ENDOCYTE
A Novartis Company

PROTOCOL NO. PSMA-617-01 / NCT03511664

# 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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| Clinical Protocol No.: | PSMA-617-01 |
| Version No.: | 7.0 |
| Date: | 14 September 2022 |
| IND No.: | 133,661 ($^{177}$Lu-PSMA-617)<br>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<br>8910 Purdue Road - Suite 250<br>Indianapolis, Indiana 46268 |
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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. |
| 1.1 | 03 July 2018 | GB only amendment:<br>AE assessment timing to start from consent.<br>Added wording regarding birth control |
| 1.2 | 26 September 2018 | DE only amendment:<br>AE assessment timing to start from consent.<br>Added wording regarding birth control |
| 2.0 | 16 January 2019 | Incorporated GB and DE only amendment changes.<br>Added statement of compliance as required by Sweden.<br>Incorporated the addition of the alternative primary endpoint of rPFS and update to 1 rPFS analysis and 1 overall survival analysis.<br>Clarified inclusion of and timing of start for best supportive/best standard of care.<br>Clarified inclusion/exclusion criteria.<br>Clarified procedures and timing<br>Clarified progression of disease is not considered an AE or SAE.<br>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.<br>• Updated background information data.<br>• Clarified rPFS is an alternate primary endpoint.<br>• 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.<br>• After Cycle 6, visits are now every 12 weeks (+/- 4 days)<br>• 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.<br>• Plasma testosterone was added as an acceptable form of testosterone testing.<br>• Window for QOL and Pain questionnaires added.<br>• 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.<br>• 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 5$^{th}$, 2019 were added. |

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| | | • 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.<br>• 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.<br>• 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.<br>• Additional wording to clarify intent to collect radiographic imaging for patients who stop treatment for reasons other than radiographic progression, |
| 5.0 | 26 April 2021 | • Extend Long-Term Follow-Up for up to an additional 12 months after V5.0 of the protocol is implemented at each site.<br>• Reduce the procedures required for each Long-Term Follow-Up visit.<br>• Add the requirement to report Serious Adverse Events related to the study drug during Long-Term Follow-Up as well as reporting details of renal toxicities and secondary malignancies.<br>• Updated Serious Adverse Event reporting to reflect the change to Novartis Safety vs PrimeVigilance.<br>• Update footers and headers so that all pages read V5.0. In V4.0 pages 73 to 95 still read “V3.0”. No change was made to the content of these pages from V3.0 to V4.0; the error was typographical. |
| 6.0 | 26 May 2022 | • Extend the Long-Term Follow-Up for patients on this study to ensure consistent collection of long-term safety data until a new long-term safety follow-up study is available (to comply with FDA Postmarketing Requirement; estimated in 2Q2023). |
| 7.0 | 14 September 2022 | The purpose of this protocol amendment V7 is to document the gap between the last visit of the patient under protocol amendment V5 and the first visit of the patient under protocol amendment V6 as there might be a time gap due to late finalization of protocol amendment V6.<br><br>Details of the protocol amendments are as follows:<br>· V5 extended the long-term follow-up by one year.<br>· V6 extended further the long-term follow-up until a separate long-term follow-up study is available.<br><br>Despite the time gap between these two protocol amendments V5 and V6, we suggest to continue the patient on the trial in order to comply with FDA post marketing requirements, so we continue to collect long-term safety data (with the same patient ID) for reconsented patient. |

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| | | An additional addendum of the informed consent is released with this protocol amendment V7 to document the patient's understanding to continue on study. |

# Clinical Trial Summary

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| 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.<br>Key secondary objectives are an arm-to-arm comparison of the following:<br>• Response Evaluation Criteria in Solid Tumors (RECIST) response<br>• Time to a first symptomatic skeletal event (SSE)<br>Additional Secondary Objectives:<br>• Safety and tolerability of $^{177}$Lu-PSMA-617<br>• Health-related quality of life (HRQoL; EQ-5D-5L, FACT-P and Brief Pain Inventory – Short Form (BPI-SF))<br>• Health economics<br>• Progression-free survival (PFS) (radiographic, clinical, or prostate-specific antigen [PSA] progression-free survival)<br>• 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.<br>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.<br>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.<br>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.<br><br>**Before final analysis of alternate primary endpoint OS:**<br>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.<br>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.<br>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 |

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| | 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).<br>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.<br>**After final analysis of alternate primary endpoint OS:**<br>All randomized patients on the active part of the study after the final analysis of alternate primary endpoint OS will have an EOT visit at the next planned visit after implementation of V5.0 of the protocol and will move into long-term follow-up. All patients in long-term follow-up will continue to be followed on this study under the same patient ID until a long-term safety follow-up study is available in the respective country, until death or until withdrawal of consent, whichever occurs first.<br>The long-term follow-up period in this study will include the collection of survival and new treatment information, adverse events assessment for renal toxicity and secondary malignancies, and results of hematology and chemistry testing. During follow-up, patients will be followed for safety and survival. They will be seen or contacted by a clinician every 3 months (±1 month) via phone, in person or via telemedicine visit, email or letter until a long-term safety follow-up study is available for enrollment, until death or until withdrawal of consent, whichever occurs first. Every opportunity to continue to collect long-term safety data should be made for each willing participant, regardless of gap between release of protocol amendment v5.0 and v6.0.<br>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.<br>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.<br>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.<br>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 |

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| | each cycle and through the End of Treatment visit. Patients will be monitored throughout the study for SSEs.<br>After the final analysis of OS, patients in the active part of the study will have an end of treatment (EOT) visit and move into long-term follow-up. Long-term follow-up will be extended on this study until a long-term safety follow-up study is available in the respective country (estimated in 2nd quarter of 2023). |
| 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.<br>This trial has at least 90% overall power and an overall Type I error rate of at most 0.025 1-sided.<br>After the final analysis of OS is performed, additional analyses of the primary endpoints (e.g. OS) will be presented descriptively without statistical inference and at the same nominal alpha level used for the primary analysis for each endpoint. |
| Duration of Study: | Total duration of the study will be up to approximately 66 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 glutamate-urea-lysine and a DOTA-chelator, which are connected by a naphthyl-containing linker. By design, $^{177}$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 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 adverse 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 was 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, 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).

Hofman et al. 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).

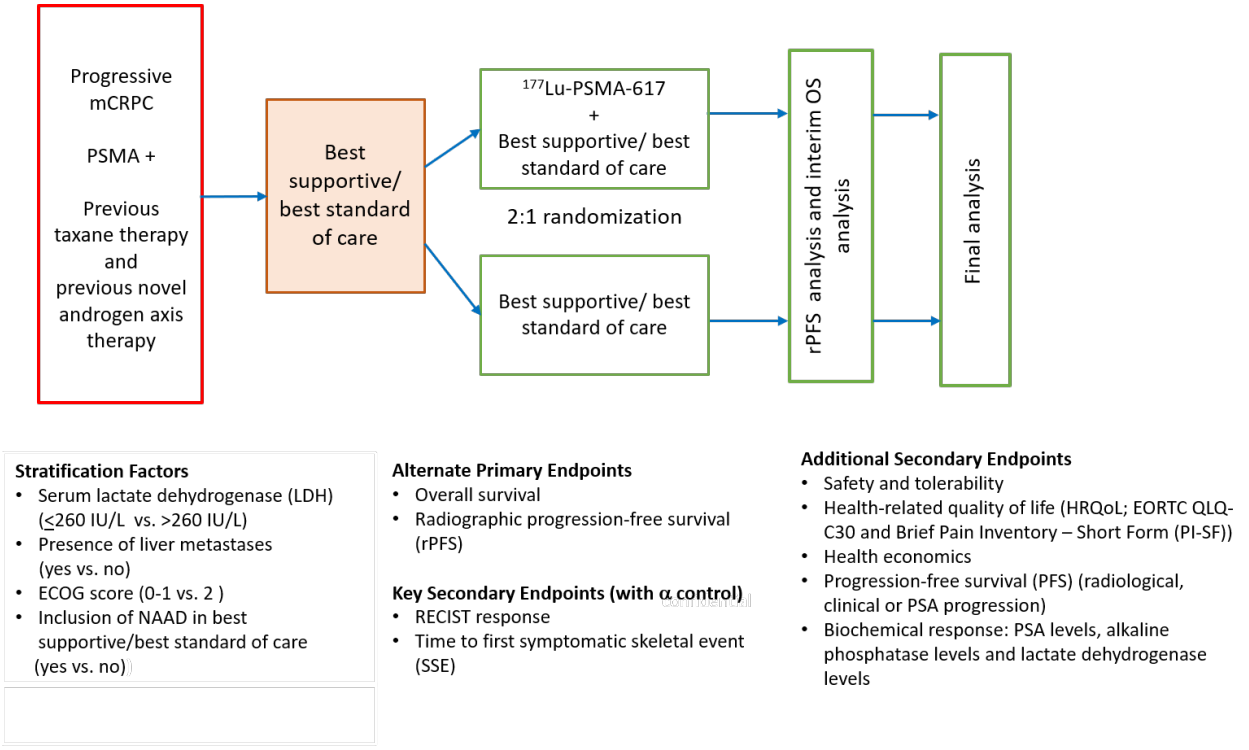


Figure 1 Diagram of trial design

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.

**Before final analysis of alternate primary endpoint OS:**
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.

**After final analysis of alternate primary endpoint OS**:
All randomized patients on the active part of the study, after the final analysis of the OS primary endpoint will have an EOT visit at the next planned visit after implementation of V5.0 of the protocol at the site and will move into long-term follow-up. All patients in long-term follow-up will continue to be followed on this study under, the same patient ID, until a long-term safety follow-up study is available in the respective country, until death or until withdrawal of consent, whichever occurs first. Every opportunity to continue to collect long-term safety data should be made for each willing participant, regardless of time gap between release of protocol amendment v5 and v6.0.

The long-term follow-up period will include the collection of survival and new treatment information, adverse events assessment for renal toxicity and secondary malignancies, and results of hematology and chemistry testing. During follow-up, patients will be followed for safety and survival. They will be seen or contacted by a clinician every 3 months (±1 month) via phone, in person or via telemedicine visit, email or letter on this study until a long-term safety follow-up study is available, until death or until withdrawal of consent, whichever occurs first.

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.

After final analysis of the OS primary endpoint, long-term follow-up will be extended until a separate long-term safety follow-up study is available in the respective country, until patient death or until patient withdrawal of consent, whichever occurs first. The maximum duration of the study, from first date of randomization to last follow-up, will therefore be up to approximately 66 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 until a separate long-term safety follow-up study is available. 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 ≥$2.5 \times 10^9$/L ($2.5 \times 10^9$/L is equivalent to $2.5 \times 10^3$/μL and 2.5 × K/μL and $2.5 \times 10^3$/cumm and 2500/μL) OR absolute neutrophil count (ANC) ≥$1.5 \times 10^9$/L ($1.5 \times 10^9$/L is equivalent to $1.5 \times 10^3$/μL and 1.5 × K/μL and $1.5 \times 10^3$/cumm and 1500/μL)
        - Platelets ≥$100 \times 10^9$/L ($100 \times 10^9$/L is equivalent to $100 \times 10^3$/μL and 100 × K/μL and $100 \times 10^3$/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 at which time all follow-up procedures will end.

**Before final analysis of alternate primary endpoint OS:**
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.

**After final analysis of alternate primary endpoint OS:**
All randomized subjects on the active part of the study after the final analysis of the OS primary endpoint, will have an EOT visit and will move into long-term follow-up. This may include collection of survival and new treatment information, adverse events assessment for renal toxicity and secondary malignancies, and results of hematology and chemistry testing. Patients may choose to be followed for survival only long-term follow-up.

All randomized patients on the active part of the study at the time of final analysis of the alternate primary endpoint OS are to be followed for safety and survival on this study, under the same patient ID, until a long-term safety follow-up study is available, until death, or until withdrawal of consent, whichever occurs first. Every opportunity to continue to collect long-term safety data should be made for each willing participant, regardless of time gap between release of protocol amendment v5.0 and v6.0.

# 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:<br>• Hemoglobin <10 g/dL<br>• WBC count <3.0 × $10^9$/L<br>• ANC <1.5 × $10^9$/L | ≥Grade 2 | Hold $^{177}$Lu-PSMA-617 administration until improvement to Grade 1 or baseline.<br>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<br>(platelet count of < 75 x $10^9$/L) | ≥ Grade 2 | Hold $^{177}$Lu-PSMA-617 administration until improvement to Grade 1 or baseline.<br><br>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.<br>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 |

**Table 1 Toxicity management and dose modification recommendations**

| Event | Grade | Management recommendations |
|---|---|---|
| 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<br>Reduce $^{177}$Lu-PSMA-617 dose by 20% on the next cycle |
| 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.

**Before final analysis of alternate primary endpoint OS:**
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, unless they specifically withdraw consent from continued participation in the study.

**After final analysis of alternate primary endpoint OS:**
If a patient discontinues the treatment part of the study for any reason other than radiographic progression, no additional scanning will be required.

# 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):<br>• Date of initial diagnosis<br>• Approximate start and stop date of each therapy<br>• Date and type of progression (e.g. PSA, radiological, bone, or no clinical benefit)<br>• 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<br>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 |

**Table 2 Screening procedures and baseline assessments**

| Screening Procedure or Baseline Assessment | Notes |
|---|---|
| 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. |
| 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.<br>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.<br>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.<br>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<br>*total carbon dioxide or equivalent is acceptable<br>** urea is acceptable | • Sodium<br>• potassium<br>• total and direct bilirubin<br>• ALP<br>• AST<br>• ALT | • LDH<br>• blood urea nitrogen**<br>• creatinine<br>• uric acid<br>• phosphorus<br>• chloride | • bicarbonate*<br>• calcium<br>• glucose<br>• total protein<br>• albumin |
| Urinalysis | • urine pH<br>• protein content<br>• specific gravity<br>• appearance and color | • glucose<br>• ketones | |
| Hematology | • complete blood count (white blood cell count and differential)<br>• red blood cell count<br>• hemoglobin<br>• hematocrit<br>• 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

**Before final analysis of alternate primary endpoint OS:**

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.

**After final analysis of alternate primary endpoint OS:**

All randomized patients on the active part of the study at the time of final analysis of the alternate primary endpoint OS will have an EOT visit at the next planned visit after implementation of V5.0 of the protocol and will move into long-term follow-up. All patients in long-term follow-up will continue to be followed on this study, under the same patient ID, until a separate long-term safety follow-up study is available in the respective country, until death or until withdrawal of consent, whichever occurs first.

The long-term follow-up period will include the collection of survival and new treatment information, adverse events assessment for renal toxicity and secondary malignancies, and results of hematology and chemistry testing. During follow-up, patients will be followed for safety and survival. They will be seen or contacted by a clinician every 3 months (±1 month) via phone, in person or via telemedicine visit, email or letter on this study until a long-term safety follow-up study is available, until death or until withdrawal of consent, whichever occurs first. Every opportunity to continue to collect long-term safety data should be made for each willing participant, regardless of time gap between release of protocol amendment v5.0 and v6.0.

# 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.<br>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.<br>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.<br>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:<br>• results in death; except for deaths due to progression of disease<br>• is life-threatening;<br>• requires inpatient hospitalization or prolongation of existing hospitalization;<br>• results in persistent or significant disability/incapacity; or<br>• is a congenital anomaly/birth defect.<br>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

**Before final analysis of alternate primary endpoint OS:**
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.

**After final analysis of alternate primary endpoint OS:**

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. In addition, SAE recording and reporting will be continued in the long-term follow-up period. During long-term follow-up, SAEs are to be reported only if the investigator suspects a causal relationship to the study treatment.

SAEs experienced after the 30-day period following the last administration of randomized treatment, including during long-term follow-up, should be reported to Novartis Safety if the investigator suspects a causal relationship to the study treatment.

During long-term follow-up, for all renal toxicities, secondary malignancies and all SAEs, 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 $^{177}$Lu-PSMA-617, and/or best supportive/best standard of care. SAEs, renal toxicities and secondary malignancies felt to be associated with $^{177}$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, $^{177}$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. Renal toxicities and secondary malignancies will be recorded as AEs. Any AE determined to meet the criteria for a serious adverse event and considered related to the study drug (even a questionable relationship) should be recorded as an AE and reported as an SAE.

## 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. 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. 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 Novartis Safety. Detailed instructions regarding the submission process can be found in the Change in Safety Reporting Process Training provided to each site detailing the reporting of SAEs to Novartis Safety.

# 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.

After the final analysis of OS is performed, additional analyses of the primary endpoints (e.g. OS) will be presented descriptively without statistical inference and at the same nominal alpha level used for the primary analysis for each endpoint. Final safety analyses will be performed when the last patient is followed on this study until a long-term safety follow-up study is available in the respective country, dies or withdraws consent, whichever occurs first.

## 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 5$^{th}$, 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 5$^{th}$, 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 5$^{th}$, 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.

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# 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** (Before final analysis of alternate primary endpoint OS) | **Long-term follow-up Extension** (after final analysis of primary alternate endpoint OS) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle Week:** | **Week 1** | **Week 2** | **Week 3** | **Week 4** | **Week 5** | **Week 6** | **Every 12 weeks (± 4 days)** | | **Every 3 months (± 1 month)** | **Every 3 months (± 1 month)** |
| **Cycle Day:** | **Day 1** | **Day 8** | **Day 15** | **Day 22** | **Day 29** | **Day 36** | | | **Collect:**<br>• Hematology<br>• Chemistry<br>• Survival<br>• New treatment:<br>  • Start/stop dates<br>  • Best response<br>  • Type of response<br>• AE assessment<br>• Radiographic imaging (only if pt came off the active part of the study for any reason other than radiographic disease progression) | **Collect:**<br>• Hematology<br>• Chemistry<br>• Survival<br>• New treatment:<br>  • Start/stop dates<br>• AE assessment for renal toxicity and reporting of secondary malignancies.<br>• SAE reporting: only if the investigator suspects a causal relationship to study treatment. |
| 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 (Before final analysis of alternate primary endpoint OS)** | **Long-term follow-up Extension (After final analysis of alternate primary endpoint OS)** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle Week:** | **Week 1** | **Week 2** | **Week 3** | **Week 4** | **Week 5** | **Week 6** | **Every 12 weeks (± 4 days)** | | **Every 3 months (± 1 month)** | **Every 3 months (± 1 month)** |
| **Cycle Day:** | **Day 1** | **Day 8** | **Day 15** | **Day 22** | **Day 29** | **Day 36** | | | **Collect:**<br>• Hematology<br>• Chemistry<br>• Survival<br>• New treatment:<br>  • Start/stop dates<br>  • Best response<br>  • Type of response<br>• AE assessment<br>• Radiographic imaging (only if pt came off the active part of the study for any reason other than radiographic disease progression) | **Collect:**<br>• Hematology<br>• Chemistry<br>• Survival<br>• New treatment:<br>  • Start/stop dates<br>• AE assessment for renal toxicity and secondary malignancies.<br>• SAE reporting: only if the investigator suspects a causal relationship to study treatment. |
| 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 | | |
| (continued) | | | | | | | | | | |

| | | | | |
|---|---|---|---|---|
| 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<br><br>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<br><br>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<br><br>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<br><br>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<br><br>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<br>• Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression<br>• Ignore early rises (prior to 12 weeks) in determining PSA response<br>**For control/relieve/eliminate endpoints:**<br>• Describe absolute changes in PSA over time from baseline to best response<br>**For delay/prevent endpoints: Decline from baseline:**<br>• 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)<br>**No decline from baseline:**<br>• PSA progression ≥25% and ≥2 ng/mL after 12 weeks |
| Soft-tissue lesions | **For control/relieve/eliminate end points:**<br>Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats:<br>• Record up to 5 lesions per site of disease<br>• Record changes in nodal, lung, liver adrenal and central nervous system (CNS) sites separately<br>• Only report changes in lymph nodes that were ≥1.5 cm in diameter in short axis at baseline<br>• Record changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separately<br>• Only report changes in visceral lesions (liver, lung, adrenal, CNS) that were ≥1.0 cm in the longest dimension<br>• Record complete elimination of disease at any site separately<br>• Confirm favorable change with second scan<br>• Record changes using waterfall plot<br>**For delay/prevent end points:**<br>• Record changes in nodal and visceral disease separately<br>• Record up to 5 lesions per site of spread<br>• 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)<br>• 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:<br>• Record outcome as new lesions, no new lesions or resolved lesion<br>• First scheduled reassessment:<br>o No new lesions: continue therapy<br>o New lesions: perform a confirmatory scan 6 or more weeks later<br>• Confirmatory scan:<br>o No new lesions: continue therapy<br>o Additional new lesions: progression<br>• Subsequent scheduled reassessments:<br>o No new lesions: continue<br>o New lesions: progression<br>• Changes in intensity or uptake do not constitute regression or progression<br>For prevent/delay end points (progression):<br>• Exclude pseudoprogression in the absence of symptoms or other signs of progression<br>• At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)<br>• 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<br>• 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<br>• Date of progression is the date of the scan that first documents the second lesion<br>• Changes in intensity of uptake alone do not constitute either progression or regression<br>• 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).<br>**For control/relieve eliminate end points:**<br>• Serial (eg, daily x 7 days) assessments at each time point can improve the stability of values<br>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.<br>**For delay/prevent end points:**<br>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).<br>Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later).<br>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 ☐ MAR ☐ MAY ☐ JUL ☐ SEP ☐ NOV

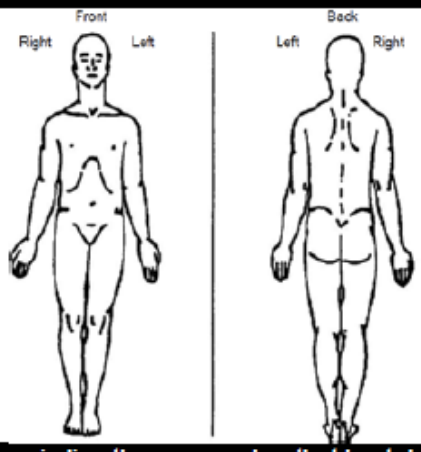
☐ FEB ☐ APR ☐ JUN ☐ AUG ☐ OCT ☐ DEC

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**

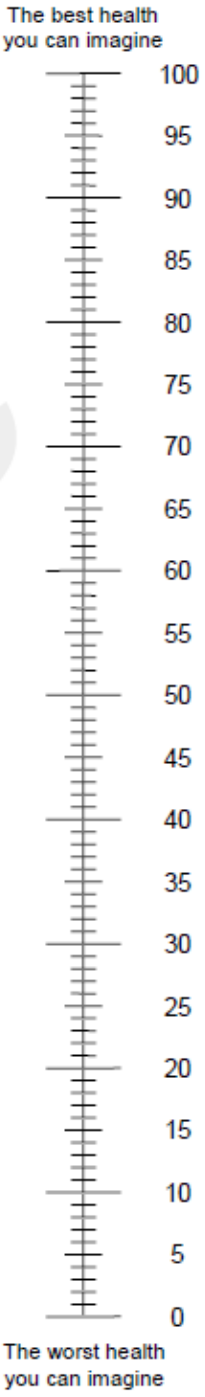
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

**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.**

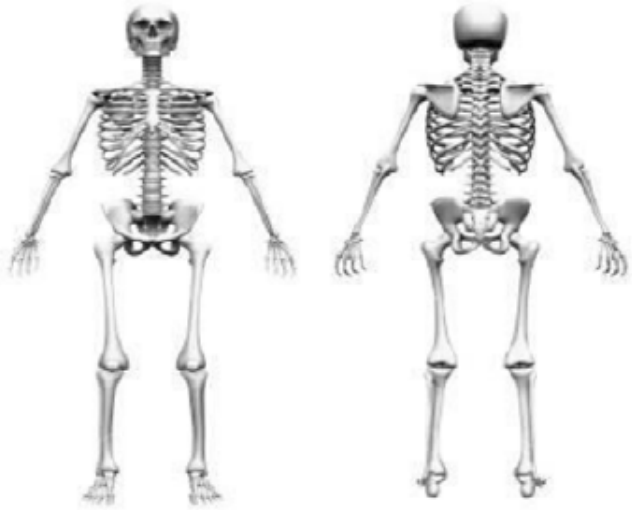
| | ADDITIONAL CONCERNS | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| C2 | I am losing weight | 0 | 1 | 2 | 3 | 4 |
| C6 | I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| P1 | I have aches and pains that bother me | 0 | 1 | 2 | 3 | 4 |
| P2 | I have 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

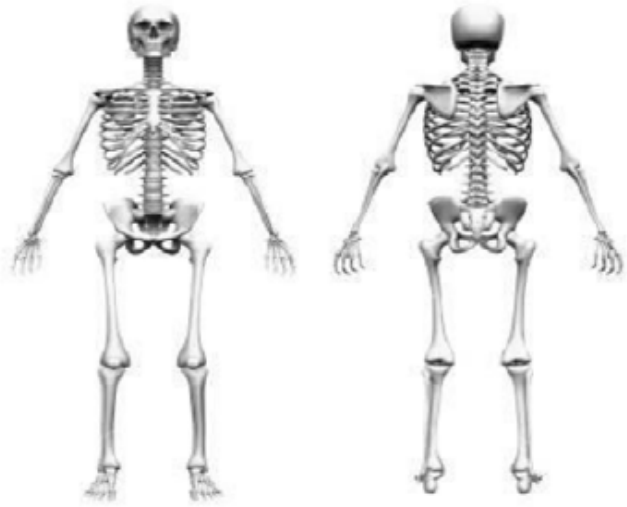
## Screening Scan

| | |
|---|---|
| **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<br>☐ No [do not fill out the rest of the form] |
| **If yes, indicate total number of lesions related to metastatic disease at Screening:**<br>☐ 1 ☐ 2-4 ☐ 5-9 ☐ 10-20 ☐ >20 | |
| **Comments regarding the image (if needed):** | |
| **Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:** | |

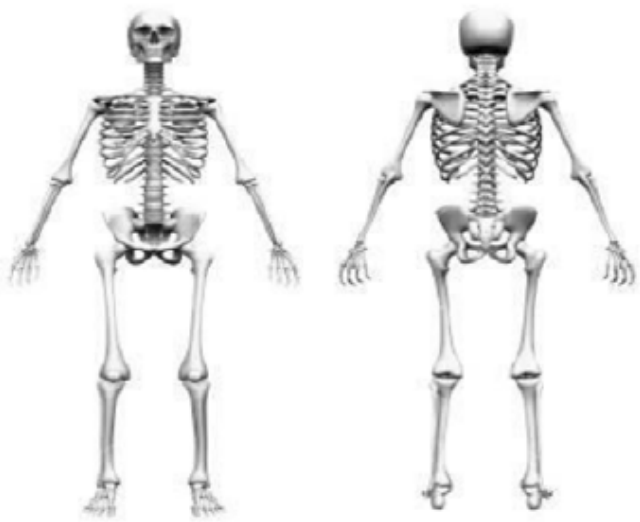
## Week 8 BASELINE Scan

| | |
|---|---|
| **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:** | |

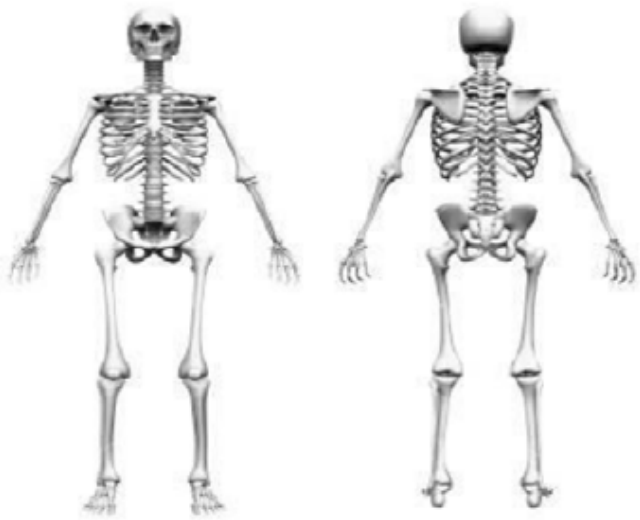
## Week 16 Scan

| | |
|---|---|
| **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:** | __ __ - __ __ __ - __ __ __ __<br>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:**<br>☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ >5 | |
| **Check Region(s) of NEW Disease Post-Screening:**<br>☐ Skull<br>☐ Thorax<br>☐ Spine<br>☐ Pelvis<br>☐ Extremities | **Draw site(s) of NEW lesion(s) on skeleton:**<br>  |
| **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:** | __ __ - __ __ __ - __ __ __ __<br>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:**<br>☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ >5 | |
| **Check Region(s) of NEW Disease Post-Screening:**<br>☐ Skull<br>☐ Thorax<br>☐ Spine<br>☐ Pelvis<br>☐ Extremities | **Draw site(s) of NEW lesion(s) on skeleton:**<br>  |
| **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:** | |