSoC alone for analyses pertaining to the main study and will refer to ^{177}Lu-PSMA-617+BSC/BSoC for analyses pertaining to the sub-study.

Best supportive/best standard of care (BSC/BSoC): BSC/BSoC in either arm will be administered as per physician's orders and protocol at the institution and whenever feasible, it should be optimized prior to randomization. Patients will continue to be treated with BSC/BSoC until they require a treatment regimen not allowed on study or have radiographic progressive disease as measured by Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria. BSC/BSoC is defined as follows:

- Concomitant medications indicated as study BSC/BSoC, coded using WHO Drug Global dictionary. A pre-specified list of concomitant medications, based on the interventions allowed as BSC/BSoC per protocol (protocol section 5.2) will be used to indicate and flag concomitant medications as study BSC/BSoC. The BSC/BSoC flag captured on the CRF will not be used to identify concomitant medications indicated as study BSC/BSoC.

- Concurrent procedures other than radiotherapy indicated as study BSC/BSoC, are coded using the Medical Dictionary for Regulatory Activities (MedDRA). The BSC/BSoC flag captured on the CRF will be used to identify concurrent procedures other than radiotherapy indicated as study BSC/BSoC.

- Concurrent radiotherapy indicated as study BSC/BSoC. The BSC/BSoC flag captured on the CRF will be used to identify concurrent radiotherapy indicated as study BSC/BSoC.

Reference date is the date of first dose of randomized treatment unless otherwise noted.

Date of first dose of randomized treatment is defined as the date of first ^{177}Lu-PSMA-617 administration (non-zero dose) on Cycle 1 Day 1 (C1D1) or the date of first administration of BSC/BSoC.

- The date of first ^{177}Lu-PSMA-617 administration will be defined as the earliest date of administration as captured on the ^{177}Lu-PSMA-617 Administration CRF page with a non-zero dose.
- The date of first administration of BSC/BSoC will be defined as the date of C1D1.
- The date of first administration of a NAAD as study BSC/BSoC will be defined as follows:
    - = earliest start date of a NAAD indicated as study BSC/BSoC (captured on concomitant medications CRF) if after the date of first administration of BSC/BSoC, otherwise
    - = date of first administration of BSC/BSoC.

  For example: if the earliest start date of a NAAD indicated as study BSC/BSoC is 01MAR2019 and the date of first administration of BSC/BSoC is 03JAN2019, then the date of first administration of a NAAD as study BSC/BSoC is 01MAR2019.

The number of days until a study assessment or procedure is calculated as:

- Study Day= Assessment date – Reference date +1 if assessment date is after or on the reference date
- Study Day= Assessment date – Reference date if assessment date is before the reference date

Note: The reference date for safety assessments during randomized treatment (e.g. adverse event onset, laboratory measurement, vital sign measurement, ECOG performance status, etc.) is the date of first dose of randomized treatment and the reference date for efficacy assessments (i.e. survival, tumor response, health related

quality of life) is the date of randomization. The reference date for all assessments in the sub-study is the date of first dose of ^{177}Lu-PSMA-617.

Baseline for a given variable will be defined as the last non-missing assessment, including unscheduled assessments, for that variable obtained prior to or on the reference date but before the first treatment dose, unless otherwise noted.

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as "baseline" value or "baseline" assessment. For RECIST/PCWG3-based endpoints using CT/MRI, and bone scans (i.e. rPFS, ORR, DCR, duration of response, PFS), a window of 28 days from the start of randomized treatment will be allowed, i.e. the investigator/central review-reported responses will be maintained and baseline considered valid if the baseline assessment is within 28 days of randomized treatment start date. In the context of baseline definition, the efficacy evaluations also include the laboratory parameters PSA, ALP and LDH, and HRQoL (e.g. FACT-P). For safety evaluations of randomized treatment (i.e. laboratory assessments, ECOG performance status and vital signs), the last available assessment on or before the date of start of randomized treatment is taken as "baseline" assessment. For vital signs where time of assessment is captured (e.g. pre-dose and post-dose vital sign), the 15 minutes pre-dose value on or before the date of start of randomized treatment is taken as "baseline" assessment. For safety evaluations of ^{68}Ga-PSMA-11 (i.e. laboratory assessments and vital signs), the last available assessment on or before the date of ^{68}Ga-PSMA-11 is taken as "baseline" assessment.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If multiple values are from the same laboratory or collected for ECGs or vital signs, then the last value should be considered as baseline.

If patients have no value as defined, the baseline result will be considered as missing.

Refer to the table below for specific details on the baseline definitions for key study parameters.

Parameter	Baseline Definition[1]	Evaluation
Baseline Height, Weight, Body Mass Index (BMI)	the last available assessment on or before the date of randomization	Baseline demographics and disease characteristics for randomized treatment
Baseline Height, Weight, Body Mass Index (BMI) prior to ^{68}Ga-PSMA-11 dosing	the last available assessment on or before the date of ^{68}Ga-PSMA-11 dosing	Baseline demographics and disease characteristics for ^{68}Ga-PSMA-11
Baseline ECOG score	ECOG score captured on the Enrollment CRF page Note: ECOG performance is not collected at the time of screening, therefore it will not be available for those not enrolled.	Baseline demographics and disease characteristics and Stratification Factor for randomized treatment
Baseline PSA, LDH and ALP	the last available assessment on or before the date of randomization	Baseline demographics and disease characteristics and Efficacy for randomized treatment
Baseline PSA,LDH and ALP prior to ^{68}Ga-PSMA-11 dosing	the last available assessment on or before the date of ^{68}Ga-PSMA-11 dosing	Baseline demographics and disease characteristics for ^{68}Ga-PSMA-11
Baseline lesions (per investigator and central review)	the last available assessment on or before the date of randomization and/or within 28 days of start of randomized treatment	Baseline disease characteristics and Efficacy for randomized treatment
Baseline lesions (per investigator) prior to ^{68}Ga-PSMA-11 dosing	the last available assessment on or before the date of ^{68}Ga-PSMA-11 dosing	Baseline demographics and disease characteristics for ^{68}Ga-PSMA-11

Baseline EQ-5D-5L, FACT-P and BPI-SF	the last available assessment on or before the date of randomization	Efficacy
Laboratory tests at baseline (chemistry, hematology, testosterone, urinalysis)	the last available assessment on or before the date of start of randomized treatment	Safety for randomized treatment
Laboratory tests at screening (chemistry, hematology, testosterone, urinalysis)	the last available assessment on or before the date of ^{68}Ga-PSMA-11 dosing	Safety for ^{68}Ga-PSMA-11
ECOG score at baseline	the last available assessment on or before the date of start of randomized treatment	Safety for randomized treatment
Vital signs at baseline	the last available assessment on or before the date of start of randomized treatment or if a time assessment is captured, the 15 minutes pre-dose value on or before the date of start of randomized treatment	Safety for randomized treatment
Vital signs at screening	the last available assessment on or before the date of ^{68}Ga-PSMA-11 dosing	Safety for ^{68}Ga-PSMA-11
ECG at baseline	the last available assessment on or before the date of start of randomized treatment	Safety for randomized treatment
ECG at screening	the last available assessment on or before the date of ^{68}Ga-PSMA-11 dosing	Safety for ^{68}Ga-PSMA-11
1.For the sub-study, randomized treatment refers only to ^{177}Lu-PSMA-617+BSC/BSoC.		

Cycle 1 Day 1 (C1D1) is date of first study procedures, randomized treatment and assessments.

Date of randomization is used for the start date of "time to" endpoints for efficacy analyses.

^{68}Ga-PSMA-11 dosing is the date ^{68}Ga-PSMA-11 was administered.

Date of last randomized treatment administration is the date of last administration of randomized treatment which is the date of last administration of ^{177}Lu-PSMA-617 or date of last administration of BSC/BSoC, whichever is later. For example: if the last dose administration of ^{177}Lu-PSMA-617 is on 15APR2019, and the end of treatment decision

date for BSC/BSoC is on 17APR2019, then the date of last administration of randomized treatment is on 17APR2019.

- Date of last administration of ^{177}Lu-PSMA-617 is the last date when ^{177}Lu-PSMA-617 was administered (non-zero dose), i.e. the latest date of administration as captured on the ^{177}Lu-PSMA-617 Administration CRF page with a non-zero dose.
- Date of last administration of BSC/BSoC is the end of treatment decision date recorded on the End of Treatment – BSC/BSoC CRF.
- Date of last administration of a NAAD as study BSC/BSoC will be defined as follows:
    - = latest end date of a NAAD indicated as study BSC/BSoC (captured on concomitant medications CRF) if before date of last administration of BSC/BSoC, otherwise
    - = date of last administration of BSC/BSoC.

  For example: if the latest end date of a NAAD indicated as study BSC/BSoC is 01AUG2019 and the date of last administration of BSC/BSoC is 03OCT2019, then the date of last administration of a NAAD as study BSC/BSoC is 01AUG2019.

Last date of exposure to randomized treatment: The ^{177}Lu-PSMA-617 treatment schedule is organized in cycles of 42 days. The last date of exposure to randomized treatment is derived to be the latest date of the last date of exposure to either ^{177}Lu-PSMA-617 or BSC/BSoC. The last date of exposure to ^{177}Lu-PSMA-617 or BSC/BSoC will be derived as follows:

- The last date of exposure to ^{177}Lu-PSMA-617 is calculated as (last date of administration of Lu-PSMA-617) + (length of time interval - 1) i.e. [last date of ^{177}Lu-PSMA-617 administration + (42-1)].
- If the subject died or was lost to follow-up (i.e. discontinued early from the study) within the last date of administration of ^{177}Lu-PSMA-617 + 42 days, the last date of exposure to ^{177}Lu-PSMA-617 is the date of death or date of last contact, respectively.
- The last date of exposure to BSC/BSoC is the last date of administration of BSC/BSoC (i.e. the end of treatment decision date recorded on the End of Treatment –BSC/BSoC CRF).
- The last date of exposure to a NAAD as study BSC/BSoC is the last date of administration of a NAAD as study BSC/BSoC.

Last contact date: The last contact date is derived for patients not known to have died at the analysis cut-off date based on the latest date among the following:

- Assessment dates (e.g. laboratory, vital signs, ECOG performance status/HRQoL (e.g. FACT-P), ECG, tumor imaging, end of treatment decision, etc.).
- Medication and procedure dates including ^{177}Lu-PSMA-617 administration, concomitant medications/therapies, concurrent surgical and therapeutic procedures (including radiation therapy), post-treatment cancer-related therapies after randomized treatment discontinuation (with non-missing medication/procedure term).
- Adverse event start and end dates (with non-missing verbatim AE term present).
- "Date of Last Contact" collected on the "Long Term Follow Contact" CRF.
- Randomized treatment start/end date
- Randomization date

The last contact date is defined as the latest complete date from the above list or the cut-off date, whichever comes first. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date.

The last contact date is used for censoring of patients in the analysis of overall survival.

Time unit: A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

5.1 Study Periods and Visit Window Definitions

5.1.1 Study Periods

The study consists of 3 periods: screening, treatment (with no maximum number of cycles defined), and a follow-up period (end of treatment, long-term follow-up). Results will be presented by time point and not by period. However, the naming of the time points will reflect the period. In the investigational treatment arm, a patient will be treated with ^{177}Lu-PSMA-617 + BSC/BSoC up to a maximum of 6 cycles, and then BSC/BSoC only for the duration of the on-treatment period. Note that for cycles 1-6, cycle duration is 6 weeks, and for cycles 7 and beyond, cycle duration is 12 weeks.

5.1.2 Visit Windows

For data collected at multiple time points, the scheduled collection date/time will be used to summarize the data, unless otherwise indicated. Visits are scheduled from time of previous cycle's Day 1.

Scan assessments are scheduled from the reference date (date of first dose). Scan dates are not associated with a visit number. Dates are used for analyses and patient listings.

Unscheduled assessments will not be taken into account in summary variable calculations, except for baseline assessments and unscheduled RECIST, bone scan, PSA and HRQoL evaluations for evaluating efficacy (Section 8). All measurements will be presented in the listings.

Unless otherwise indicated, if more than one measurement (a lab result for example) exists for a patient on a particular time point/visit, the last value obtained at that time point/visit will be used when summarizing the data.

Refer to protocol section 6.1 and protocol Appendix 1 for schedules of study assessments during each study period.

5.2 Partial/Missing Dates

In general, the database requires a valid full date, including dates used for the alternate primary endpoints, rPFS and OS. However, for partial or missing dates for initial cancer diagnosis, prior therapies, and concomitant medication start dates, the rules shown below will be applied. (Concomitant medication stop dates and start and end dates for adverse events, concurrent radiotherapy, and concurrent surgical/therapeutic procedures are full date required fields.)

The imputed dates will only be used for the assignment to prior and/or concomitant medication or concurrent therapy and for deriving time since initial cancer diagnosis. The imputed dates will not be used in any other calculation and will not be listed.

For the calculation of the time since initial cancer diagnosis, the following imputation rules will be applied when the date of initial cancer diagnosis is incomplete:

- If the day is missing: first day of the month.
- If the day and month are missing: first day of January.

For the assignment of medication, therapy and procedure to prior or concomitant/concurrent collected on the Concomitant Medication/Therapy, Concurrent Surgical / Therapeutic Procedures, and Radiotherapy CRF pages, the following rules will be applied for incomplete dates:

- If start date is incomplete:
    - if end date is before the date of first dose of randomized treatment, the start date will remain missing (i.e. prior);
    - if end date is on or after date of first study drug administration or the medication is ongoing,
        - if the day is missing: the start date will be imputed with the first day of the month;
        - if the day and month are missing: the start date will be imputed with 01 January of the year.

Note: Prior cancer related therapies, procedures and medications with missing or partial dates as captured on the Prior Cancer Related Surgery, Prior Radiotherapy and Prior Cancer Systemic Therapy CRF pages will not be imputed or included in the assignment of medications, procedures or therapies to prior or concomitant. Prior cancer related therapies will be summarized separately as described in Section 7.4.

The following rule should be used for the imputation of the date of last administration (end date) for BSC/BSoC:

- If the end date is completely missing and there is no End of Treatment (EOT) page and no death date/End of Study (EOS) date, the patient is considered as on-going. The patient should be treated as on-going and the cut-off date should be used as the end date.

After imputation, compare the imputed date with start date of BSC/BSoC, if the imputed date is < start date of BSC/BSoC: Use the BSC/BSoC start date.

The following rules will be used for imputing adverse event (AE) start dates to assign as treatment emergent:

If day, month and year are missing:

- Completely missing start dates will not be imputed.

If day and month are missing:

- If partial start date year = year of randomized treatment start date then
    - If end date contains a full date and end date is earlier than randomized treatment start date then set start date = 01 January of the year
    - Else set start date = randomized treatment start date.
- If partial start date year > year of randomized treatment start date then 01 January of the year
- If partial start date year < year of randomized treatment start date then 01 July of the year

If day is missing:

- If partial start date month and year = month and year of randomized treatment start date then
    - If end date contains a full date and end date is earlier than randomized treatment start date then set start date= first day of the month and year.
    - Else set start date = randomized treatment start date.
- If partial start date month and year > month and year of randomized treatment start date then first day of the month and year
- If partial start date month and year < month year of randomized treatment start date then 15th day of the month and year

Note: If randomized treatment start date is missing, apply the same rules but use the ^{68}Ga-PSMA-11 administration date instead.

For the assignment of an adverse event as a randomized treatment-emergent adverse event, the following rules will be applied when there is a partial date of subsequent anti-cancer treatment as captured on the post-treatment anti-cancer therapies or procedures CRF pages:

- if the day is missing: if the month of the partial subsequent anti-cancer treatment is in the same month as the date of last administration of randomized treatment (see Section 5), then impute using the date of last administration of randomized treatment. Otherwise, impute using the first day of the month.

5.3 Definition of Populations

5.3.1 Efficacy Populations

- **Full Analysis Set (FAS)**: All randomized patients. Patients will be included in the treatment arm to which they were randomized regardless of actual treatment received. This is an intent to treat analysis set. This analysis set will be used for the primary analysis of OS.

- **PFS Full Analysis Set (PFS-FAS)**: All patients randomized on or after 5 March 2019. Patients will be included in the treatment arm to which they were randomized regardless of actual treatment received. This analysis set will be used for the primary analyses of rPFS and all secondary endpoints excluding ORR and DCR.

- **Response Evaluable Analysis Set**: The subset of patients in the PFS-FAS with evaluable disease by RECIST at baseline (i.e. at least one target and/or non-target lesion per independent central review radiologist assessment used as the final radiology assessment. See section 8.1 for details on how the final radiology assessment is selected.). Patients will be included in the treatment arm to which they were randomized. Soft tissue response as measured by RECIST will be assessed in this dataset. This analysis set will be used for the primary analyses of ORR and DCR.

5.3.2 Safety Populations

- **PSMA-11 Safety Analysis Set:** All patients who received a dose of ^{68}Ga-PSMA-11. This includes screened patients that are not enrolled (i.e., not randomized). Patients enrolled will be included in the treatment arm to which they were randomized.

- **FAS Safety Analysis Set:** The subset of patients in the FAS who received at least one dose of randomized treatment. Patients will be included in the treatment arm corresponding to the actual treatment received.

5.3.3 Sub-study Populations

- **PSMA-11 Sub-study Analysis Set:** All patients who received a dose of ^{68}Ga-PSMA-11 in the sub-study conducted at sites in Germany. This includes screen failure patients who are not enrolled in the sub-study.

- **Sub-study Safety Analysis Set:** All patients who received at least one dose of the investigational treatment (^{177}Lu-PSMA-617+BSC/BSoC) in the sub-study conducted at sites in Germany.

5.4 Subgroup Definitions

The following subgroups are defined for the study:

1. Stratification Factor (based on CRF data) – Inclusion of NAADs (e.g., enzalutamide, abiraterone, or apalutamide) as part of assigned BSC/BSoC treatment at start of study (Yes vs. No). See Section 5.6 for derivation.
2. Number of cycles in the ^{177}Lu-PSMA-617 + BSC/BSoC treatment arm (≤ 4 cycles vs. 5-6 cycles).
3. Stratification factor (based on CRF data) – Baseline LDH (≤ 260 IU/L vs. > 260 IU/L). See Section 5.6 for derivation.
4. Stratification factor (based on CRF data) - Presence of liver metastases at baseline (Yes vs. No). See Section 5.6 for derivation.
5. Stratification factor (based on CRF data) – ECOG score at baseline (0 or 1 vs. 2). See section for derivation.
6. Age (< 65 years vs. ≥ 65 years)
7. Race (White vs. Black or African American vs. Asian vs. Other (includes "Native Hawaiian or Other Pacific Islander", "American Indian or Alaska Native" or more than one race reported)

5.4.1 Analyses on subgroups

All subgroup analyses are to be considered exploratory and descriptive; p-values presented with efficacy results will be treated as nominal.

Efficacy analyses The alternate primary endpoints, rPFS and OS, will be summarized and analyzed by the following subgroups (defined in Section 5.4) to assess the consistency of treatment effect provided either or both primary endpoints are statistically significant:

- Inclusion of NAADs as part of assigned BSC/BSoC treatment at start of study
- Baseline LDH
- Presence of liver metastases at baseline
- ECOG score at baseline
- Age
- Race

No formal statistical test of hypotheses will be performed for the subgroups. For each subgroup, a stratified cox regression model will be used to estimate the treatment effect

stratifying for the randomization factors from IRT. When one of the stratification factors is the subgroup of interest, that factor will be excluded from the stratified model. The model will include three terms: treatment, subgroup (e.g. ECOG score at baseline) and treatment by subgroup interaction. The HR and associated confidence interval for each subgroup will be estimated from the model. Kaplan-Meier estimates as described for the alternate primary endpoints (Section 8.2.1) will also be provided excluding the log-rank test p-value. Subgroup analyses of rPFS and OS will be presented graphically using forest plots.

The efficacy analyses in subgroups will only be performed if at least 10% of patients or 10 patients are present in each class.

Key safety analyses of exposure, adverse events and clinical laboratory values will be performed as described in Section 9, on the FAS and PSMA-11 safety analysis sets (defined in Section 5.3.2) in the following subgroups (defined in Section 5.4):

- Inclusion of NAADs as part of assigned BSC/BSoC treatment at start of study (FAS Safety Analysis Set only)
- Number of cycles received in the ^{177}Lu-PSMA-617 + BSC/BSoC treatment arm (FAS Safety Analysis Set only)
- ECOG score at baseline (FAS Safety Analysis Set only)
- Age (FAS Safety Analysis Set and PSMA-11 Safety Analysis Set)
- Race (FAS Safety Analysis Set and PSMA-11 Safety Analysis Set)

The objective for carrying out these subgroup analyses is to identify potential safety issues that may be limited to a subgroup of patients, or safety issues that are more commonly observed in a subgroup of patients. Summary tables will only be performed if at least 10% of patients or 10 patients are present in each subgroup.

The results of the efficacy and safety subgroup analyses will be presented in separate tables and figures from study arm results.

Separate listings will not be created for subgroups.

5.5 Treatment Arms

The following treatment arm labels will be used in the analysis:

- Lu-PSMA-617+BSC/BSoC: ^{177}Lu-PSMA-617 + Best supportive/best standard of care (investigational treatment arm)
- BSC/BSoC only: Best supportive/best standard of care only (control arm)

5.6 General Variable Definitions

- Time to withdrew consent from ^{177}Lu-PSMA-617 (days): (Date of withdrew of consent from ^{177}Lu-PSMA-617 treatment – date of randomization + 1).
- Time to withdrew consent from BSC/BSoC (days): (Date of withdrew of consent from BSC/BSoC – date of randomization + 1).
- Time to withdrew consent from study (days): (Date of withdrew of consent from study – date of randomization + 1).
- Age (years): year of informed consent - year of birth; calculated within clinical database.

- Time since initial prostate cancer diagnosis (years): (Date of informed consent - Date of initial prostate cancer diagnosis)/(365.25). For incomplete dates, see Section 5.2.
- Weight (kg) = weight (lb) * 0.45359237
- Height (cm) = height (in) * 2.54
- BMI (kg/m^2) = weight[kg] / (height[m]^2) using weight and height at baseline.
- Best % change (where a decrease over time is desirable) = ((smallest post baseline assessment – baseline)/baseline) x 100
- Last taxane therapy treatment-free interval (months): (randomization date - last taxane therapy end date)/(30.4375). For incomplete dates, the see Section 5.2. Taxanes included are those identified as 'Taxane' per WHO Drug ATC Level 4 (e.g. cabazitaxel, docetaxel or paclitaxel).
- Baseline PSA doubling time (months): PSA doubling time will be calculated as natural log of 2 (0.693) divided by the sum of the fixed slope (common to all patients) and the random slope (specific for the patient) of the random coefficient linear model between the natural log of PSA and time of PSA measurement (Svatek et al., 2006). If the PSA doubling time is less than zero (i.e. stable, nonincreasing, or decreasing PSA levels as defined by a negative slope from the random coefficient linear model), the PSA doubling time is set to 0. PSA is collected at screening visit and for the most recent 2 PSA measurements available prior to screening. Calculations will be performed only for subjects with (1) all 3 PSA values with each value ≥ 0.2 ng/mL and (2) for which the interval between the first and last PSA values are ≥8 weeks but ≤ 12 months as stated in PCWG3 guidelines (Scher et al., 2016; Pound et al., 1999).

  For interpretation of PSA doubling time it should be noted that PCWG3 guidelines state the calculation should be based on the most recent PSA values during androgen deprivation therapy, and that 3 PSA values ≥ 0.2 ng/mL should be consecutive. These additional criteria will not be applied since the information is not available.

- Randomized Treatment (i.e. ^{177}Lu-PSMA-617 and BSC/BSoC) Exposure Variables:

  Average duration of randomized treatment cycles (months) = mean across cycles of (date of dosing for cycle n+1 – date of dosing for cycle n)/30.4375, where n=1 to total number of cycles minus 1.

  Duration of exposure (months) = (Date of last exposure to randomized treatment – Reference date + 1)/30.4375. Date of first administration to randomized treatment and date of last exposure to randomized treatment are defined in Section 5.

  For duration of exposure to ^{177}Lu-PSMA-617, the date of last exposure is the date of last exposure to ^{177}Lu-PSMA-617 and the reference date is the date of first administration of ^{177}Lu-PSMA-617.

  For duration of exposure to BSC/BSoC, the date of last exposure is the date of last exposure to BSC/BSoC and the reference date is the date of first administration of BSC/BSoC (i.e. date of C1D1).

  For duration of exposure to a NAAD as study BSC/BSoC, the date of last exposure is the date of last exposure to a NAAD as study BSC/BSoC and the reference date is the date of first administration of a NAAD as study BSC/BSoC.

Dose intensity of ^{177}Lu-PSMA-617

Dose intensity overall (GBq/month) = (actual total dose of ^{177}Lu-PSMA-617 during the study) / (actual duration of the study (months)) Note: The duration of the last cycle will be set to 6 weeks (or ~ 1.37 months = 42 /30.4375).

Planned dose intensity overall (GBq/month) = (planned total dose of ^{177}Lu-PSMA-617 during the study) / (planned duration of the study (months))

Relative dose intensity overall (%) = (dose intensity overall) / (planned dose intensity overall)

Dose intensity of ^{177}Lu-PSMA-617 per cycle

Dose intensity per cycle (GBq/cycle) = (actual total dose of ^{177}Lu-PSMA-617 during the cycle)

Planned dose intensity per cycle (GBq/cycle) = (planned total dose of ^{177}Lu-PSMA-617 during the cycle)

Relative dose intensity per cycle (%) = (dose intensity per cycle) / (planned dose intensity per cycle)

Randomization Stratification Factors based on CRF data

Stratification factor (based on CRF data) – Baseline LDH (≤ 260 IU/L vs. > 260 IU/L) is defined as the latest LDH value on or before the date of randomization as collected on the laboratory CRF page.

Stratification factor (based on CRF data) - Presence of liver metastases at baseline (Yes vs. No) is defined as at least one target and/or non-target liver lesion on or before the date of randomization and/or within 28 days of start of randomized treatment as captured on either the target or non-target lesion CRF pages.

Stratification factor (based on CRF data) – ECOG score at baseline (0 or 1 vs. 2) is defined as the ECOG score captured on the Enrollment CRF page.

Stratification Factor (based on CRF data) – Inclusion of NAADs (e.g., enzalutamide, abiraterone, or apalutamide) as part of assigned BSC/BSoC treatment at start of study (Yes vs. No) is defined as having a NAAD indicated as study BSC/BSoC (see Section 5) on or before the date of C1D1.

6. Study Patients

6.1 Patient Disposition

Sample size flow will be displayed in a consort diagram, and the following patient data will be summarized in tables.

Patient disposition for all patients who signed an informed consent:

- Number of patients who signed informed consent
- Number of patients screened
- Number of patients who were screen failures and the reason for screen failure
- Number of patients administered ^{68}Ga-PSMA-11 (PSMA-11 Safety Analysis Set)

  By treatment arm and combined:
- Number of randomized patients – Full Analysis Set
- Number of randomized patients on or after March 5, 2019 – PFS Analysis Set
    - Number (%) of patients in Response Evaluable Analysis Set
- Number of randomized patients administered study treatment (FAS Safety Analysis Set)

Enrollment by country and center will be summarized for all screened patients and also by treatment arm using the FAS.

End of treatment status and the end of study status for all patients in the FAS, PFS-FAS and in the FAS randomized prior to 5 March 2019 will be summarized, by treatment arm and combined:

- Number (%) of patients treated, not treated and still on treatment
- Number (%) of patients discontinued from ^{177}Lu-PSMA-617 and BSC/BSoC, separately and all study treatments
- Number (%) for each primary reason for discontinuation from ^{177}Lu-PSMA-617 and BSC/BSoC, separately
    - Number (%) for reason for withdrawal of consent for ^{177}Lu-PSMA-617 and BSC/BSoC, separately
    - Time to withdrew consent (in days) continuous and categorical (1,2-28, 29-56, >56)
    - Number (%) of patients continuing in long-term follow-up period (i.e. patients who agreed to long-term follow-up and have not discontinued from the study)
- Number (%) of patients discontinued from study
- Number (%) for each primary reason for discontinuation from study
    - Number (%) for reason for withdrawal of consent for ^{177}Lu-PSMA-617 and BSC/BSoC, separately
    - Time to withdrew consent (in days) continuous and categorical (1, 2-28, 29-56, >56)

6.1.1 Sub-study

Patient disposition for all patients who signed an informed consent in the sub-study will be summarized and will include the following: Number of patients who signed informed consent, Number of patients screened, Number of patients who were screen failures and the reason for screen failure, Number of patients administered ^{68}Ga-PSMA-11 (PSMA-11 Sub-study Analysis Set), Number of patients administered ^{177}Lu-PSMA-617 and BSC/BSoC (Sub-study Safety Analysis Set). End of treatment and end of study status will also be summarized as described above for all patients in the Sub-study Safety Analysis Set.

6.2 Protocol Deviations

For the FAS, major protocol deviations will be summarized for each treatment arm and overall. The details of all deviations (major and minor) will also be listed by treatment and patient ID. All Protocol deviations (major and minor) will be recorded as part of the Trial Master File (TMF).

Specific protocol deviation categories will be assigned to important deviations related to COVID-19 (e.g. missing efficacy assessments and treatment interruptions) and these will be summarized separately and flagged in the listings.

6.2.1 Sub-study

A listing of all deviations (major and minor) will be listed for the Sub-study Safety Analysis Set. Specific protocol deviations related to COVID-19 will be flagged in the listing.

6.3 Inclusion and Exclusion Criteria

For all screened patients, a summary of all inclusion criteria not met and exclusion criteria met will be provided. An additional summary will be provided for the PSMA-11 Safety Analysis Set. A listing, including the protocol version the patient was consented under and a flag for the FAS population, will be provided for all screened patients.

6.3.1 Sub-study

A listing of all inclusion criteria not met and exclusion criteria met will be provided for all screened patients in the sub-study.

6.4 Stratification Information

For the FAS,PFS-FAS and the Response Evaluable Analysis Set, the number (%) of patients in each randomization stratum based on data obtained from the IRT system and data collected on the CRF (see Section 5.6) will be summarized by treatment arm and overall. The randomization stratification factors are: LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in best supportive/standard of care (yes vs no) at time of randomization. Discordance between the stratum recorded in the IRT system and the actual stratum through data collected in the CRF will be cross-tabulated for the FAS, PFS-FAS and Response Evaluable Analysis Set and listed for the FAS.

7. Baseline Characteristics and Prior and Concurrent Therapies and Medications

All tables in Section 7 will be presented by treatment arm and for all patients combined for the FAS, PFS-FAS, the Response Evaluable Analysis Set, FAS Safety Analysis Set and the PSMA-11 Safety Analysis Set (defined in Section 5.3) unless otherwise specified. For tables using the PSMA-11 Safety Analysis Set, an additional column will be included for patients not enrolled (i.e. not randomized).

7.1 Demographic and baseline assessments

Descriptive statistics of patient characteristics at baseline will be presented for the following:

- Age (years): continuous and categorical (<65 vs. ≥65, <65 vs. ≥65-84 vs. ≥85)
- Race (White vs. Black or African American vs. Asian vs. Others (includes "Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native")

- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- ECOG performance status (0 or 1 vs. 2) Note: ECOG performance status is captured on the Enrollment CRF page and not collected at the time of screening. Thus, ECOG performance status will not be available for those not enrolled.

7.2 Baseline Disease Characteristics

Descriptive statistics of patient disease characteristics at baseline will be presented for the following variables:

- Time since initial prostate cancer diagnosis (years)
- Initial Histopathological Classification
- Initial Histopathological Grade
- Initial Gleason score
    - Categorical: 2-3,4-7,8-10, unknown
- Stage at Initial Diagnosis
- Total Sum of Target Lesions Diameters per RECIST 1.1
- Baseline Target Lesions (Yes vs. No) and Non-Target Lesions (Yes vs. No)
- Site of disease (lung (yes/no), liver (yes/no), lymph node (yes/no), bone (yes/no), other (yes/no) using target and non-target lesions or bone scan assessments (bone only); sponsor to provide categorization)
- Baseline PSA doubling time (months): continuous and categorical (≤ 6 vs. >6)
- Baseline PSA
- Baseline ALP
- Baseline LDH

Note: The baseline variables 'Total Sum of Target Lesions Diameters', 'Target Lesions and Non-Target Lesions' will be based on the data collected on target/non-target lesion assessment according to RECIST 1.1 according to local investigator assessment and documented in the CRF. 'Site of disease' will be based on the data collected on either the target/non-target lesion assessment (per RECIST 1.1) or the bone scan assessment per local investigator assessment and documented in the CRF.

7.3 Medical History

Relevant medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version used for reporting will be specified as a footnote in the applicable tables and listings.

The relevant medical conditions will be tabulated separately for active (ongoing) and not-active conditions by system organ class (SOC) and preferred term (PT). Medical history events will be marked as ongoing if still active at time of informed consent.

7.4 Prior Cancer Related Therapy

Descriptive statistics with respect to prior therapy will be displayed. A listing of all data recorded on the Prior Cancer Related Surgery, Prior Radiotherapy and Prior Cancer Systemic Therapy CRF pages will also be provided.

Prior cancer related surgery will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and prior cancer systemic therapy will be coded using the WHO Drug Global dictionary. The MedDRA and WHO Drug Global dictionary versions used for reporting will be specified as a footnote in the applicable tables and listings.

The variables to be summarized in tables are:

- Prior Prostate Cancer-related Surgery
  - Number of patients with at least one prostate cancer-related Surgery (including biopsies)
  - Prior number of prostate cancer-related surgeries/biopsies
  - Reason for prior surgery (Therapeutic, Diagnostic/Biopsy, Palliative, Other)
- Prior Prostate Cancer-related Radiotherapy
  - Number of patients with at least one Prostate Cancer-related Radiotherapy
  - Prior number of radiotherapies
  - Unique Sites
- Prior Prostate Cancer-related Systemic Therapy: All Therapies
  - Prior number of NAAD-containing regimens
  - Prior number of taxane-containing regimens
  - Reason for therapy
  - Number of unique agents
  - Type of prior therapy (by ATC Level 4 and WHO Drug preferred name). Type of prior therapy will be presented by ATC level alphabetically and preferred name is sorted within ATC class alphabetically.
- Prior Prostate Cancer-related Systemic Therapy: Last Taxane Therapy
  Last taxane therapy is defined as the last taxane as part of a taxane-containing regimen, prior to study entry.
  - Reason for Therapy
  - Number of cycles
  - Duration of therapy (months): (last taxane therapy stop date – last taxane therapy start date + 1)/30.4375. Incomplete dates will not be imputed.
  - Progression
    - PSA progression (yes, no, not applicable, unknown)
    - Bone progression (yes, no, not applicable, unknown)
    - Soft tissue progression (yes, no, not applicable, unknown)
    - Type(s) of progression (New lesions, existing lesions, new and existing lesions, not applicable, unknown)
  - Treatment-free interval (months, defined in Section 5.6)
  - Best overall response (BOR) to last taxane-therapy (Complete response (CR), Partial response (PR), Stable disease (SD), Progressive Disease (PD), Not Available, Unknown)
  - Duration of historic BOR (CR or PR) (months): (date of progression (earliest of PSA, bone or soft tissue) - date of best response (CR or PR) + 1)/30.4375. Incomplete dates will not be imputed.
  - Reason last taxane therapy ended

7.5 Sub-study

Baseline demographics and baseline disease characteristics will be summarized for the Sub-study Safety Analysis Set and will be summarized and listed for PSMA-11 sub-study analysis set. Medical history and prior cancer therapy will be listed for the PSMA-11 Sub-study Analysis Set.

8. Efficacy Evaluation

8.1 Efficacy Variable Definitions

In general, time to event and duration endpoints (e.g. rPFS), in number of days, is calculated as:
Days = event/censor date – reference date (e.g. randomization date) +1. If a patient has no assessment after first dose, censoring is at date of randomization. See Section 5 for converting time units.

Radiographic imaging will be assessed locally by each site and entered into the CRF. Additionally, patient scans will be collected for independent central review and data will be enter into the imagining CRF at the vendor. The independent central review will be used for the primary analyses of radiographic progression-free survival per PCWG3, overall response rate, disease control rate and duration of response using RECIST 1.1 and progression-free survival. The final radiology assessment as determined by the independent reviewer and described in the imagining review charter will be used for the analysis of these endpoints. At the time of analysis and prior to database lock, the two independent radiologists (radiologist 1 and radiologist 2) will each perform a global read and make a final determination of rPFS for the patient. If there is a difference in patient level determination of progressive disease (PD) between the two independent radiologists, a third radiologist will adjudicate the final assessment. The adjudicator will select which of the two independent radiologists' reads (radiologist 1 or radiologist 2) he/she agrees with more for RECIST/PCWG3 PD determination. The selected radiology read (i.e. radiologist 1 or radiologist 2) by the adjudicator will be the final radiology assessment for the patient. If there is no adjudication, the final radiology assessment defaults to radiologist 1. Refer to Imagining Review Charter for more details.

The local radiographic imaging assessment will be used for patient management at the site and will be compared to central assessments to evaluate concordance as described in the IDMC charter and mock tables. The local investigator assessment as captured on the CRF will be used as a sensitivity analysis for radiographic progression-free survival only.

8.1.1 Primary Efficacy Definitions

Overall Survival (OS) (months): (Date of death/censor - Date of randomization + 1)/30.4375. OS is defined as the time (in months) from the date of randomization to the date of death due to any cause. If the patient is not known to have died, then OS will be censored. The censoring date is date of last contact (see Section 5), i.e. the date the patient was last known to be alive).

Radiographic progression-free survival (rPFS) (months): (Date of radiographic PD/death/censor – date of randomization + 1) / 30.4375. rPFS is defined as the time (in months) from the date of randomization to the date of radiographic disease progression as outlined in PCWG3 Guidelines (Scher et al 2016; protocol Appendix 7, RECIST v1.1; FDA guidance, 2007; EMA guideline, 2012) or death due to any cause.

- Note:
  - In the investigational treatment arm, a patient continues to be in the treatment period of the study on BSC/BSoC after receiving their final dose of ^{177}Lu-PSMA-617.

- Patients are at risk of the different types of rPFS events for different lengths of time:
  - RECIST v1.1 (Soft tissue) PD can occur up through last scan, which can be during long term follow-up (LTFU).
  - Bone PD can occur up to scan prior to last scan (with confirmation at last scan), which can be during LTFU.
  - Death can occur up through 24 weeks past the last study scan, or if no post treatment scans, up to 24 weeks after the first randomized treatment dose (based on the 2 missed visits censoring rule)

- Date of radiographic progressive disease (radiographic PD) event: date of the first CT/MRI/bone scan PD/death due to any cause occurs with no more than 1 immediately prior missing assessment.
  - RECIST 1.1 PD
    - Assessment in which Overall RECIST v1.1 Response is PD
    - Date of PD is date of first appearance of the new lesion(s), if applicable.
  - Bone scan PD must be confirmed as follows (rules allow for a flare effect at the first post-treatment scan). See examples in Appendix B:
    - Rule 1 (Progression at week 8 confirmed at week 16): If there are at least two new lesions on the first post-treatment scan, they must be confirmed with at least two additional lesions on the next scan (2+2 rule). The date of progression is the date of the first post-treatment scan.
    - Rule 2 (Progression at week 16 or later confirmed at next scan): For scans after the first post-treatment scan, there must be at least two new lesions relative to the first post-treatment scan (treating as a new baseline) that remain persistent (confirmed) on a subsequent scan. The date of progression is the date of the scan that first documents the second lesion compared to first post-treatment scan.

- Date of Censoring for rPFS:
  - The censoring date is the date when the last evaluable radiographic assessment (CT/MRI/bone scan) determined a lack of progression.
  - If there were no evaluable assessments, censoring occurs at the date of randomization.
  - Patients who have 2 or more consecutive missed tumor assessments immediately prior to progressive disease (PD) or death will be censored at the date of the last evaluable tumor assessment prior to those missing tumor assessments. Study scans are every 8 weeks +/- 4 days for the first 24 weeks, then every 12 weeks +/- 4 days and are scheduled relative to date of first dose of randomized treatment. Thus, subjects are considered as having 2 missed assessments if:

• day 117 ≤ study day of event scan ≤ day 229 and time since last evaluable assessment ≥ 118 days

(2 missed visits, 117 = 16 weeks + 4 days + 1; 229 = 24 weeks + 8 weeks + 4 days + 1)

• day 230 ≤ study day of event scan ≤ day 313 and time since last evaluable assessment ≥ 146 days

(2 missed visits, 145 = 20 weeks + 4 days + 1; 313 = 24 weeks + 20 weeks + 4 days +1)

• study day of event scan ≥ day 314 and time since last evaluable assessment ≥ 174 days

(2 missed visits, 173 = 24 weeks + 4 days + 1)

8.1.2 Key Secondary Efficacy Definitions

- RECIST responses for patients with measurable disease at baseline (RECIST guidelines v1.1, Eisenhauer et al., 2009)
  - Overall Response Rate (ORR) = Proportion of patients with a best overall response (BOR) of Complete Response (CR) or Partial Response (PR). ORR is based on RECIST v1.1 response for patients with measurable disease at baseline.

    Patients with no evaluable RECIST evaluations after baseline will be considered non-responders.

    Soft tissue CR or PR needs to be confirmed at the next scan that is evaluable at least 4 weeks later. The following rules will be taken into account to define the BOR:
    - CR = at least two determinations of CR at least 4 weeks or later
    - PR = at least two determinations of PR or better (i.e. CR) at least 4 weeks or later apart (and not qualifying for CR)
    - SD = at least one Stable Disease (SD) assessment or better (i.e. CR or PR) > 6 weeks after first dose of randomized treatment (and not qualifying for CR or PR)
    - Non-CR/Non-PD = at least one non-CR/non-PD assessment (or better) > 6 weeks after first dose of randomized treatment (and not qualifying for CR or PD).
    - PD = Progressive Disease (PD) at first evaluable scan after first dose of randomized treatment (and not qualifying for CR, PR or SD)
  - Disease Control Rate (DCR) = Proportion of patients with BOR of CR, PR, SD, or Non-CR/Non-PD according to RECIST v1.1.
    - Same rules for no post baseline evaluations and for confirmation of CR and PR
    - Also, best response of SD or Non-CR/No-PD must be at least 6 weeks after date of first dose.

    Duration of response (DOR) (months) (only for patients with a tumor response of CR or PR): (Date of RECIST PD/death/censor – Date of Best Overall Response + 1)/30.4375.) DOR is defined as the duration between the date of first documented best overall response and the date of first documented radiographic progression or death due to any cause. Date of Best Overall Response is the date of the first RECIST response of CR or PR of the confirmed response endpoint Overall Response Rate. Censoring rules are the same as for rPFS, except using only soft tissue scan dates (excluding bone scan dates).
- Time to first symptomatic skeletal event (SSE, months): (Date of SSE/censor – Date of randomization + 1)/30.4375. Time to first SSE is defined as the time (in months) from the date of randomization to the date of the SSE or death from any cause. SSE date is 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 due to any cause, whichever occurs first. SSE

data for this endpoint is collected up through EOT visit.

Censoring date is date of the last study visit (on or before EOT visit).

8.1.3 Additional Secondary Efficacy Definitions

- Progression-free survival (PFS) (months): (Date of first radiographic progression/clinical progression/PSA progression/death/censor – Date of randomization + 1)/30.4375. PFS is defined as the time (in months) from the date of randomization to the date of first evidence of radiographic, clinical or PSA progression or death due to any cause, whichever occurs first. The dates of radiographic, clinical and PSA progression are defined as follows:
  - Date of radiographic progression: defined in Section 8.1.1.
  - Date of clinical progression: earliest date of assessment for when the investigator indicates clinical progression has occurred.
  - Date of PSA progression: Where a decline from baseline is documented, date that a ≥ 25% increase in PSA and an absolute increase of 2 ng/mL or more from the nadir (from all scheduled and unscheduled visits prior to the current visit being evaluated) is documented and confirmed by a second value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks of date of first dose of randomized treatment will be ignored.
    Where no decline from baseline is documented, PSA progression is defined as a ≥ 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks from the date of first dose of randomized treatment (with confirmation obtained 3 or more weeks later) as specified in PCWG3 guidelines.
  - Date of censoring for PFS: Censoring date is the same as defined for rPFS.

- PSA doubling time (months): PSA doubling time will be calculated as natural log of 2 (0.693) divided by the sum of the fixed slope (common to all patients) and the random slope (specific for the patient) of the random coefficient linear model between the natural log of PSA and time of PSA measurement (Svatek et al., 2006). If the PSA doubling time is less than zero (i.e. stable, nonincreasing, or decreasing PSA levels as defined by a negative slope from the random coefficient linear model), the PSA doubling time is set to zero. The calculation will be based on (1) latest baseline PSA measurement ≥ 0.2 ng/mL, (2) at least three consecutive (scheduled and unscheduled) post-baseline PSA values with each value ≥ 0.2 ng/mL, and (3) interval between first and last PSA values of ≥8 weeks but ≤ 12 months as stated in PCWG3 guidelines (Scher et al., 2016; Pound et al., 1999).

  If the baseline PSA value prior to first dose of randomized treatment is missing or < 0.2 ng/mL, PSA doubling time will be missing.

  For interpretation of PSA doubling time it should be noted that PCWG3 guidelines state the calculation should be based on the most recent PSA values during androgen deprivation therapy. These additional criteria will not be applied.
- PSA response: PSA response is defined as the proportion of patients who have a ≥50% decrease in PSA from baseline that is confirmed by a second PSA measurement ≥4 weeks later. All scheduled and unscheduled PSA assessments will be used to determine and confirm PSA response.
- PSA > 80% decrease: PSA ≥ 80% decrease is defined as the proportion of subjects that have a ≥80% decrease in PSA from baseline that is confirmed by a second PSA

measurement ≥4 weeks later. All scheduled and unscheduled PSA assessments will be used to determine and confirm a PSA ≥ 80% decrease.

- Duration of PSA response (only for patients with response) (months): (date of PSA progression/censor – Date of PSA response + 1)/30.4375. Duration of PSA response is defined as the duration (in months) between the date of first document PSA response (i.e. ≥50% decrease in PSA from baseline) and earliest date of PSA progression as defined above. The censoring date is the date of last PSA assessment.

8.1.4 Sub-study

For all efficacy variable derivations, the date of first dose of ^{177}Lu-PSMA-617+BSC/BSoC, as defined in Section 5, will be used as the reference date instead of the date of randomization. All efficacy derivations will be based on local investigator assessment; no central assessments will be performed.

8.2 Efficacy Analyses

The primary analysis of rPFS per independent central review will be based on the PFS-FAS while the primary analysis of OS will be based on the FAS. The analyses of the secondary efficacy endpoints will be performed on the PFS-FAS , defined in Section 5.3, except for soft tissue response (ORR and DCR) as measured by RECIST 1.1, for which the primary analysis will be performed on the Response Evaluable Efficacy Analysis Set. The randomization stratification factors from the IRT system will be used for all efficacy analyses unless otherwise specified.

All data summaries will be presented by treatment arm.

8.2.1 Primary Efficacy Analyses

The alternate primary efficacy endpoints are OS and rPFS (defined in Section 8.1.1). For the primary analysis of rPFS with an interim analysis of OS, and final analysis of OS (see Section 4), the analyses described below will be done using 1-sided tests of treatment differences. If the formal interim OS analysis is met at the pre-specified alpha level, the final OS will only be presented descriptively without statistical inference at the nominal alpha level specified in Section 3.4. However, if the interim analysis of OS is not performed, the alpha level applicable to the OS analysis will depend on the final rPFS results as described in Section 4.

Overall Survival

The null hypothesis for OS, as stated in Section 3.4, will be tested at a one-sided level of significance. The primary analysis is to test the null hypothesis and compare the two treatment arms using a stratified log-rank test stratifying for the randomization stratification factors. The alternate primary efficacy variable, OS, will be analyzed at the interim analysis and final analysis as defined in Section 4.

The primary analysis of OS at the interim and final analysis will be based on the FAS population. The OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves (including number at risk and confidence limits), median, 25th percentile, and 75th percentile and associated 99.8% confidence intervals at the interim analysis and 95% or 96% confidence intervals at the final analysis (depending on the earlier rPFS and interim OS results, Section 3.4 or depending on the final rPFS results if the interim OS analysis is not performed, Section 4) will be presented for each treatment arm. The OS Kaplan-Meier estimate along with 99.8% confidence intervals at the interim analysis and 95% or 96% confidence intervals at the final analysis, will be presented at different time points (e.g. 6, 12, and 18 months) for each treatment arm. The one-sided p-value from the log-rank test will be presented at the interim and final analysis.

A supportive analysis will be performed in terms of a stratified Cox regression model with a single covariate for randomized treatment arm, stratifying again for the randomization stratification factors. The hazard ratio for OS will be calculated, along with its 99.8% confidence interval at the interim analysis and its 95% or 96% confidence interval at the final analysis, from the stratified Cox model. The HR and CI from this model will be used as an adjunct to the primary stratified log-rank test p-value to provide the quantification of the treatment effect on OS.

The following data will be provided for the analysis of OS:

- Median follow-up (months) with 95% CI using the Kaplan-Meier method, censoring for deaths, and range
- Kaplan-Meier curves with 99.8% confidence limits at interim and 95% or 96% confidence limits at final and number at risk
- Number (%) events and censored, reason censored (alive, lost to follow-up, withdrew consent)
- Kaplan-Meier median, 25th percentile, and 75th percentile with 99.8% CIs at interim and 95% or 96% CIs at final
- Overall Survival rates and standard errors at 6 months, 12 months, and 18 months with 99.8% CIs at interim and 95% or 96% CIs at final
- Cox regression HR (active: control) with 99.8% CI at interim and 95% or 96% CI at final
- Log-rank test 1-sided p-value

Visual checks of the proportional hazard assumption will be performed based on the Plots (SURVIVAL LOGSURV LOGLOGS) generated by LIFETEST procedure in SAS. No formal analysis will be generated. If the proportional hazard assumption doesn't hold, additional methods may be explored to assess the treatment effect. Further details will be provided in a separate post-hoc analysis plan.

Radiographic Progression-Free Survival

The null hypothesis for rPFS per independent central review, as stated in Section 3.4, will be tested at a one-sided level of significance. The primary analysis is to test the null hypothesis and compare the two treatment arms using a stratified log-rank test stratifying for the randomization stratification factors. The alternate primary efficacy variable, rPFS, will be analyzed when 364 rPFS events have occurred (Section 4).

The primary analysis of rPFS will be based on the PFS-FAS population. The rPFS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves (including number at risk and confidence limits), median, 25th percentile, and 75th percentile and associated 99.2% confidence intervals will be presented for each treatment arm. The rPFS Kaplan-Meier estimate along with 99.2% confidence intervals will be presented at different time points (e.g. 3, 6, and 12 months) for each treatment arm. The one-sided p-value from the log-rank test will be presented.

A supportive analysis will be performed in terms of a stratified Cox regression model with a single covariate for randomized treatment arm, stratifying again for the randomization stratification factors. The hazard ratio for rPFS will be calculated, along with its 99.2% confidence interval, from the stratified Cox model. The HR and CI from this model will be used as an adjunct to the primary stratified log-rank test p-value to provide the quantification of the treatment effect on rPFS.

The following data will be provided for the analysis of rPFS:

- Median follow-up (months) with 95% CI using the Kaplan-Meier method, censoring for radiographic progressions or deaths, and range
- Kaplan-Meier curves with 99.2% confidence limits and number at risk

- Number (%) events and censored, reason censored (ongoing without event, event documented after 2 or more missed tumor assessments, adequate assessment not available)
- Kaplan-Meier median, 25th percentile, and 75th percentile with 99.2% CIs
- rPFS rates and standard errors at 3 months, 6 months, and 12 months with 99.2% CIs
- Cox regression HR (active: control) with 99.2% CI
- Log-rank test 1-sided p-value

Visual checks of the proportional hazard assumption will be performed based on the Plots (SURVIVAL LOGSURV LOGLOGS) generated by LIFETEST procedure in SAS. No formal analysis will be generated. If the proportional hazard assumption doesn't hold, additional methods may be explored to assess the treatment effect. Further details will be provided in a separate post-hoc analysis plan.

Sensitivity and supportive analyses for rPFS:

For all sensitivity and supportive analyses of the alternate primary endpoints, rPFS and OS, the nominal one-sided p-value will be provided without any statistical inference.

First Sensitivity analysis of rPFS: This sensitivity analysis is the same as the primary rPFS analysis (Section 8.1.1) except with additional rPFS events as follows:

- Includes events regardless of intervening missed assessments.
- Bone PDs are indicated by one of the following per PCWG3 guidelines:
  - Rule 1 (Progression at week 8 and confirmed at week 16): same as Rule 1 described in Section 8.1.1.
  - Modified Rule 2 (Progression at week 16 or later without confirmation): PD can still only occur at the second post treatment scan or later. The date of bone PD is the date when there are at least two new lesions relative to the first post-treatment scan without confirmation.
- Includes all radiographic PD and deaths captured in the study, including scans not centrally read that are captured on the LTFU CRF page.

This sensitivity analysis will use the PFS-FAS population and will compare the two treatment arms using the same analysis conventions described in Section 8.2.1.

Second Sensitivity analysis: This sensitivity analysis is the same as the primary rPFS analysis except with additional censoring as follows:

- Deaths occurring after start of a new anti-cancer therapy will be censored at start date of new therapy.

This sensitivity analysis will use the PFS-FAS population and will compare the two treatment arms using the same analysis conventions described in Section 8.2.1.

Third Sensitivity analysis: This sensitivity analysis is the same as the primary rPFS analysis except rPFS will be defined from the date of first dose of randomized treatment. This sensitivity analysis will use the PFS-FAS population and will compare the two treatment arms using the same analysis conventions described in Section 8.2.1.

Fourth Sensitivity analysis: This sensitivity analysis is the same as the primary rPFS analysis except using local investigator assessments. This sensitivity analysis will use the PFS-FAS population and will compare the two treatment arms using the same analysis conventions described in Section 8.2.1.

Sensitivity analyses to assess the impact of COVID-19:

The impact of missing PCWG3 (bone scans) and/or RECIST assessments on the primary rPFS analysis caused by COVID- 19 will be evaluated by the existing first sensitivity analysis.
The following analyses of rPFS will be used to estimate the treatment effect in the absence of the COVID-19 virus:

- Analysis as per the primary rPFS analysis but censoring COVID-19 related deaths at the last adequate assessment prior to the death.
- An analysis as per the 'first sensitivity analysis' but censoring COVID-19 related deaths at the date of death.

For the analyses above, the patients with COVID-19 related deaths will be determined in a blinded fashion by clinical review of the data and will be documented prior to database lock.
The same analyses conventions used for the primary analyses of rPFS, as described in section 8.2.1, will be performed (without p-values).

Supportive analyses of rPFS:

rPFS will be derived in all patients randomized (FAS population) using the same conventions as described in Section 8.1.1 but will consider patients randomized before March 5, 2019 who withdrew consent from the study (i.e. no further data on radiographic progression is available) as (1) censored at time of withdrawal and (2) a rPFS event at the time of withdrawal.

The following data will be summarized using the FAS:

- (1): Number (%) rPFS events (radiographic PD, deaths) and censored, reason censored (ongoing without event, withdrew consent, event documented with two or more missed tumor assessments, adequate assessment not available)
- (2): Number (%) rPFS events (radiographic PD, deaths, withdrew consent) and censored, reason censored (ongoing without event, withdrew consent, event documented with two or more missed tumor assessments, adequate assessment not available)

Missing tumor assessments: The number of patients with at least one missing/not evaluable tumor assessment (TA) based on independent central review will be presented together with the following breakdown categories: number of patients with 1, 2, 3, 4, 5, >5 missing/not evaluable TAs. The purpose of this analysis is to gain an insight as to whether the TAs have been carried out in accordance with the protocol and to understand if any meaningful discrepancies exist between the pattern of missing assessments by treatment arms. Timing of all tumor assessments will be depicted graphically and displayed by treatment arm.

Since the planned tumor assessments are every 8 weeks in the first 24 weeks from C1D1 and every 12 weeks thereafter, the following time windows (in weeks) will be constructed for each patient from the date of randomization: (note the open parenthesis such as (12, 20] indicates that week 12 doesn't belong to this interval and week 12+1 day belongs to that interval)

- Until ~24 weeks post randomization [0, 12], (12, 20], (20, 28]
- After ~24 weeks post randomization (28, 42], (42, 54], (54, 66], …

where '0' is the patient's date of randomization. Every time-window (with the exception of the initial, broader one) is centered at the scheduled time of a TA, i.e., around week 16, week 24 for second and third window respectively, etc. A patient will be considered 'at risk' of missing a TA for any one of these time-windows if the patient either:

- is 'on study' for at least the first 4 weeks of the time-window for the first 24 weeks (8 weeks for the first time window), or at least the first 6 weeks of time-window thereafter, i.e., if the patient is ongoing at the time of the scheduled TA, or
- discontinued treatment due to documented disease progression within the specific time window.

For example, if a patient discontinued due to documented disease progression during Week 24, then the patient would have been 'at risk' of a missing/not evaluable TA for the [20, 28] week time window.

For the purpose of this analysis, 'not evaluable' TAs (i.e., evaluations with an overall tumor response of 'not evaluable' per central independent review) will be considered to be missing. However, a clear distinction between 'truly missing' and 'present but not evaluable' needs to be made in the derived dataset to allow for both a combined analysis, i.e. missing and not evaluable treated the same, and separate analyses.

TAs performed after a documented radiographic disease progression per independent central review will not be considered. In other words, the final time-window for which a patient would be at risk of a missing/not evaluable scan would be that during which the documented radiographic progression occurred.

For patients without documented radiographic progression per independent central review, all TAs are considered up to the earliest of the following dates: death, the analysis cut-off, discontinuation due to disease progression, withdrawal of consent or loss to follow-up.

Concordance between local and central review: A summary on censoring reasons will be produced for rPFS by investigator and central radiology. The censoring patterns will be compared between investigator and central review. A comparison of rPFS event type/censor between local radiology review and central radiology review will be provided using the PFS-FAS population.

Sensitivity and supplementary analyses for OS:

Supplementary analysis of OS:

A supplementary descriptive analysis of OS will be performed using the PFS-FAS population. This analysis will use the same analysis conventions described in Section 8.2.1 but will be descriptive with the nominal p-value presented.

Sensitivity analyses to assess the impact of COVID-19:
The following analyses of OS will be used to estimate the treatment effect in the absence of the COVID-19 virus:

- Analysis as per the primary OS analysis but censoring COVID-19 related deaths at the date of death.

For the analyses above, the patients with COVID-19 related deaths will be determined in a blinded fashion by clinical review of the data and will be documented prior to database lock.

The same analyses conventions used for the primary analyses of OS, as described in section 8.2.1, will be performed (without p-values).

Subgroup analyses for rPFS and OS:

If either of the primary efficacy analyses of the alternate endpoints are statistically significant, the alternate primary endpoints of rPFS and/or OS will be summarized for subgroups, as specified in Section 5.4.1. Subgroup analyses of rPFS and OS will be presented graphically using forest plots.

8.2.2 Key Secondary Efficacy Analyses

Refer to Section 8.2 for analysis sets and presentation of summary statistics. To control the overall Type I error rate, if either alternate primary endpoint is met (see Section 4), then the key secondary endpoints will be assessed using the Hochberg closed test procedure at the alpha level applicable to the successful alternate primary endpoint. This procedure is reasonable given the positive correlation between the key secondary endpoints.

The alpha level applicable to the analysis of the key secondary endpoints will depend on the statistically significant results of the final rPFS or the statistically significant results of OS at either the interim or final analysis as follows:

Analysis of Key Secondary Endpoints at Interim and Final OS Analysis

	Final rPFS/Interim OS Analysis			**Final OS Analysis**	
Scenario	**Final rPFS 1-sided p-value**	**Interim OS 1-sided p-value**	**2-sided alpha (CI) for Key Secondary Endpoints**	**Final OS 1-sided p-value**	**2-sided alpha (CI) for Key Secondary Endpoints**
A	p<0.004	p<0.001	0.01 (99%)	Not re-tested[1]	Not re-tested[2]
B	p<0.004	NS	Not tested[3]	p<0.024	0.048 (95.2%)
				NS	Not tested[4]
C	NS	p<0.001	0.002 (99.8%)	Not re-tested[1]	Not re-tested[2]
D	NS	NS	Not tested[3]	p<0.02	0.040 (96%)

NS: Not statistically significant at pre-specified alpha level.
CI: Confidence interval

1. Final OS will not be re-tested if the interim OS is met. The final OS results will be presented descriptively including 95% CI and the nominal p-value.
2. The key secondary endpoints will not be re-tested if the final OS is met however, the results will be presented descriptively including 95% CI and the nominal p-value.
3. The key secondary endpoints will not be tested if interim OS is not met however, the results will be presented descriptively including 95% CI and the nominal p-value.
4. If the key secondary endpoints are tested when final OS is not met using the successful rPFS 1-sided (2-sided) alpha level of 0.004 (0.008), there will be, at most, a type I error inflation of 0.004 because the rPFS alpha level has already been allocated to the final OS test. Therefore, if final OS is not met, the key secondary endpoints will only be presented descriptively including 95% CI and the nominal p-value.

Analysis of Key Secondary Endpoints at Final rPFS/Final OS Analysis

	Final rPFS/Final OS Analysis		
Scenario	**Final rPFS 1-sided p-value**	**Final OS 1-sided p-value**	**2-sided alpha (CI) for Key Secondary Endpoints**
A	p<0.004	p<0.025	0.05 (95%)
B	p<0.004	NS	Not tested[1]
C	NS	p<0.021	0.042 (95.8%)
D	NS	NS	Not tested[2]

NS: Not statistically significant at pre-specified alpha level.
CI: Confidence interval

1. If the key secondary endpoints are tested when final OS is not met using the successful rPFS 1-sided (2-sided) alpha level of 0.004 (0.008), there will be, at most, a type I error inflation of 0.004 because the rPFS alpha level has already been allocated to the final OS test. Therefore, if final OS is not met, the key secondary endpoints will only be presented descriptively including 95% CI and the nominal p-value.
2. The key secondary endpoints will not be tested if final OS is not met however, the results will be presented descriptively including 95% CI and the nominal p-value.

A table summarizing the results of the Hochberg closed test procedure will be provided indicating the applicable alpha level used.

Key secondary endpoints subject to Type I error control:

1. RECIST response: ORR and DCR
2. Time to SSE

Time to Symptomatic Skeletal Event

Time to SSE (defined in Section 8.1.2) will be summarized and analyzed in the same manner as described for rPFS (both primary and supportive analyses using the alpha levels and confidence intervals as described in the table above) using the PFS-FAS, except using 2-sided p-values from the stratified log-rank test as the primary comparison. An additional analysis will be done on the FAS population using the same methods as for the primary analysis.

Overall Response and Disease Control Rate

Percent change of sum of diameters of target lesions (in mm) from baseline per independent central review will be summarized as follows:

- Continuous variable summaries of baseline and best % change from baseline

Overall response rate and disease control rate per independent central review (defined in Section 8.1.2) will be analyzed using logistic regression with a single covariate for randomized treatment arm and stratification for the randomization stratification factors. The following will be reported:

- Odds ratio (active: control) with CI as described in the table above
- The associated 2-sided p-value
- DOR will be displayed using Kaplan-Meier curves, median, 25th percentile, and 75th percentile with 95% CIs, number (%) events and censored, and will be analyzed using mixture distribution methodology (Ellis et al. 2008) outlined below.

The primary analysis of RECIST ORR and DCR will be on the Response Evaluable Analysis Set.

Mixture distribution analysis for duration of response

Duration of Response (DOR) per independent central review will be analyzed in the Response Evaluable Analysis Set using mixture distribution methodology (Ellis et al. 2008). To avoid an inflated estimate of duration of response that occurs when estimating only in the subset of patients that have a response, the following methods, paraphrasing from Ellis et al., will be used. Treatment arm differences in duration of response will be analyzed using a mixture distribution to test the hypothesis that the expected duration of response (EDoR) is equal for the experimental treatment, E, and the control treatment, C, that is:

$$\text{Ho: } R = EDoR_E/EDoR_C = 1 \text{ versus } \text{Ha: } R = EDoR_E/EDoR_C \neq 1 \quad (1)$$

The test will be performed as follows.

(i) Estimate the proportions of patients with RECIST response as

$$p_E = r_E/N_E \text{ and } p_C = r_C/N_C \quad (2)$$

Where r_E and r_C are the number of patients responding to treatment arms E and C;

N_E and N_C are the number of all patients in each treatment arm.

(ii) Estimate the mean duration of response in each treatment arm, M_E and M_C, and their standard errors, using a time to event probability distribution, in responding patients, some of which may be censored in response. This can be done using SAS PROC LIFEREG for distributions such as the exponential, the Weibull, the gamma, the Normal, and the log Normal. The choice in the distribution will be made based upon overall data (ignoring randomized treatment arm) prior to the planned analysis after the database is locked.

(iii) Combine the estimates from step (i) and (ii) to calculate estimates of R and Var[ln(R)]. Then assess the difference between treatment arms E and C using the test statistic:

$$z = \frac{\ln\left(\hat{R}\right)}{\sqrt{\widehat{\text{Var}}\left[\ln\left(\hat{R}\right)\right]}}$$

8.2.3 Additional Secondary Efficacy Analyses

Refer to Section 8.2 for analysis sets and presentation of summary statistics. The Additional Secondary Endpoints will be assessed and presented at the nominal 5% level, i.e., there will be no alpha control applied at the planned analyses as described in Section 4. These endpoints are PFS, Biochemical Response (PSA response endpoints, LDH and ALP assessments), Health-related QoL, and Health Economics. Analysis will be performed on the PFS-FAS population

8.2.3.1 Progression-free Survival Analysis

PFS (defined in Section 8.1.3), will be summarized and analyzed in the same manner as those described for the alternate primary endpoint rPFS using the PFS-FAS, except using 2 sided p-values from the Cox regression model instead of the p-value from the Log-Rank test. Radiographic progressions per independent central review will be used. No sensitivity analyses will be performed for PFS. Additionally, the following will be presented:

- Number and % of PFS events that are due to death, radiographic progression, clinical progression (including the primary criteria of clinical progression), and PSA progression

8.2.3.2 Biochemical Response Analysis

All biochemical response analyses will be performed using the PFS-FAS. PSA, ALP, and LDH values will be summarized descriptively as follows:

- Continuous variable summary statistics for baseline, each time point, and % change from baseline for each treatment arm
- Plots of the mean (±standard error) values over time for PSA, ALP, and LDH.
- Summary statistics of PSA doubling time with 95% CI for the mean PSA doubling time
- Summary statistics of maximum % change from baseline
- Categorical variable summary statistics and 95% CIs of PSA response (≥50% decrease and PSA $\geq$ 80% decrease)
- Waterfall plot of the maximum % change from baseline in PSA for each patient
- Duration of PSA response (≥50% decrease) will be presented descriptively the same as DOR (Section 8.2.2).

Unscheduled labs will not be included in tables but will be provided in listings.

Treatment arm differences of % change from baseline in PSA, ALP, and LDH across all time points will be analyzed using mixed effects general linear models for repeated measures, under the assumption of Missing at Random (MAR). The fixed effects will include treatment arm, time (as a categorical variable), treatment by time interaction, and randomization stratification factors. An unstructured variance-covariance matrix for the repeated measures for a single patient will be used. In case of problems with fitting the model, as an alternative, a heterogeneous Toeplitz and AR(1) structures will be considered to reduce the number of parameters of the model. If necessary for the model fit, the outcome variables might be transformed. Details of any transformations used will be provided in the CSR. The differences in least square means between the treatment arms and corresponding 95% confidence interval at selected time points will be presented.

For PSA response, analyses will be the same as those described for binary outcome ORR (Section 8.2.2).

Duration of PSA response will be analyzed using a mixture distribution analysis, as described for DOR (Section 8.2.2).

8.2.3.3 *Quality of Life (QoL) Analysis*

For QoL analyses, patient reported outcomes (PROs) will be assessed using the questionnaires EQ-5D-5L, FACT-P, and BPI-SF.

Analyses will be done on the PFS-FAS, and all results will be reported by treatment arm. QoL measures are collected on Day 1 of each treatment cycle and at the EOT visit. Analyses over time will include time up through EOT visit.

For analysis of each outcome, only patients with a baseline value and at least one post baseline time point will be included. As with all efficacy analyses, main models will be adjusted for randomization stratification factors. Type I error is not controlled in the multiple health related QoL analyses. Thus, all p-values presented will be unadjusted and are nominal and descriptive.

8.2.3.3.1 EQ-5 Dimension-5 Level (EQ-5D-5L) Questionnaire

The EQ-5D-5L is shown in protocol Appendix 9. The higher the EQ-VAS score, the better the QoL. The higher the EQ-5D items, the worse the QoL.

Description and Scoring

The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-VAS records the respondent's self-rated health on a vertical, visual analogue scale.

Each of the five dimension-scales contain five levels, with level 1 indicating no problems, level 2 indicating slight problems, level 3 indicating moderate problems, level 4 indicating severe problems, and level 5 indicating unable to/extreme problems.

The EQ-VAS is scored by assigning an integer value, ranging from 0 (Worst imaginable health state) to 100 (Best imaginable health state), corresponding to the mark placed by the patient on the VAS. Ambiguous answers (e.g., two marks placed on the scale by a patient) should be treated as missing values.

Scale name	**Number of items**	**Item range***
Descriptive System Dimension		
Mobility	1	1-5
Self-Care	1	1-5
Usual Activities	1	1-5
Pain/Discomfort	1	1-5
Anxiety/Depression	1	1-5
Health State Evaluation		
EQ-VAS*	1	0-100

* EQ-VAS is a continuous visual analog scale, with integer scores ranging from 0 to 100.

A utility score will be obtained by using a weighted combination of the levels of the five dimension-scales. The weights are based on value sets which are country-specific. The country specific code for the U.K. will be used for all sites in this study since the health economics modeling will target the U.K. population for developing the core economic model. Each patient's 5 digit health states code (response to question 1,2,3,4, and 5

concatenated (ex., 41325 results in a utility score of 0.193)) is converted to a utility score using the EQ-5D-5L value set, available in the cross-walk index value calculator which can be downloaded from the web site https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation/crosswalk-index-value-calculator/ . (Scroll to the bottom of the web page and download the Excel file. Use the sheet labelled 'EQ-5D-5L Value Sets.')

Since utility score depends on the combination of all items' responses, any missing response results in a missing utility score. If a patient dies, for analysis he will be assigned a score of 0 on the date of death. In the U.K. value set, utility scores ranges from the lowest possible score for a living patient of -0.594 (when all responses are '5') to 1 (when all responses are '1').

Analysis

For each of the five dimension-scales, frequency count and percentage of each reporting level (1 to 5) over time will be presented.

Utility score and EQ-VAS, will be summarized as continuous variables and will be presented for each time point. For EQ-VAS and Utility score, a plot of the mean values with standard errors by treatment group at each time point (showing number of subjects at each visit), will be constructed.

The proportion of patients and associated 95% CI who experience any improvement relative to baseline in utility score (an increase of .001 or more) at any time up through EOT will be summarized for each treatment.

Similarly, the proportion of patients with worsening relative to baseline, indicated by no change or any decrease in score, will be summarized.

Time to worsening for utility score is defined as the time (in months) from randomization to the first occurrence of worsening in score relative to baseline (no change or any decrease), clinical disease progression (excluding radiographic and PSA progression), or death, whichever is earlier. If no event is experienced, the censoring date will be time of the last QoL assessment.

Survival curves for the time to worsening (months) for each treatment arm will be computed using the Kaplan-Meier method. The two treatment arms will be compared using a cox regression analysis stratified for randomization stratification factors (LDH $\leq$ 260 UI/L vs $>$, liver metastases (yes vs no), ECOG (0-1 vs 2), Inclusion of NAAD in BSC/BSoC at time of randomization (yes vs no)). The 25th percentile of and median time to worsening will be presented, in case less than 50% of subjects experienced worsening for some variables.

Change from baseline in utility score will also be analyzed using general linear models for repeated measures. Baseline value (as a continuous variable), treatment arm, time (as visit number), treatment by time interaction, baseline by time interactions, and randomization stratification factors as main effects will be the fixed factors. A general (unstructured) variance-covariance matrix for the repeated measures for a single patient will be used. In case of problems with fitting the model, as an alternative, a heterogeneous Toeplitz and AR(1) structures will be considered to reduce the number of the parameters of the model. The differences in least square means between the treatment arms and corresponding 95% confidence interval at selected time points will be presented.

8.2.3.3.2 FACT-P

The Functional Assessment of Cancer Therapy – Prostate (FACT-P) is shown in protocol Appendix 10. The higher the FACT-P score (for all subscales and total scales), the better the QoL.

Description

Scale/Sub-scale Name	Number of Items	Scale Range	FACT-P Item numbers	Threshold for worsening*
Subscale				
Physical Well-Being (PWB)	7 items	0-28	GP1-GP7	3
Social/Family Well-Being (SFWB)	7 items	0-28	GS1-GS7	3
Emotional Well-Being (EWB)	6 items	0-24	GE1-GE6	3
Functional Well-Being (FWB)	7 items	0-28	GF1-GF7	3
Prostate Cancer Subscale (PCS)	12 items	0-48	All items in "Additional Concerns" section	3
PCS pain-related subscale (PRS)	4 items	0-16	P1, P2, P3, GP4	2
FACT Advanced Prostate Symptom Index-8 (FAPSI-8)**	8 items	0-32	GP1, GP4, GE6, C2, P2, P3, P7, P8	3
Total Scale				
Trial Outcomes Index (TOI) score	3 subscales	0-104	PWB, FWB, PCS	9
FACT-G (General)	4 subscales	0-108	PWB, SFWB, EWB, FWB	9
FACT-P Total	39 items	0-156	All	10

*Minimally important difference for both 1) decrease from baseline for within subject change and 2) between group differences for treatment comparisons.

** Symptom index of important clinician-rated symptoms/concerns to monitor when assessing value of treatment for advanced prostate cancer (FAPSI-8; Yount et al. 2003)

Scoring

Scoring of FACT-P subscales and total scores (Trial Outcome Index (TOI), FACT-G Total Score (G for general), and FACT-P Total Score (P for prostate)) are shown below. These are from the FACT-P Scoring Guidelines (Version 4). Item codes in scoring guidelines are shown on the FACT-P form in Appendix 10 of the protocol.

FACT-P Instructions:

1) Record answers in "item response" column. If missing, mark with an X
2) Perform reversals as indicated, and sum individual items to obtain a score.
3) Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4) Add subscale scores to derive total scores (TOI, FACT-G, FACT-P).
5) Handling missing items. The FACT scale is considered to be an acceptable indicator of patient quality of life as long as **overall item response rate** is greater than 80% (e.g., at least 32 of 39 FACT-P items completed). In addition, a total score should only be calculated if ALL of the component subscales have valid scores. For subscales, as long as **more than** 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc), prorate the subscale score by following the scoring instructions below, producing an observed sum weighted by the inverse of the proportion of observed items.

Subscale	Item Code	Reverse item?		Item response		Item Score
Physical Well-Being (PWB)	GP1	4	-		=	
	GP2	4	-		=	
	GP3	4	-		=	
Score range:	GP4	4	-		=	
0-28	GP5	4	-		=	
	GP6	4	-		=	
	GP7	4	-		=	
				Sum individual item scores:		
				Multiply by 7:		
				Divide by number of items answered:		= PWB subscale score
Social/Family Well-Being (SFWB)	GS1	0	+		=	
	GS2	0	+		=	
	GS3	0	+		=	
	GS4	0	+		=	
Score range:	GS5	0	+		=	
0-28	GS6	0	+		=	
	GS7	0	+		=	
				Sum individual item scores:		
				Multiply by 7:		
				Divide by number of items answered:		= SFWB subscale score
Emotional Well-Being (EWB)	GE1	4	-		=	
	GE2	0	+		=	
	GE3	4	-		=	
Score range:	GE4	4	-		=	
0-24	GE5	4	-		=	
	GE6	4	-		=	
				Sum individual item scores:		
				Multiply by 6:		
				Divide by number of items answered:		= EWB subscale score
Functional Well-Being (FWB)	GF1	0	+		=	
	GF2	0	+		=	
	GF3	0	+		=	
Score range:	GF4	0	+		=	
0-28	GF5	0	+		=	
	GF6	0	+		=	
	GF7	0	+		=	
				Sum individual item scores:		
				Multiply by 7:		
				Divide by number of items answered:		= FWB subscale score

Subscale	Item Code	Reverse item?		Item response		Item Score
Prostate Cancer Subscale (PCS)	C2	4	-		=	
	C6	0	+		=	
	P1	4	-		=	
Score range: 0-48	P2	4	-		=	
	P3	4	-		=	
	P4	0	+		=	
	P5	0	+		=	
	P6	4	-		=	
	P7	4	-		=	
	BL2	4	-		=	
	P8	4	-		=	
	BL5	0	+			
				Sum individual item scores:		
				Multiply by 12:		
				Divide by number of items answered:		= PC Subscale score

To derive a FACT-P Trial Outcome Index (TOI):
Score range: 0-104

_____ + _____ + _____ = _____ = FACT-P TOI
(PWB score) *(FWB score)* *(PCS score)*

To derive a FACT-G Total score:
Score range: 0-108

_____ + _____ + _____ + _____ = _____ = FACT-G Total score
(PWB score) *(SFWB score)* *(EWB score)* *(FWB score)*

To derive a FACT-P Total score:
Score range: 0-156

_____ + _____ + _____ + _____ + _____ = __ = FACT-P Total score
(PWB score) *(SFWB score)* *(EWB score)* (FWB *score*) (PCS *score*)

To derive Pain-related subscale (PRS):

Subscale	Item Code	Reverse item?		Item response		Item Score
Pain-related subscale	P1	4	-		=	
	P2	4	-		=	
	P3	4	-		=	
Score range: 0-16	GP4	4	-		=	
				Sum individual item scores:		
				Multiply by 4:		
				Divide by number of items answered:		= PR Subscale score

To derive FACT Advanced Prostate Symptom Index-8 (FAPSI-8):

Using the 8 items GP1, GP4, GE6, C2, P2, P3, P7, P8, do the following:

Reverse code individual items as needed following guidelines in scores above.

Sum individual item scores.

Multiply by 8.

Divide by the number of items answered.

Analysis

For each FACT-P related total scale and subscale described in the table in the Description section above, will be summarized as continuous variables and will be presented for each time point. A plot of the mean values with standard errors by treatment group at each time point (showing number of subjects at each visit), will be constructed for FACT-P total scale only.

Subscale analysis criteria:
When a treatment difference in the time to worsening in FACT-P total score results in a $p < 0.05$, the FACT-P total subscales defined above (PWB, SFWB, EWB, FWB, PCS) will be analyzed to determine which are associated with the differences.

The proportion of patients that experience improvement relative to baseline in FACT-P total score indicated by a $\geq$10 point increase at any time up through EOT will be summarized as described in Section 8.2.3.3.1 for EQ-5D-5L utility score, and subsequently for the subscales when the .05 criteria described above is met.

The proportion of patients that experience worsening relative to baseline in FACT-P total score indicated by a $\geq$10 point decrease will be summarized similarly.

Time to worsening for FACT-P total score is defined as the time (in months) from randomization to the first occurring of a $\geq$10 point decrease in FACT-P compared to baseline, clinical disease progression (excluding radiographic and PSA progression), or death. If no event is experienced, the censoring date will be time of the last QoL assessment.

Survival analyses will be conducted as described in Section 8.2.3.3.1 for EQ-5D-5L utility score, and subsequently for the subscales when the .05 criteria described above is met.

Change from baseline in FACT-P total score will also be analyzed using general linear models for repeated measures produced as described in Section 8.2.3.3.1for EQ-5D-5L utility score, and subsequently for the subscales (PWB, SFWB, EWB, FWB, PCS) when the .05 criteria described above is met.

The same analyses as described for FACT-P total score will be performed for the PRS, FAPSI-8, TOI, and FACT-G, except using the appropriate threshold values as defined in the Description table above and plots for TOI and FACT-G only. No subscale analyses will be performed if $p<0.05$.

8.2.3.3.3 BPI-SF

The Brief Pain Inventory - Short Form (BPI-SF) is shown in protocol Appendix 8. The higher the BPI-SF score, the worse the pain.

Description and Scoring

The BPI-SF consists of 4 questions regarding pain intensity, 2 questions on the use of analgesics, and 7 questions on how the level pain has interfered with the subject's life. Intensity items consist of an 11-response rating scale scored from 0 ("No Pain") to 10 ("Pain As Bad As You Can Imagine"). Interference items consist of scores from 0 ("Does Not Interfere") to 10 ("Completely Interferes").

Scale Name	Number of Items	Scale Range	BPI-SF Item numbers	Threshold for worsening*
Individual Item Scales				
Worst pain intensity	1	0-10	3	Either of ≥30% of baseline or ≥2-point increase**
Least pain intensity	1	0-10	4	
Average pain intensity	1	0-10	5	
Pain intensity right now	1	0-10	6	
Summary Scales				
Pain Intensity Scale	4	0-10	3-6	≥30% of baseline
Pain Interference Scale	7	0-10	9a-9g	≥30% of baseline

*Minimally important difference for both 1) increase from baseline for within subject change and 2) between group differences for treatment comparisons.

**Analysis of worst pain intensity is included in Section 8.2.3.4 Health Economics Analysis as time to disease related pain (TDRP).

BPI-SF Intensity is the mean of non-missing items of the 4 items in the table above, if there are 3 or more items not missing; otherwise this scale is set to missing.

BPI-SF Interference scale is the mean of non-missing items of the 7 items in the table above, if there are 4 or more items not missing; otherwise this scale is set to missing.

Analysis

The Pain Intensity Scale, Pain Interference Scale, and the four individual pain intensity items in the table above, will be summarized as continuous variables and will be presented for each time point. A plot of the mean values with standard errors by treatment group at each time point (showing number of subjects at each visit), will be constructed for Pain Intensity Scale, Pain Interference Scale and Worst Pain Intensity Scale, only.

Time to worsening of Worst Pain Intensity (item 3), also called Time to Disease Related Pain (TDRP), Pain Intensity Scale, and Pain Interference Scale are defined as the time (in months) from randomization to the first occurring of 1) an increase of worsening threshold (in the table above) compared to baseline, 2) clinical disease progression (excluding radiographic and PSA progression), or 3) death. If no event is experienced, the censoring date will be time of the last BPI-SF assessment.

Survival analyses of time to worsening of Worst Pain Intensity, Pain Intensity Scale, and Pain Interference Scale will be conducted as described in Section 8.2.3.3.1 for EQ-5D-5L utility score.

Additionally, the time to improvement following initial pain worsening in Pain Intensity Scale and Pain Interference Scale will be analyzed using mixture distribution methodology described in Section 8.2.2. Time to pain improvement is defined as time from worsening of intensity or interference to a score $\leq$ baseline.

Change from baseline in Worst Pain Intensity, Pain Intensity Scale, and Pain Interference Scale will also be analyzed using general linear models for repeated measures as described in Section 8.2.3.3.1 for EQ-5D-5L utility score.

8.2.3.4 Health Economics Analysis

The health economics analysis will be done by a separate vendor and is not a part of this SAP; however, data relating to health resource utilization, feeding into the health economics analysis, will be summarized using the PFS-FAS as described in this section. All data relating to health resource utilization will be listed.

Health resource utilization data will be used to support health economic evaluations. Study specific analyses will focus on descriptive statistics of the variables described below occurring during the randomized treatment period and will be summarized by treatment arm as described in Section 5 for categorical and continuous variables. Survival analyses of time to disease-related pain and time to first use of opioid analgesics will be conducted similarly as described in Section 8.2.3.3.1 for EQ-5D-5L utility score.

1. Hospital admissions
    - Number of hospitalizations both as a categorical variable and a continuous variable
    - Hospitalizations (yes/no) (admitted as in-patient)
    - LOS per hospitalization episode will be estimated and the total LOS in the hospital per patient will be summarized.
    - Total Number of symptomatic skeletal events (SSEs; includes symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to

relieve bone pain; captured in 3 CRFs: Adverse Events, Concurrent Surgical/Therapeutic Procedures, and Radiotherapy)

- Number of hospitalizations for SSEs

2. Duration of time in hospital following ^{177}Lu-PSMA-617 administration (hours) is the time span of patient discharge as captured on the ^{177}Lu-PSMA-617 administration CRF.
3. Concomitant drug category use (frequency of administration, dose (listed only); total number of days administered = end date-start date + 1). The list of concomitant drugs as captured on the concomitant medication/therapy CRF page to include in each category will be pre-specified and flagged prior to the pre-planned analyses.
    (1) Bisphosphonates (including but not limited to zoledronic acid, alendronic acid, etc.), denosumab, and other bone targeted therapies)
    (2) Corticosteroids for systemic use
    (3) Antifungals for systemic use (i.e. ketoconazole)
    (4) ESA (erythropoietin stimulating agents, i.e. epoetin alfa)
    (5) Granulocyte macrophage colony-stimulating factor (GM-CSF)
    (6) Novel androgen axis drugs (NAADs; i.e. enzalutamide, abiraterone, apalutamide)
    (7) Antiemetics
    (8) Opioid analgesics use for cancer-related pain
        1. Time to disease-related pain (TDRP or Time to worsening of Worst Pain Intensity as defined in Section 8.2.3.3.3)
        2. Time to first use of opioid analgesics (TFOA, defined below)
4. Therapeutic interventions (frequency; total number of days administered = end/stop date – start date + 1)
    - Local external beam radiotherapy, including palliative external radiation as captured on the concurrent radiotherapy CRF page.
    - Blood transfusion (full blood or derivates). The list of concomitant blood tranfusions captured on the concomitant medication/therapy CRF page to include will be pre-specified and flagged prior to the pre-planned analyses.

Variable definitions:

Time to first use of opioid analgesic (TFOA) – TFOA is defined as days from randomization to the first occurrence of first need of pain and opioid analgesic use (OAU) as indicated in concurrent medications), clinical disease progression (excluding radiographic and PSA progression), or death. If no event is experienced, censoring date is the later of date of last visit and last concomitant medication recorded.

8.2.4 Sub-study

At the time of the final analysis of cumulative safety data of the sub-study patients (Section 4.2), limited efficacy data (excluding patient reported outcomes) will be summarized

descriptively (i.e. no hypothesis testing will be performed) for the ^{177}Lu-PSMA-617+BSC/BSoC arm using the Sub-study Safety Analysis Set.

9. Safety Evaluation

Safety analyses will be presented using the PSMA-11 Safety Analysis Set or the FAS Safety Analysis Set except for study drug exposure (specifics in Section 9.1), ^{68}Ga-PSMA-11 adverse events (PSMA-11 Safety Analysis Set only), randomized treatment adverse events and adverse events during long-term follow-up (FAS Safety Analysis Set only) and prior/concurrent/post-therapies (specifics in Section 9.5, 9.6 and 9.7). Safety analyses of laboratory values and vital signs using the PSMA-11 Safety Analysis Set will only include assessments done at screening.

For the PSMA-11 and FAS safety analysis sets, tables will show results by treatment arm and for all patients combined. For the PSMA-11 Safety Analysis Set, an additional column will be included for patients not enrolled (i.e. not randomized).

Listings will be created by treatment arm.

9.1 Extent of Exposure

<u>^{68}GA-PSMA-11 Exposure</u>

For the PSMA-11 Safety Analysis Set, the variables to be summarized for ^{68}GA-PSMA-11 exposure are:

- ^{68}GA-PSMA-11 activity injected-decay corrected dose (MBq)
- ^{68}GA-PSMA-11 activity injected-decay corrected dose per body weight (MBq/kg)

<u>Randomized Treatment Exposure, Summary of Cycles</u>

For the FAS Safety Analysis Set, summary of treatment cycles variables to be included are:

Randomized treatment exposure, for both treatment arms:

- Duration of exposure to randomized treatment (months) (definition in Section 5.6)
- Number of cycles started per patient (both as categorical and continuous variable)
- Average duration of randomized treatment cycles (months) (definition in Section 5.6)
- Number of patients with at least one cycle delayed
- Number of cycles delayed with reasons for delay

^{177}Lu-PSMA-617 exposure, for the Lu-PSMA-617 + BSC/BSoC arm:

- Number of patients with at least one dose interrupted (omitted) with the reasons for interruption overall and by cycle
- Number of patients with at least one dose reduced with the reasons for dose reduction overall and by cycle

<u>Randomized Treatment Exposure, By Cycle and Across Cycles Combined</u>

^{177}Lu-PSMA-167 exposure, for the Lu-PSMA-617 + BSC/BSoC arm

For the FAS Safety Analysis Set investigational treatment arm, ^{177}Lu-PSMA-167 exposure variables to be summarized (definitions in Section 5.6) are:

- Cumulative dose (GBq) of patient for the entire study overall
- Dose intensity per cycle (GBq/cycle) for each cycle
- Dose intensity (GBq/month) for the entire study overall
- Relative cycle dose intensity (%) for each cycle
- Relative dose intensity (%) for the entire study overall

BSC/BSoC exposure, for both treatment arms

For the FAS Safety Analysis Set (both treatment arms), variables to be tabulated for BSC/BSoC for the entire study and for each treatment cycle are:

- Concomitant medications indicated as study BSC/BSoC, coded using WHO Drug Global dictionary. The WHO Drug Global dictionary version used for reporting will be specified as a footnote in the applicable tables and listings. A pre-specified list of concomitant medications, based on the interventions allowed as BSC/BSoC per protocol (protocol section 5.2) will be used to indicate and flag concomitant medications as study BSC/BSoC. The BSC/BSoC flag captured on the CRF will not be used to identify concomitant medications indicated as study BSC/BSoC.

- Concurrent procedures other than radiotherapy indicated as study BSC/BSoC, coded using MedDRA. The MedDRA version used for reporting will be specified as a footnote in the applicable tables and listings. The BSC/BSoC flag captured on the CRF will be used to identify concurrent procedures other than radiotherapy indicated as study BSC/BSoC.

- Concurrent radiotherapy indicated as study BSC/BSoC. The BSC/BSoC flag captured on the CRF will be used to identify concurrent radiotherapy indicated as study BSC/BSoC.

Additionally, a summary of the number (%) of patients who received a NAAD as study BSC/BSoC, type of NAAD received (by WHO Drug preferred name) and duration of exposure will be provided by treatment arm and overall using the FAS Safety Set. All concomitant medications, concurrent procedures and radiotherapies flagged as study BSC/BSoC will be listed.

9.1.1 Sub-study

^{68}GA-PSMA-11 exposure will be summarized using the PSMA-11 Sub-study Analysis Set. Study treatment and ^{177}Lu-PSMA-617 exposure will be summarized as described above using the Sub-study Safety Analysis Set.

9.2 Adverse Events and Deaths

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and system organ class (SOC) and will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE criteria [v5.0]). The MedDRA version used for reporting will be specified as a footnote in the applicable tables and listings.

9.2.1 Definition of Treatment Emergent Adverse Events (TEAEs)

A ^{68}Ga-PSMA-11 TEAE is defined as an AE that was not present prior to dosing with ^{68}Ga-PSMA-11 but appeared following dosing, or was present at time of dosing but worsened during or after dosing.

The treatment-emergent period will be defined as the period from the date of ^{68}Ga-PSMA-11 dosing up to 6 days after the date of ^{68}Ga-PSMA-11 dosing as long as prior to the first dose of ^{177}Lu-PSMA-617 for the investigational arm and prior to Cycle 1 Day 1 for the BSC/BSoC arm.

AEs reported as "possibly", "probably", or "definitely" related to ^{68}Ga-PSMA-11 that occur beyond the 6-day reporting window but occur before the initiation of randomized treatment are also ^{68}Ga-PSMA-11 TEAEs. Unrelated ^{68}Ga-PSMA-11 AEs that occur beyond 6 days will not be TEAEs.

Randomized treatments

A randomized treatment TEAE is defined as an AE that was not present prior to initiation of randomized treatment, defined as first dose of ^{177}Lu-PSMA-617 for the investigational arm and Cycle 1 Day 1 for the BSC/BSoC arm, but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated).

The treatment-emergent period will be defined as the period from the date of initiation of randomized treatment up to 30 days after the date of the last administration of randomized treatment or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

9.2.2 General Convention

Any treatment-emergent event as defined in Section 9.2.1 missing the assessment of relatedness will be considered study drug-related.

In case a patient experienced the same event more than once, the maximum toxicity grade will be presented.

In all AE tables except the ones presented by Cycles, multiple occurrences of the same adverse events occurring in one individual are counted only once.

In all AE tables presented by cycle of onset, multiple occurrences of the same adverse events occurring in one individual within one cycle are counted only once.

AE summaries for ^{68}GA-PSMA-11 and Randomized Treatment will include AEs occurring during the treatment-emergent period whereas AE summaries for Long-term Follow up will include new and existing AEs during the long-term follow-up period captured on the Long-Term Follow up CRF page. All AEs will be listed along with the information collected on those AEs. AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary SOC and for each PT using MedDRA coding. The total number of events will also be provided. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE toxicity grades for the same preferred term will be summarized under the maximum CTCAE toxicity grade recorded for the event. AE with missing CTCAE toxicity grade will be included in the total across all grades of the summary table.

In all AE summaries, the primary SOC will be presented alphabetically and the PTs will be sorted within primary SOC in descending frequency. The sort order for the PT will be based on their frequency in the ^{177}Lu-PSMA-617+BSC/BSoC arm for randomized treatment and long-term follow-up AE summaries and the frequency in the overall column for ^{68}Ga-PSMA-11 AE summaries.

9.2.3 ^{68}Ga-PSMA-11 Adverse Events

A summary table using the PSMA-11 Safety Analysis Set including the number of patients with at least one event, and the total number of events will be presented for the following variables:

- TEAE[1]
- serious TEAE[1]
- grade 3/4/5 TEAE[2]
- drug-related TEAE[1]
- serious drug-related TEAE[1]
- drug-related grade 3/4/5 TEAE[2]
- fatal TEAE[2]

[1]AE variables to be tabulated by SOC and PT by grade including a total across all grades and all grades 3/4/5.

[2]AE variables to be tabulated by SOC and PT.

A summary of serious and non-serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

A listing will include the participant identifier, age, race, verbatim, preferred term, duration of the event, toxicity grade, seriousness, action taken regarding ^{68}Ga-PSMA-11, outcome, relationship to study drug, and start and end date. Non-treatment-emergent adverse events will be flagged.

9.2.3.1 Sub-study

Similar analyses as described in Section 9.2.3 will be done using the PSMA-11 Sub-study Analysis Set.

9.2.4 Randomized Treatment Adverse Events

A summary table using the FAS Safety Analysis Set including the number of patients with at least one event, and the total number of events will be presented for the AE variables below.

- TEAE[1, 3]
- Serious TEAE[1, 3]
- Grade 3/4/5 TEAE[2]
- Drug-related TEAE[1]
- Serious drug-related TEAE[1]
- Drug-related grade 3/4/5 TEAE[2]
- TEAE leading to reduction of ^{177}Lu-PSMA-617 dose[1] or of BSC/BSoC[1]
- TEAE leading to interruption of ^{177}Lu-PSMA-617 treatment[1] or of BSC/BSoC[1]
- TEAE leading to permanent discontinuation of ^{177}Lu-PSMA-617 treatment[1] or of BSC/BSoC[1]
- Fatal TEAE[2]

[1]AE variables to be tabulated by SOC and PT by grade (including a total across all grades and all grades 3/4/5).

[2]AE variables to be tabulated by SOC and PT.

[3]TEAEs are to be tabulated by SOC and PT, including a total across all grades and all grades 3/4/5), and by ^{177}Lu-PSMA-167 cycle of onset.

A summary of serious and non-serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

A listing for each patient will include the same variables as mentioned above in Section 9.2.3 except will include action taken regarding ^{177}Lu-PSMA-617 and action taken regarding Best supportive/Best standard of care. Non-treatment-emergent adverse events will be flagged.

To help evaluate the impact of the COVID-19 virus on the safety, the incidence of COVID-19 related adverse event preferred terms will be presented incorporating (a) COVID-19 related adverse events with an onset date prior to the start of the outbreak (i.e. pre-2020) and (b) all COVID-19 related adverse events occurring before the data cut-off. All COVID-related AEs will be included in the listings.

9.2.4.1 Sub-study

Similar analyses as described in Section 9.2.4 (excluding TEAEs by ^{177}Lu-PSMA-167 cycle of onset due to the small number of patients) will be performed using the Sub-study Safety Analysis Set. All AEs will be listed including COVID-related AEs.

9.2.5 Deaths

Summaries of all deaths, including deaths within 6 weeks and 3 months (12 weeks) of randomization (using the FAS and FAS Safety Set), on-treatment deaths or within 30 days of randomized treatment discontinuation (using the FAS Safety Set), and ^{68}Ga-PSMA-11 on-treatment deaths (using the PSMA-11 Safety Analysis Set) will be provided including the primary cause of death (including deaths due to COVID-19). All deaths will be listed and will include the details for 'other cause'.

9.2.5.1 Sub-study

A summary of all deaths and on-treatment deaths will be provided using the Sub-study Safety Analysis Set. A summary of ^{68}Ga-PSMA-11 on-treatment deaths will be provided using the PSMA-11 Sub-study Analysis Set. All deaths in the sub-study will be listed.

9.2.6 Long-term Follow up Adverse Events

During LTFU, new and existing AEs will continue to be followed, capturing only AE term and grade.

A summary table including the number of patients with at least one event, and the total number of events will be presented for the AE variables captured on the Long Term Follow-Up – Adverse Events CRF page below using the FAS Safety Analysis Set.

- AE[1]
- Grade 3/4/5 AE[2]
- Fatal AE[2]

[1]AE variables to be tabulated by SOC and PT by grade including a total across all grades and all grades 3/4/5.

[2]AE variables to be tabulated by SOC and PT.

A listing will include the participant identifier, age, race, verbatim, preferred term, and toxicity grade.

9.2.6.1 Sub-study

A listing of all AEs captured during long-term follow up will be provided.

9.2.7 Safety Topics of Interest

A safety topic of interest is a grouping of adverse events that are of scientific and medical concern specific to ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617. These groupings are defined on a program level using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. The groups are defined according to the MedDRA terms defined in the program Case Retrieval Strategy (CRS) document and will be summarized. The latest version of the CRS document available at the time of the analyses will be used. For each specified safety topic of interest, number and percentage of patients with at least one event of the safety topic of interest occurring during the on treatment period will be summarized.

Summaries of these Safety Topics of Interest during ^{68}Ga-PSMA-11 treatment period (using PSMA-11 Safety Analysis Set) and during randomized treatment period (using the FAS Safety Analysis Set) will be provided by treatment arm, (specifying grade, SAE, relationship, leading to treatment discontinuation (if applicable), leading to dose interruption (if applicable), hospitalization, death etc.).

A listing of all grouping levels down to the MedDRA preferred terms used to define each Safety Topic of Interest will be generated.

9.2.7.1 Sub-study

A listing of Safety Topics of Interest during ^{68}Ga-PSMA-11 treatment period (using PSMA-11 Sub-study Analysis Set) and during ^{177}Lu-PSMA-617treatment period (using the Sub-study Safety Analysis Set) will be provided.

9.3 Clinical Laboratory Determination

Local labs will perform hematology, chemistry, serum testosterone, and urinalysis testing. The following laboratory parameters are to be summarized:

• Testosterone			
• Chemistry	sodium potassium total and direct bilirubin ALP AST ALT	LDH blood urea nitrogen[2] creatinine urate phosphate chloride	Bicarbonate[1] calcium glucose total protein albumin
• Urinalysis[3]	urine pH protein content specific gravity appearance and color	glucose ketones	
• Hematology	complete blood count (white blood cell count and differential) red blood cell count hemoglobin hematocrit platelet count		

1. total carbon dioxide or equivalent is acceptable
2. urea is acceptable
3. Urinalysis parameters are only collected at screening. Appearance and color, glucose, ketones and protein content are captured as free-text and will only be listed (not summarized).

Hematology, chemistry and serum testosterone laboratory values and the change from baseline during randomized treatment will be summarized for each parameter by visit. Shift tables of the worst post-baseline on-treatment laboratory toxicity based on CTCAE v5.0 grading relative to baseline will be presented as well as the frequency of grade 3/4 toxicities. For laboratory tests where CTCAE grades are not defined, shift tables using low/normal/high/(low and high) classification to compare baseline to worst post-baseline on-treatment value will be presented. Frequency statistics for qualitative laboratory parameters will also be presented by visit. The summaries will include all laboratory assessments collected no later than 30 days after the last administration of randomized treatment (i.e. on-treatment).

The mean (±standard error) values over time will be plotted for hemoglobin, hematocrit, platelets, WBC, absolute neutrophil count, AST, ALT, BUN, and creatinine by treatment arm.

An additional summary of hematology, chemistry and serum testosterone laboratory values at screening will be provided for the PSMA-11 Safety Analysis Set.

Listings of all laboratory data and listings of laboratory toxicities ≥ Grade 3 will be provided. Values outside of the laboratory's reference range will be flagged. Values collected later than 30 days after the last randomized treatment date will also be flagged. If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X. The patient listings will indicate the CTCAE grade.

During long-term follow up, hematology and chemistry are collected every 3 months. Shift tables of the worst post-baseline laboratory toxicity during LTFU based on CTCAE v5.0

grading relative to baseline will be presented as well as the frequency of grade 3/4 toxicities. For laboratory tests where CTCAE grades are not defined, shift tables using low/normal/high/(low and high) classification to compare baseline to worst post-baseline value during LTFUP will be presented. These will be displayed in similar tables separately for LTFU using the FAS Safety Analysis Set. Laboratory assessments collected during LTFU will be included in the listings.

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values will be summarized by treatment arm using the FAS Safety Analysis Set only. The following summaries will be produced during the randomized treatment and long-term follow up, separately:

- ALT > 3xULN
- ALT > 5xULN
- ALT > 8xULN
- ALT > 10xULN
- ALT > 20xULN
- AST > 3xULN
- AST > 5xULN
- AST > 8xULN
- AST > 10xULN
- AST > 20xULN
- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- Concurrent ALT > 3xULN & TBL > 2xULN
- Concurrent AST > 3xULN & TBL > 2xULN
- Concurrent ALT or AST > 3xULN & TBL > 2xULN
- Concurrent ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN
- Concurrent ALT or AST > 3xULN & TBL > 2xULN & ALP ≥ 2xULN

For single parameters (e.g. AST>3xULN), the worst value post-baseline is considered. For the combination of various parameters, the lab values need to be from the same assessment (concurrent assessment). Concurrent measurements are those occurring on the same date. In addition, a listing of all TBL, ALT, AST and ALP values for subjects with a post-baseline TBL > 2xULN, ALT> 3xULN or AST > 3xULN will be provided using the FAS Safety Analysis Set. Values meeting the criteria during randomized treatment and LTFU will be listed.

9.3.1 Sub-study

Shift tables as described above will be presented using the Sub-study Safety Analysis Set. Listings of all laboratory data will be provided using the PSMA-11 Sub-study Analysis Set. Hematology and chemistry data collected during long-term follow up will be listed using the Sub-study Safety Analysis Set.

9.4 Vital Signs, Physical Findings, and ECG

Vital signs (blood pressure, pulse, and respiratory rate) and weight, will be summarized by visit (observed and change from baseline during randomized treatment). The summaries will include all assessments collected no later than 30 days after the last

administration of randomized treatment (i.e. on-treatment). For those treated with ^{177}Lu-PSMA-617, the vital sign taken at 15 minutes pre-dose during the first 6 cycles will be used for the summary of changes by visit. The number (%) of patients with notable vital signs during randomized treatment (high/low) will be presented by treatment arm and overall using the FAS Safety Analysis Set. An additional summary of vital signs at screening will be provided using the PSMA-11 Safety Analysis Set. The clinically notable vital sign criteria are provide below:

Vital Sign (unit)	**Clinically notable criteria**	
	Above normal value	**Below normal value**
Weight (kg)	Increase > 10% from baseline	Decrease > 10% from baseline
Systolic blood Pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood Pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of >25%

ECOG performance status and change from baseline classified as improved, no change and worsened will be summarized as a categorical variable by visit for the FAS Safety Analysis Set only.

ECG will be done at screening only. Overall ECG interpretation will be summarized. PR, RR, and QRS Intervals and heart rate will be summarized as continuous variables. QTc, as captured on the CRF, will not be summarized as the correction method is site specific and will be recorded in the TMF. QTc will only be included in the listings with the correction method "unspecified." The number (%) of patients with notable ECG values at screening will also be presented using the PSMA-11 Safety Set and the FAS Safety Set:

Clinically notable ECG values	
HR	• Value of > 120 bpm • Value of < 40 bpm
PR	• Value of > 200 ms
QRS	• Value of > 110 ms

Abnormal findings from physical examinations will be assessed for clinical significance and will be presented in the AE listings and tables as appropriate.

9.4.1 Sub-study

Notable vital signs (high/low) will be summarized using the Sub-study Safety Analysis Set. Vital signs will be listed using PSMA-11 sub-study analysis set. ECOG performance status will be listed using the Sub-study Safety Analysis Set. The analyses pertaining to the ECG data collected in the sub-study will be described in a separate SAP. These analyses will be performed by a separate vendor and are not part of this SAP.

9.5 Prior and Concurrent Surgical and Therapeutic Procedures

Prior and concurrent surgical and therapeutic procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized using the FAS Safety

Set. The MedDRA version used for reporting will be specified as a footnote in the applicable tables and listings.

Procedures as captured on the Concurrent Surgical / Therapeutic Procedures CRF page will be classified as prior and/or concurrent. Prior procedures are all procedures occurring before the date of the first randomized drug administration (prior to first dose of ^{177}Lu-PSMA-617 for the investigational arm and prior to Cycle 1 Day 1 for the BSC/BSoC arm). Concurrent procedures are all procedures continued or started on or after the date of the first randomized study drug administration but not more than 30 days after end of randomized treatment Assignment will be done after applying the imputation rules as specified in Section 5.2 for partial start and end dates.

Prior and concurrent surgical and therapeutic procedures will be tabulated separately by system organ class and preferred term. All procedures will be listed including all details from the concurrent surgical and therapeutic procedures CRF page.

9.5.1 Sub-study

Prior and/or concurrent surgical and therapeutic procedures during ^{177}Lu-PSMA-617+BSC/BSoC treatment period will be summarized using the Sub-study Safety Analysis Set.

9.6 Prior and Concurrent Radiotherapy

Descriptive statistics of prior and concurrent radiotherapy as captured on the Radiotherapy CRF page will be summarized using the FAS Safety Set. Prior radiotherapy are all radiotherapies occurring before the date of the first randomized drug administration (prior to first dose of ^{177}Lu-PSMA-617 for the investigational arm and prior to Cycle 1 Day 1 for the BSC/BSoC arm). Concurrent radiotherapy are all radiotherapies that continued or started on or after the date of the first administration of randomized treatment but no more than 30 days after the end of randomized treatment. Assignment will be done after applying the imputation rules as specified in Section 5.2 for partial start and end dates.

Prior and concurrent radiotherapy will be tabulated separately. The variables to be summarized in tables are:

- Number of patients with at least one prior (concurrent) radiotherapy
- Number of prior (concurrent) radiotherapies
- Unique Sites

All prior and concurrent radiotherapies recorded on the Radiotherapy CRF will be listed.

9.6.1 Sub-study

Prior and concurrent radiotherapy will be summarized using the Sub-study Safety Analysis Set.

9.7 Prior and Concomitant Medications

Prior and concomitant medications during the randomized treatment period will be coded using the WHO Drug Global dictionary and will be summarized using the FAS Safety Analysis Set. The WHO Drug Global dictionary version used for reporting will be specified as a footnote in the applicable tables and listings.

The medications as captured on the Concomitant Medication/Therapy CRF page will be classified as prior and/or concomitant during randomized treatment period. Prior medications are all medications taken before the date of the first randomized drug administration (prior to first dose of ^{177}Lu-PSMA-617 for the investigational arm and prior to Cycle 1 Day 1 for the BSC/BSoC arm). Concomitant medications are all medications continued or started on or after the date of the first randomized study drug administration but not more than 30 days after end of randomized treatment. Assignment will be done

after applying the imputation rules as specified in Section 5.2 for partial start and end dates.

The number and percentage of patients will be tabulated by ATC level 4 and Preferred Term, by prior or concomitant medications during randomized treatment period.

Prior and concomitant medications during the ^{68}Ga-PSMA-11 dosing period will be summarized separately using the PSMA-11 Safety Analysis Set. Medications as captured on the Concomitant Medication/Therapy CRF page will be classified as prior and/or concurrent to ^{68}Ga-PSMA-11 dosing. Medications prior to ^{68}Ga-PSMA-11 dosing are all medications occurring before the date of ^{68}Ga-PSMA-11 dosing. Medications concurrent to ^{68}Ga-PSMA-11 dosing are all medications continued or started on or after the date of ^{68}Ga-PSMA-11 but not more than 6 days after administration or start of randomized treatment.

A listing of all medications recorded on the concomitant medications CRF page will provide details including flag for Best Supportive/Best Standard of Care, indication, dose, route, frequency, and start and stop dates.

9.7.1 Sub-study

Prior and/or concurrent medications during ^{177}Lu-PSMA-617+BSC/BSoC treatment period will be summarized using the Sub-study Safety Analysis Set. Prior and concomitant medications during the ^{68}Ga-PSMA-11 dosing period will be listed using the PSMA-11 Sub-study Analysis Set.

9.8 Post-Treatment Cancer-related Therapy

Drug or other non-radiation therapies will be classified according to WHO Drug Global dictionary and will be summarized using the FAS. The WHO Drug Global dictionary version used for reporting will be specified as a footnote in the applicable tables and listings.

The number and percentage of participants receiving a post- treatment cancer-related therapy since discontinuation of randomized treatment will be displayed by preferred term within each ATC. Post-treatment anti-cancer therapy summaries will be sorted alphabetically by preferred term within ATC class.

Best response to post treatment anti-cancer therapy and type of response will be summarized.

Descriptive statistics of post-treatment radiotherapy received after the randomized treatment period will be summarized. The variables to be summarized in tables are:

- Number of patients with at least one post-treatment radiotherapy
- Number of post-treatment radiotherapies
- Unique Sites

A listing of all data recorded on the post-treatment disease assessment, post-treatment radiotherapy, and post-treatment anti-cancer therapies CRFs will be provided.

9.8.1 Sub-study

Post-treatment cancer-related therapy since discontinuation of ^{177}Lu-PSMA-617+BSC/BSoC will be listed using the Sub-study Safety Analysis Set.

10. REFERENCES

- Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating Clinically Meaningful Changes for the Functional Assessment of Cancer Therapy—Prostate: Results from a Clinical Trial of Patients with Metastatic Hormone-Refractory Prostate Cancer. Value in Health 12(1): 124-129, 2009.
- Cella D, Zagari MJ, Vandoros C, Gagnon DD, Hurtz HJ, and Nortier JWR. Epoetin Alfa Treatment Results in Clinically Significant Improvements in Quality of Life in Anemic Cancer Patients When Referenced to the General Population. JCO 21(2): 366-373, 2003
- Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, dd. June 14, 2010 - National Cancer Institute.
- Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer 2009;45:228-247.
- Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. Contemp Clin Trials. Jul 2008;29(4):456-65.
- European Medicines Agency. Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man. Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials. Science Medicines Health. 13 Dec 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137126.pdf
- EQ-5D-5L User Guide: https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf
- Fitzmaurice G, Laird N, Ware J. Applied Longitudinal Analysis, 2004; https://content.sph.harvard.edu/fitzmaur/ala/
- Lin DY, Feuer EJ, Etzioni R, Way Y. Estimating medical costs from incomplete follow-up data. Biometrics. Jun 1997; 53(2):419-434. http://dlin.web.unc.edu/files/2013/04/LinEA97.pdf
- Mihaylova B, Briggs A, O'Hagan A, Thompson SG. Review of statistical methods for analyzing healthcare resources and costs. Health Economics. 2011; 20:897-916. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3470917/pdf/hec0020-0897.pdf
- Newcombe RG. Interval estimation for the difference between independent proportions: Comparison of eleven methods. Statistics in Medicine 1998;17:873–90.
- Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. Journal of the American Medical Association. 05 May 1999; 281(17): 1591-1597.
- Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Work Group 3. J Clin Oncol 2016;34(12):1402–18.
- Svatek RS, Shulman M, Choudhary PK, Benaim E. Critical Analysis of Prostate-Specific Antigen Doubling Time Calculation Methodology. Cancer 2006;106:1047–53.
- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research. Guidance for industry. Clinical trial endpoints for the approval of cancer

drugs and biologics. May 2007.
https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf

- Yount S, Cella D, Banik D, Ashraf T, Shevrin D. Brief assessment of priority symptoms in hormone refractory prostate cancer: The FACT advanced prostate symptom index (FAPSI). Health and Quality of Life Outcomes. 21 Nov 2003; 1:69
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC305353/pdf/1477-7525-1-69.pdf

Appendix A: Quality of Life Questionnaire References

References regarding EQ-5D-5L

Full scoring details for the EQ-5D-5L are described at the site https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

The derivation and performance of the value set for conversion of questionnaire responses to a utility score is described in the manuscript http://eprints.whiterose.ac.uk/121473/1/Devlin_et_al-2017-Health_Economics.pdf

Repeated measures analysis of PROs: Fitzmaurice G, et al., 2004. (full reference in Section 10)

References regarding the FACT-P

Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System, version 4.0 (November 1997) is located on-line at www.facit.org

Minimally important differences in FACT-P related scales

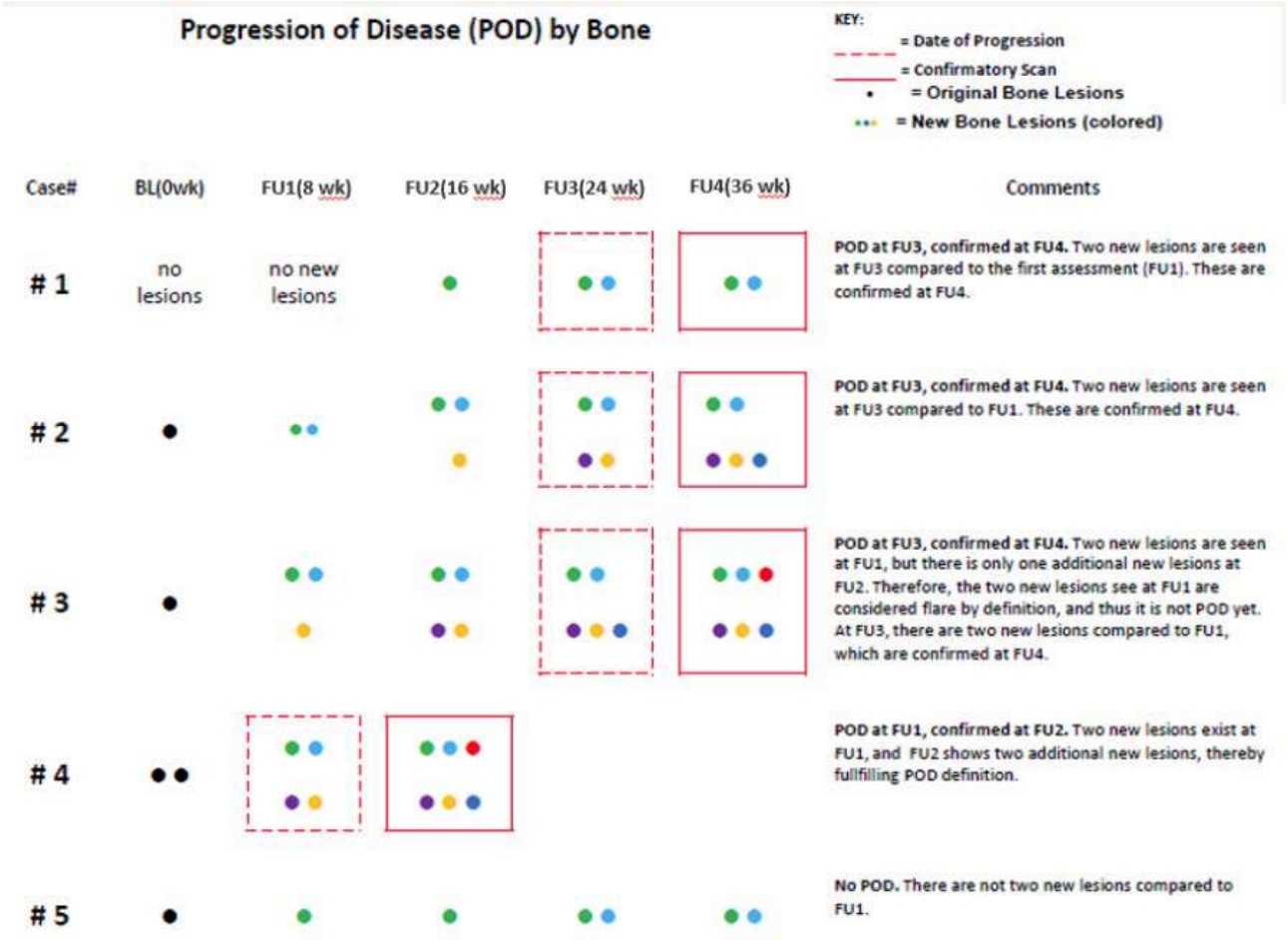
Score type	Source	Total possible score	Range of MID	MID used in analyses
Physical well-being (PWB)	Cella et al. Qual Life Res 2002; 11: 207-221; Yost et al. Eval Health Prof 2005; 28: 172-191	28	2-3	3
Social/family well-being (SFWB)	Yost et al. Eval Health Prof 2005; 28: 172-191	28	2-3	3
Emotional well-being (EMB)	Yost et al. Eval Health Prof 2005; 28: 172-191	24	2-3	3
Functional well-being (FWB)	Cella et al. Qual Life Res 2002; 11: 207-221; Yost et al. Eval Health Prof 2005; 28: 172-191	28	2-3	3
FACT-G total score[a]	Cella et al. Value Health 2009; 12: 124-129	108		9
Prostate cancer subscale (PCS) score	Cella et al. Value Health 2009; 12: 124-129	48	2-3	3
FACT-P total score[b]	Cella et al. Value Health 2009; 12: 124-129	156	6-10	10
Pain-related subscale (PRS)[c]	Cella et al. Value Health 2009; 12: 124-129	16	1-2	2
TOI score	Yost et al. Eval Health Prof 2005; 28: 172-191	104	5-9	9
FAPSI-8	Cella et al. Value Health 2009; 12: 124-129	32	2-3	3
Notes: (a) Composite of the scores on the PWB+SFWB+EWB+FWB (b) Composite of the scores PWB+SFWB+EWB+FWB+PCS. Impaired QoL has been defined arbitrarilty in published literature as a FACT-P score of ≤122-128, of the 156 maximum score (c) Calculated using the 4 questions on pain in the FACT-P, but the scores are reversed				

such that higher score indicates better health and less pain. A decrease in score signifies pain progression

Change thresholds for deterioration on the FACT-P PCS, TOI, and FACT-P Total scales are based upon Cella et al. 2009, which provided clinically meaningful change estimates in a prostate cancer sample based upon an anchoring methodology. The FACT-G scales (PWB, SFWB, EWB, FWB, and the FACT-G) were not addressed in that article, and so the clinically meaningful change estimates for those scales are derived from an earlier reference, which reports normative values from a large sample from the general population for the FACT-G scales. Standard errors (once normalized back to their original scales from the zero to 100 scale reported in the article) for the PWB, SFWB, EWB, FWB, and the FACT-G were 5.35, 6.80, 4.78, 6.83, and 18.04, respectively. Taking one half the standard deviation is equivalent to finding a 0.5 effect size. Using this distributional technique to find the clinically meaningful change estimates produced values of about 3 points for PWB, SFWB, EWB, and FWB and about 9 points for the FACT-G.

Appendix B: Examples of Date of Bone Progression

Cases 1, 2 and 3 represent the date of bone progression by Rule 2 and Case 4 represents the date of bone progression by Rule 1, as described in Section 8.1.1. In Case 5, even though there are 2 new lesions compared to baseline at Week 24, there is only 1 new lesion compared to Week 8 thus indicating that there is no bone progression.



Revision History

Version	Date	Revised by:	Changes
1.0	08 Jun 2018	[redacted]	Original version
2.0	24 Oct 2019	[redacted]	Title page: Updated reviewers/approvers of SAP based on current SOP. Section 1: Updated the List of Abbreviations and Definitions of Terms based on current changes to document. Section 2: Updated protocol version and clarified that decisions will be made prior to database lock. Section 2.1: Revised based on changes reflected in protocol amendment v4.1 (e.g. updated Time to first SSE definition based on protocol amendment and clarified the analysis sets to be used for the key secondary endpoints). Section 3.1, 3.3 and 3.4: Revised based on changes reflected in protocol amendment v4.1 including the dosimetry, PK and ECG sub-study in Germany. Section 3.2: Minor clarifications on the type of randomization system used and who is blinded/unblinded. Added language indicating that patients enrolled into the sub-study will not be randomized. Section 3.3: Added additional secondary objective for the sub-study. Section 4 and 4.1: Revised based on changes reflected in protocol amendment v4.1. Section title revised. Section 5: Minor clarifications and updates including the adding the definition of time units. Added a definition for randomized treatment for the main study and the sub-study. Sections 5.1.1, 5.2, 6.2, 8.1 and 9.3: Minor clarifications and corrections. Section 5.1.2: Minor clarifications and corrections. Removed reference to Appendix A (Schedules of study Assessments) and added reference to protocol section and appendix. Section 5.3.1:

Version	Date	Revised by:	Changes
			Revised based on changes reflected in protocol amendment v4.1. Added PFS Analysis Set and updated definition of the Response Evaluable Analysis Set. Section 5.3.2: Added two additional safety population: Sub-study Safety Analysis Set and PSMA-617 Safety Analysis Set. Section 5.4: Additional subgroup definitions were added. Section 5.4.1: Removed descriptive statistics at baseline summaries by subgroups. Clarified that subgroup analyses for efficacy will only be performed for rPFS and OS and removed analyses for secondary endpoints. Clarified which subgroups will be used for efficacy and safety analyses. Section 5.6: Minor clarifications and updates including: added definition for best % change, identified list of taxanes for Last taxane therapy treatment-free interval, and updated derivation and statistical model for PSA doubling time including applicable references. Section 6.1: Minor clarifications and corrections. Added summaries for screen failures, PFS Analysis Set, Sub-study Safety Analysis Set, enrollment by country and center and end of study status. Section 6.4: Added an additional summary of discordance between interactive response technology (IRT) system versus CRF collected stratification factors. Added PFS analysis set. Section 7: Minor clarifications and added PFS Analysis set. Added additional summaries for the Sub-study and PSMA-617 Safety Analysis Sets for section 7.1 and 7.2 only. Section 7.1: Minor clarifications including defining Age and Race groupings. Section 7.2: Minor clarifications including defining PSA doubling time groupings. Added summary of baseline Target and Non-Target Lesions. Section 7.3:

Version	Date	Revised by:	Changes
			Minor clarifications and corrections. Removed version of MedDRA being used and added that the version will be specified in the applicable tables and listings. Section 7.4: Minor clarifications and corrections. Added definition for Duration of Therapy and Duration of historic BOR for (1) Last Taxane Therapy and (2) Last Therapy. Section 8.1.1: Revised based on changes reflected in protocol amendment v4.1. Moved sensitivity analyses to Section 8.2.1. Section 8.1.2: Minor clarifications on the key secondary efficacy definitions. Moved sensitivity analyses to Section 8.2.2. Section 8.1.3: Minor clarifications on the additional secondary efficacy definitions. Updated derivation and statistical model for PSA doubling time including applicable references. Section 8.2: Revised based on changes reflected in protocol amendment v4.1. Removed all unadjusted analyses. Added a statement that the stratification factors from the IRT system will be used for all analyses. Section 8.2.1: Revised based on changes reflected in protocol amendment v4.1. Updated statistical test model to use from stratified Cox model to stratified log-rank test, updated analysis set for rPFS and moved sensitivity analyses from Section 8.1.1 to this section. Added additional supportive analyses for rPFS and added text for subgroup analyses for rPFS and OS as referenced in Section 5.4.1. Added text for assessing proportionality assumption. Section 8.2.2: Revised based on changes reflected in protocol amendment v4.1. Minor clarifications on analysis sets to use for key secondary endpoint analyses, and the alpha level to use for the Hochberg closed test procedure. Section 8.2.3: Updated analysis set to be used. Sections 8.2.3.1, 8.2.3.2, 8.2.3.3 (including subsections) and 8.2.3.4: Minor clarifications including adding the statistical model to be used for time to improvement following initial pain

Version	Date	Revised by:	Changes
			(Section 8.2.3.3.3), added duration of time in hospital following ^{177}Lu-PSMA-617 administration (section 8.2.3.4) and updated the analysis set to be used. Added waterfall plot for maximum % change from baseline in PSA (Section 8.2.3.2). Section 9: Clarified which analysis sets to use for the safety evaluation for the study (including sub-study). Section 9.1: Minor clarifications. Updated how the study BSC/BSoC will be flagged. Added new safety analysis sets due to addition of sub-study. Section 9.2: Minor clarifications and corrections. Added text that the version of MedDRA used will be specified in the applicable tables and listings. Section 9.2.1: Minor clarifications and corrections including updating the definition of the treatment emergent period for 68Ga-PSMA-11. Section 9.2.2: Clarification on how AEs will be summarized and reported. Sections 9.2.3, 9.2.4 and 9.2.5: Analyses pertaining to deaths moved to Section 9.2.5. Section 9.2.5: Added section for summary of deaths. Section 9.4: Added definition of corrected QT using Fredericia's formula (QTcF) and clarified how QTc reported by site will be handled. Section 9.5: Minor clarifications and corrections. Indicated analysis sets to use for analyses. Removed version of MedDRA to be used and added that the version will be specified in the applicable tables and listings. Section 9.6: Added section on concurrent radiotherapy summaries. Section 9.7: Indicated analysis sets to use for analyses. Section 9.8:

Version	Date	Revised by:	Changes
			Indicated analysis sets to use for analyses. Minor clarifications and corrections. Added post-treatment radiotherapy summaries. Section 10: Added additional references for PSA Doubling Time derivation. Appendices: Removed schedules of study assessments from Appendix A since the schedules can be found in the protocol. Minor clarifications and corrections to remaining appendices.
3.0	18 Jan 2021	[redacted]	Changes needed for the final rPFS/interim and final OS analyses including analyses to describe and assess the impact of COVID-19. Analyses pertaining to the sub-study are now described in sub-sections rather than embedded as done in SAP v2.0. The following is a list of all changes since SAP v2.0: List of reviewers and approvers have been updated on title page due to personnel and title/role changes. Section 1 List of Abbreviations and Definition of Terms • Additional terms added. Section 2 Introduction • Minor clarifications on protocol versions for main (randomized) and sub-study. Section 2.1 Changes from the Protocol: • Described additional changes from protocol including use of log-rank test for time to first SSE; updated PFS-FAS analysis set; not re-testing final OS if interim OS is met and clarification of alpha levels if the interim OS analysis is not done. Section 3 Study Design and Objectives: • Minor formatting edits and clarifications on the dosimetry, pharmacokinetics and ECG sub-study in Germany. Section 3.2 Randomization and Blinding: • Minor edits and clarifications on sub-study enrollment. Section 3.3 Study Objectives: • Minor formatting edits. Section 4 Planned Analyses: • Clarified re-testing of final OS if interim OS is met and added alpha levels for final OS testing if interim OS analysis is not performed; added Section 4.2 for sub-study analyses.

Version	Date	Revised by:	Changes
			Section 4.1 Interim Analyses and IDMC Oversight • Removed repeat text from sections 3.4 and 4. Section 5 General Analysis Definitions: • Clarified general analysis definitions including: definition of randomized treatment for main (randomized) and sub-study; definition of BSC/BSoC; definition of C1D1; start and end dates of NAAD as BSC/BSoC; date of last contact for overall survival; date of last administration and last exposure to randomized treatment; reference dates for safety and efficacy assessments; baseline definitions. Section 5.1.2 Visit Windows: • Clarified use of unscheduled assessments for PSA and HRQoL efficacy evaluations; removed listing of visit dates and flagging results not used in summary tables. Section 5.2 Partial/Missing Dates: • Clarified imputation rules and added rules for imputing date of last administration of BSC/BSoC, adverse event start dates and start of subsequent anti-cancer therapy. Section 5.3 Definition of Populations: • Minor clarification on analysis set definitions; removed PSMA-617 Safety Analysis Set; added Section 5.3.3 for sub-study populations. Section 5.4 Subgroup Definitions: • Minor clarifications on subgroup definitions including correcting age categories and adding multiple races to "other". Section 5.4.1 Analyses on subgroups: • Minor clarifications including clarification on key safety analyses to be performed. Section 5.6 Variable Definitions: • Clarified definition of duration of exposure and dose intensity; corrected month conversion factor for dose intensity; added definitions for: time to withdrawal of consent to randomized treatment and study, BMI, duration of exposure to BSC/BSoC, duration of exposure to NAAD as study BSC/BSoC, and stratification factors based on data collected on the eCRF. Section 6.1 Patient Disposition: • Removed reference to Appendix A (consort flow chart); clarified analyses for patient disposition

Version	Date	Revised by:	Changes
			including summarizing by subjects randomized prior to Mar 5, 2019 and on or after Mar 5, 2019; added Section 6.1.1 for sub-study analyses. Section 6.2 Protocol Deviations: • Minor edits and clarifications; added analysis to describe and assess impact of COVID-19; added Section 6.2.1 for Sub-study specific analyses. Section 6.3 Inclusion and Exclusion Criteria: • Added summary tables for screened patients and for the PSMA-11 Safety Set and added Section 6.3.1 for sub-study specific analyses. Section 6.4 Stratification Information: • Minor clarifications including analysis set to use for listing; added an additional summary for the Response Evaluable Analysis Set. Section 7 Baseline Characteristics and Prior and Concurrent Therapies and Medications • Clarified analysis sets to use; added Section 7.5 for Sub-study specific analyses. Section 7.1 Demographic and baseline assessments: • Minor clarifications and additions including: added BMI; updated age categories; updated ECOG categories and clarified that ECOG was not collected at time of screening. Section 7.2 Baseline Disease Characteristics: • Minor clarifications including use of local assessments for site of disease and target/non-target lesion variables per RECIST 1.1. Section 7.4 Prior Cancer Related Therapy: • Removed summary of prior prostate cancer-related systemic therapy: last therapy; clarified coding dictionaries for prior surgeries and systemic therapies; clarified the variables to be summarized including: reason for prior surgery, prior number of NAAD-containing regimens, type of systemic therapy and last taxane therapy. Section 8.1 Efficacy Variable Definitions: • Moved text on radiographic imagining per local and central assessment from section 8.1.1 and provided more details on which independent reviewer from the central review is used for the analysis of rPFS, ORR, DCR, duration of response and PFS; clarified that radiographic imagining by local assessment will be used for a sensitivity analysis for rPFS only added Section 8.1.4 for Sub-study efficacy definitions.

Version	Date	Revised by:	Changes
			• ; added Section 8.1.4 for Sub-study efficacy definitions. Section 8.1.1 Primary Efficacy Definitions: • Clarified last contact date will be used for OS censoring; moved text on radiographic imaging per local and central assessment to Section 8.1; and minor updates to appendix references. Section 8.1.2 Key Secondary Efficacy Definitions: • Added best overall response category (Non-CR/Non-PD) for non-target lesions only. Section 8.1.3 Additional Secondary Efficacy Definitions: • Minor clarifications on baseline PSA definition, confirming PSA progression when no decline, confirming PSA response and use of scheduled and unscheduled assessments. Section 8.2 Efficacy Analyses: • Removed supportive analysis for ORR and DCR; clarified RECIST version; clarified that primary analysis of rPFS will be based on independent central review. • Added Section 8.2.5 for sub-study specific efficacy analyses. Section 8.2.1 Primary Efficacy Analyses: • Minor formatting edits and clarifications including: re-testing of final OS if interim OS is met; cross reference to final OS analysis alpha levels when an interim OS analysis is not performed (Section 4); and rPFS will be based on independent central review. Added analyses for rPFS: based on local investigator, concordance between central and local review; modified analysis of missing and timing of tumor assessments; added descriptive analysis of OS using PFS-FAS; clarified median follow-up and 95% CI will be estimated using Kaplan-Meier method; added analyses to describe and adjust for impact of COVID-19 on rPFS and OS. Section 8.2.2 Key Secondary Efficacy Analyses: • Clarified rules for testing key secondary endpoints at final rPFS/interim OS and final OS including added confidence intervals; add rules for testing when the interim OS analysis is not performed; changed primary comparison method to stratified log-rank test for time to first SSE; clarified ORR, DCR and duration of response will be based on independent central review; removed additional analyses of ORR and DCR in PFS-FAS; corrected

Version	Date	Revised by:	Changes
			analysis set to use for duration of response; clarified mixture distribution analysis methodology. Section 8.2.3 Additional Secondary Efficacy Analyses: • Clarified timing and analysis of secondary efficacy endpoints cross referencing back to the planned analyses section 4. Section 8.2.3.1 Progression-free Survival Analysis: • Clarified PFS will be based on independent central review; added the primary criteria of clinical progression to summary. Section 8.2.3.2 Biochemical Response Analysis: • Clarified that the 95% CI for the mean PSA doubling time will be presented; Corrected "maximum % decrease from baseline" to "maximum % change from baseline"; Added that differences in least square means and 95% confidence intervals will be presented for longitudinal models. Section 8.2.3.3.1 EQ-5D-5L Questionnaire: • Added plot for Utility Score; clarified clinical disease progression excludes radiographic and PSA progression; removed forest plots; added that differences in least square means and 95% confidence intervals will be presented for longitudinal models. Section 8.2.3.3.2 FACT-P: • Added plots for FACT-P Total score, FACT-G Total score, and TOI score; clarified clinical disease progression excludes radiographic and PSA progression; clarified the subscale analysis criteria for FACT-P total score; removed forest plots. Section 8.2.3.3.3 BPI-SF: • Added plots for Pain Intensity Scale, Pain Interference Scale and Worst Pain Intensity Scale; clarified clinical disease progression excludes radiographic and PSA progression; removed forest plots. Section 8.2.3.4 Health Economics Analysis: • Clarified that study specific analyses will focus on descriptive statistics of health resource utilization data. Removed all references to statistical analyses specifically hospitalizations, clinic visits and length of stay as these may be part of the economic evaluation performed by an external vendor. Clarified health utilization data definitions and summaries; removed monitoring activities as not required for health economic analysis; clarified

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			that clinical disease progression excludes radiographic and PSA progression for time to first use of opioid analgesic. Section 9 Safety Evaluation: • Clarified analysis sets to be used for the safety evaluation and how they will be presented in the summary tables. Section 9.1 Extent of Exposure: • Clarified analysis sets to be used for the exposure summaries; amended and clarified ^{177}Lu-PSMA-167 exposure summaries including overall exposure, dose interruptions, reductions and dose intensity; changed reference to "2018 Mar 1" WHO Drug Global dictionary version and replaced with general guidance that version will be presented as a footnote in tables and listings; added summary of exposure to NAAD as study BSoC; minor formatting edits for clarification and consistency throughout document; added Section 9.1.1 for sub-study specific analyses. Section 9.2.2 General Convention: • Clarified general conventions including when to assign treatment-emergent AEs as study drug-related when the assessment of relatedness is missing; clarified which AE summaries will include treatment emergent versus non-treatment emergent (i.e. AEs in LTFUP) and how summaries will be sorted. Section 9.2.3 ^{68}Ga-PSMA-11 Adverse Events: • Added summaries of serious and non-serious with occurrences AEs for clinical trial registry reporting; added analysis set to use for summaries; minor formatting edits; added Section 9.2.3.1 for sub-study specific analyses. Section 9.2.4 Randomized Treatment Adverse Events: • Added summaries of serious and non-serious with occurrences AEs for clinical trial registry reporting; clarified that TEAEs will be summarized by ^{177}Lu-PSMA-167 cycle of onset; minor edits/clarifications; added analysis set to use for summaries; clarified that non-treatment emergent AEs will be flagged; added analyses to describe and assess impact of COVID-19 on safety; added Section 9.2.4.1 for sub-study specific analyses. Section 9.2.5 Deaths: • Clarified summaries including which analysis set to use; added analyses to describe and assess impact

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			of COVID-19 on safety; added Section 9.2.5.1 for sub-study specific analyses. Section 9.2.6 Long-term Follow up Adverse Events: • Minor formatting edits; clarified analysis sets to use for summaries; added Grade 5 to summaries; clarified that AEs captured on LTFU CRF page are to be used in summaries and listed; added analyses to describe and assess impact of COVID-19 on safety; added Section 9.2.6.1 for sub-study specific analyses. Section 9.2.7 Safety Topics of Interest: • Added new section for summarizing safety topics of interest including Section 9.2.7.1 for sub-study specific analyses. Section 9.3 Clinical Laboratory Determination: • Minor formatting edits; minor clarifications on labs to summarize and list; clarified treatment period and analysis sets to use for summaries; added rules for imputing lab values reported with ">" or "<"; added shift tables for labs not graded per CTC using low/normal/high classification; added summary of liver function parameters; added Section 9.3.1 for sub-study specific analyses. Section 9.4 Vital Signs, Physical Findings and ECG: • Added clinically notable values for vital signs and ECGs; clarified treatment period for summaries; added ECOG PS change from baseline; removed derivation of QTcF using Fredericia's formula since uncorrected QT values is not collected; clarified that abnormal findings will be presented in listings and tables if appropriate; clarified analysis sets to use; added Section 9.4.1 for sub-study specific analyses. Section 9.5 Prior and Concurrent Surgical and Therapeutic Procedures: • Clarified treatment period and analysis set for summaries; removed text on summarizing active versus non-active procedures as not applicable; added Section 9.5.1 for sub-study specific analyses. Section 9.6 Prior and Concurrent Radiotherapy: • Added summaries for prior radiotherapy; clarified treatment period and analysis set for summaries; added Section 9.6.1 for sub-study specific analyses. Section 9.7 Prior and Concomitant Medications:

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			• Clarified treatment periods and analysis sets for summaries; added Section 9.7.1 for sub-study specific analyses. Section 9.8 Post-Treatment Cancer-related Therapy: • Changed reference to "2018 Mar 1" WHO Drug Global dictionary version and stated that version used will be reported in tables and listings; clarified that post-treatment therapy are therapies since discontinuation of randomized treatment; removed listing of long-term follow-up contact data; added Section 9.8.1 for sub-study specific analyses. Appendices: • Removed the example of the Consort Flow Diagram in Appendix A and renumbered appendices.