NOVARTIS

Novartis Research and Development

AAA617

Clinical Trial Protocol CAAA617B12302 / NCT04689828

PSMAfore: A phase III, Open-label, Multi-Center, Randomized Study Comparing ^{177}Lu-PSMA-617 vs. a Change of androgen receptor-directed therapy in the Treatment of Taxane Naïve Men with Progressive Metastatic Castrate Resistant Prostate Cancer

Document type:	Amended Protocol Version
EUDRACT number:	2020-003969-19
Version number:	03 (Clean)
Clinical Trial Phase:	III
Release date:	21-Feb-2023 (content final)

Clinical Trial Protocol Template Version 4.0 dated 15-Feb-2021

Table of contents

List of tables

List of figures

List of abbreviations

^{68}Ga-PSMA-11	Radiolabeled compound gallium (68Ga) gozetotide (AAA517 / [^{68}Ga]Ga-PSMA-11)
^{177}Lu-PSMA-617	Therapeutic agent lutetium (177Lu) vipivotide tetraxetan (AAA617 / [^{177}Lu]Lu-PSMA-617)
^{177}Lu	Lutetium-177
68Ga	Gallium-68
ADR	Accord Dangereux Routier (European regulations concerning the international transport of dangerous goods by road)
ADT	Androgen deprivation therapy
AE	Adverse Event
AEs	Adverse Events
AESI	Adverse event of special interest
AIDS	Acquired immune deficiency syndrome
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear antibodies
ANC	Absolute neutrophil count
Anti-HAV	Serum antibody to hepatitis A virus
anti-HCV	Anti Hepatitis C Virus
anti-HEV	Anti Hepatitis E Virus
APTT	Activated partial thromboplastin time
AR	Androgen receptor
AR-V7	Androgen receptor variant 7
ARDT	Androgen receptor-directed therapy
ASMA	Anti smooth muscle antibody
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AV	Atrioventricular
BCR	Biochemical recurrence
BICR	Blinded independent central review
BOR	Best overall response
BP	Blood pressure
BPI-SF	Brief Pain Inventory - Short Form
BRCA	Breast Cancer gene
BSC	Best supportive care
CABG	Coronary artery bypass graft
CBC	Complete blood count
CD-transferrin	Carbohydrate-Deficient-Transferrin
CFR	Code of federal regulation
CHF	Congestive heart failure
CI	Confidence Interval
CK	Creatinine Kinase
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central nervous system
CO	Country Organization
COA	Clinical Outcome Assessment

COVID	Coronavirus disease
CR	Complete response
CRO	Contract Research Organization
CRPC	Castrate resistant prostate cancer
CSR	Clinical study report
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CVD	Cardiovascular disease
DBP	Diastolic Blood Pressure
DCR	Disease Control Rate
DDE	eSource Direct Data Entry
DILI	Drug-induced liver injury
DKFZ	German Cancer Research Center, Deutsches Krebsforschungszentrum
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
[redacted]	[redacted]
DOR	Duration of response
DOTA	Dodecane tetraacetic acid
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EF	Ejection fraction
EMA	European Medicines Agency
EOP	End of Production
EOT	End of treatment
EOT2	End of Treatment 2
EPO	Epoetin
EQ-5D VAS	EQ-5D visual analogue
EQ-5D-5L	European Quality of Life (EuroQol) 5 Domain 5 Level scale
ERCP	Endoscopic retrograde cholangiopancreatography
ESMO	European Society for Medical Oncology
Eu. Ph.	European Pharmacopoeia
FACIT	The Functional Assessment of Chronic Illness Therapy
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-P	Functional Assessment of Cancer Therapy Prostate
FAS	Full Analysis Set
FDG- PET	Fluorodeoxyglucose - Positron emission tomography
FFPE	Formalin-fixed, paraffin embedded
GBq	Gigabecquerel
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
GMP	Good manufacturing practice

HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEOR	Health Economics & Outcomes Research
HEV	Hepatitis E Virus
HIV	Human immunodeficiency virus
HRQoL	Health-Related Quality of Life
HSPC	Hormone sensitive prostate cancer
HSV	Herpes simplex virus
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	immunoglobulin M
IgM & IgG anti-HBc	Immunoglobulin M & Immunoglobulin G antibody to hepatitis B core antigen
IMP	Investigational Medical Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to treat principle
LDH	lactate dehydrogenase
LFT	Liver function test
MBq	Megabecquerel
MCH	Mean corpuscular hemoglobin
mCi	Millicuries
mCRPC	Metastatic castrate resistant prostate cancer
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
mHSPC	Metastatic hormone-sensitive prostate cancer
mL	milliliter(s)
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NED	Non Evidence of Disease
NS	Normal saline
OR	Overall response
ORR	Overall response rate
OS	Overall survival
PARP	Poly (adenosine diphosphate-ribose) polymerase
PAS	Patient Administration Systems
PC	Prostate Cancer

PCS	Prostate Cancer Subscale
PCWG	Soft Tissue Rules of Prostate Cancer Working Group
PCWG3	Prostate Cancer Working Group 3
PD	Progression Disease
PDc	Progressive Disease confirmed
PDu	Progressive Disease unconfirmed
PET	Positron emission tomography
PFS	Progression free survival
PR	Partial response
PRO	Patient Reported Outcomes
PS	Patient safety
PSA	Prostate specific antigen
PSA50	Proportion of participants who have achieved a ≥ 50% decrease from baseline that is confirmed by a second PSA measurement ≥4 weeks
PSMA	Prostate-specific membrane antigen
QC	Quality control
QMS	Quality Management System
QT	QT refers to an interval seen in an electrocardiogram (ECG) test of heart function
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RANKL	Receptor activator of nuclear factor kappa-B ligand
RAS	RECIST Analysis Set
RBC	red blood cell(s)
RECIST	Response Evaluation Criteria In Solid Tumors
RLT	Radioligand therapy
RMST	Restricted mean survival time
rPD	Radiographic progressive disease
rPFS	Radiographic progression free survival
RPSFT	Rank preserving structural failure time
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Steering Committee
SD	Stable disease
SMQ	Standardized MedDRA
SoC	Standard of Care
SOD	Sum of the diameter
[redacted]	[redacted]
SPOP	Speckle-type POZ protein
SSE	Symptomatic skeletal events
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1D	Type 1 Diabetes
T3	Triiodothyronine
T4	Thyroxin
tc	calibration time
TD	Study Treatment Discontinuation
TEAE	Treatment emergent adverse event

TMPRESS2-ERG	Transmembrane protease, serine 2
TSH	thyroid stimulating hormone
TTCT	Time to chemotherapy
TTPP	Time from randomization to pain progression
TTPSAP	Defined as time from randomization to PSA progression
TTR	Time to response
TTSE	Time to first symptomatic skeletal event
TTSSE	Time to symptomatic skeletal events
TTSTP	Time from randomization to radiographic soft tissue progression per PCWG-modified RECIST 1.1.
ULN	upper limit of normal
UNK	Unknown
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants.
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, such as include those used in the study e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.

Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection.
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location.
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.

Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 3 (21-Feb-2023)

Amendment rationale

The study started on 15-Jun-2021 (FPFV) and recruitment was completed on 08-Aug-2022 (LPFV). A total of 469 patients were randomized into the trial.

The primary analysis of rPFS was performed as per protocol using a cut-off date of 02-Oct-2022 with a total of 467 subjects included in the analysis. The analysis also included the first interim analysis of overall survival (OS).

This protocol amendment aims to add an additional interim analysis for OS at ~9 months after the cut-off date for the primary analysis for rPFS. This will:

- overall, bolster the median follow-up time for efficacy and safety as a high number of patients were enrolled shortly before the primary analysis cut-off date, resulting in short median follow-up;
- allow all patients randomized to the ^{177}Lu-PSMA-617 arm to complete the full course of treatment;
- provide more mature OS data based on a higher information fraction compared to the one observed at the time of the rPFS primary analysis.

Adding this additional OS interim results in a 4-look design where type-I error for OS is controlled with pre-specified alpha spending function. [redacted]

A new section on treatment of overdose was added to provide further guidance in the event of overdose.

Additional changes in language throughout were made for better clarity.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Protocol Summary was updated in alignment with updates made in protocol sections [redacted]
- Section 3: Clarifications on reasons for discontinuation from treatment, clarifications on crossover and addition of the study code for the separate long-term safety follow-up study
- Section 4.4: Update specifying the additional OS Interim Analysis
- Section 4.5: Addition of examples of potential risk of radiological toxicities (increased risk of carcinogenicity, risk of infertility)
- Section 6.6: Added a section on treatment of overdose to provide further guidance in event of overdose
- Section 6.7.2: Reference has been made to "Therapy Discharge instructions for guidance on general rules for bathroom use and hygiene. Recommendation to perform double toilet flush was removed.
- Table 8-2: Clarification of study days in the table and clarifications in footnotes

- Table 8-3: Clarification in footnotes
- Section 8.3.1: Clarifications made to Time points at which progression is determined locally
- Section 8.5.1: correction to remove the option for PRO assessments via phone interview as it was not implemented for this study
- [redacted]
- Section 11.3: Site Monitoring: section updated in line with the current Novartis protocol template to provide further details on site monitoring and records and documents retention period
- Section 12: Clarification on timing of CSR
- [redacted]
- Section 12.4, Section 12.5 and Section 12.7, Section 12.8: Addition of wording to specify details of the additional OS Interim Analysis

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 2 (04-Aug-2022)

The study started on 15-Jun-2021 (FPFV) and as of 07-Jul-2022, 361 patients have received study treatment in 14 countries including US.

Amendment rationale

- On 04-May-2022, there was a production halt at the radioligand therapy production sites in Ivrea, Italy and Millburn, New Jersey out of an abundance of caution whilst internal investigations were conducted. No study drug was available globally. As a result, a halt was placed on screening and enrollment for ^{177}Lu-PSMA-617 clinical trials globally, including the CAAA617B12302 trial. Production resumed in Millburn on 29-May-2022 and in Ivrea on 05-Jun-2022. Notice of the lift of the enrollment halt was sent on 25-May-2022.
- Language has been added so that patients do not need to be discontinued from study treatment if there is a dosing delay of >4 weeks related to study drug supply issues. [redacted]
- Exclusion criteria #3a and #17a were clarified so that they are aligned yet do not per se exclude prior PARP inhibitor therapy. CAAA617B12302 protocol v01 had added PARP inhibitor to the list of excluded prior therapy, however harmonization with exclusion criterion #3a is now achieved by modifying the language of exclusion criterion #17a. Patients must not be eligible at the time of randomization for non-ARDT therapy that has demonstrated molecular biomarker selection for improved outcomes, this is independent of prior exposure to PARP inhibitors.
- Added the option for patient to enroll into a separate long term safety follow-up clinical study, as requested by US Food and Drug Administration (FDA).
- The scope of reporting for adverse events after the completion of treatment is updated to capture specific toxicities [redacted] during follow-up [redacted]
- Physical exam is added to schedule of assessments performed at long term follow-up visits.
- Changes in language throughout were made for better clarity, and typos corrected.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Protocol Summary was updated in alignment to updates made in protocol sections.
- Section 2.1, Primary Estimands: Paragraph added in line with the current Novartis protocol template.
- Section 2.2, Study drug changed to “Study treatment”
- Section 3, For consistency with sections in the protocol (eg Section 8.1.1), it was added here that PSMA positivity will be assessed by central review.

- Section 3, End of treatment: "Unequivocal clinical progression" was removed from sub-section "End of Treatment", as it was inconsistent with trial design
- e.g. Section 3, Treatment period states "In the absence of safety concerns, every effort should be made to keep the participant on the randomized treatment until BICR-determined radiographic progression or completion of the 6 cycles of ^{177}Lu-PSMA-617."
- Section 3: Post-treatment Follow-up period; Additional guidance provided on safety data to be collected.
- Section 3: Post-treatment Follow-up period; Updated to indicate that physical exam will be collected.
- Section 3: Post-treatment Follow-up period; Updated to provide guidance that following withdrawal of consent for collection of blood samples, physical exams, PROs, and imaging assessments during the long-term follow-up, information on survival and AEs will be collected as specified in the protocol.
- Section 3, Crossover; Updated to provide guidance that any unresolved toxicity from prior therapy should be controlled and must be no greater than CTCAE grade 2 or baseline at the time of registration for crossover and not from start of treatment with ^{177}Lu-PSMA-617. And ECOG performance status must be 0-1 at the time of registration and organ function must be adequate and at the time of registration.
- Section 3: Post-treatment Follow-up period; Information provided on what will happen to participants who received ^{177}Lu-PSMA-617 and remain on the trial in follow-up at the time of sponsor's completion of the study.
- Section 4.5, Risks and benefits: Information from AAA517 Investigator's Brochure Edition 6 was added. "^{68}Ga-PSMA-11 is approved in the US under the trademark of LOCAMETZ® as a radioactive diagnostic agent indicated for PET imaging of PSMA-positive lesions in men with prostate cancer with suspected metastasis who are candidates for initial definitive therapy, with suspected recurrence based on elevated serum PSA level and for selection of patients with metastatic prostate cancer for whom lutetium ^{177}Lu-PSMA-617 PSMA-directed therapy is indicated. It has demonstrated a favorable safety profile with about 1% of patients experiencing mild reactions such as fatigue, nausea, constipation, and vomiting. Further details can be found in the ^{68}Ga-PSMA-11 Investigator's Brochure."
- Section 4.5, Risks and benefits: Information on approval of Pluvicto in United States added. "^{177}Lu-PSMA-617 was approved in the United States on 23-Mar-2022 under the brand name of PLUVICTO® for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy."
- Section 5.2, exclusion criteria: Exclusion criteria 3a revised to "Prior treatment with cytotoxic chemotherapy for castration resistant or castrate sensitive prostate cancer (e.g., taxanes, platinum, estramustine, vincristine, methotrexate, etc.), immunotherapy or biological therapy [including monoclonal antibodies]. [Note: Taxane exposure (maximum 6 cycles) in the adjuvant or neoadjuvant setting is allowed if 12 months have elapsed since completion of this adjuvant or neoadjuvant therapy. Prior treatment with sipuleucel-T is allowed.] "PARP inhibitor" was removed from the list of prior excluded therapies.

- Section 5.2, exclusion criteria: Exclusion criteria 17a revised to "Eligible for treatments other than ARDT based on presence of any mutations or biomarkers that are known as predictors of better response (e.g., AR-V7 or BRCA)." to allow prior PARP failures and for reconciliation of removing PARP inhibitor as a prohibited prior therapy.
- Section 6.1.2, Investigational and control drugs: Reference made toto Pharmacy Manual for details on dose preparation and administration. Statement indicating that administered dose may be flushed by 10 mL of saline after injection as per local best practice was removed.
- Section 6.1.2, For consistency with sections in the protocol (eg Section 8.1.1), it was added here that PSMA positivity will be assessed by central review.
- Section 6.2.1: Palliative radiation therapy revised from "Palliative radiation therapy may be administered to symptomatic bone disease at any time from randomization until the 1st post-baseline scan occurring at 8 weeks and it is not considered as prohibited medication, the participant will not be removed from the protocol. The need for palliative radiation during this time period will not be counted as an rPFS (i.e., radiographic progression) event, however, it will be listed as clinical progression" to "Palliative radiation therapy may be administered to symptomatic bone disease and it is not considered as prohibited medication. The need for palliative radiation may not be counted as an rPFS (i.e. radiographic progression) event, however, it will be listed as clinical progression and meet criteria for a Symptomatic Skeletal Event" for clarity and consistency with Section 8.3.3.
- Section 6.7, ARDT: Sentence that "Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document" was removed because 2-part label is not being used in the study. Guidance is provided that "As per the treatment assigned to the participant by the IRT, investigator staff will identify the study treatment to dispense to the participant"

[redacted]

- Table 8-2, Adverse events/SAEs: footnote 23 added "For participants who received ^{177}Lu-PSMA-617 in the ^{177}Lu-PSMA-617 arm or in crossover, the following adverse events will be captured beyond the 30 day safety period regardless of relationship to study treatment and whether new anticancer therapy has been initiated: hematologic toxicities (including need for transfusion or use of growth factors), renal failure, xerostomia, xerophthalmia, secondary malignancies."

[redacted]

- Table 8-3,Adverse events/SAEs: footnote 18 added "For participants who received ^{177}Lu-PSMA-617 in the ^{177}Lu-PSMA-617 arm or in crossover, the following adverse events will be captured beyond the 30 day safety period regardless of relationship to study treatment and whether new anticancer therapy has been initiated: hematologic toxicities (including need for transfusion or use of growth factors), renal failure, xerostomia, xerophthalmia, secondary malignancies."
- Section 8.2, Participant demographics/other baseline characteristics: Sentence "In addition, we need to assess the diversity of the study population [redacted] was removed and replaced with "In addition, these data are necessary to assess the diversity of the study population [redacted]" in line with the current Novartis protocol template.
- Section 8.3.1, Radiographic imaging for tumor assessment: language on radiographic imaging assessments was updated to better instruct on applying the 2+2 PCWG3 criteria. "For scans after the 12-week flare window, the first observation of at least two new lesions relative to the baseline scan must be confirmed on a subsequent scan at least 6 weeks later (2 + 2 PCWG3 criteria).
- Section 8.3.1, Radiographic imaging for tumor assessment: New tables added for additional guidance with response criteria: "Table 8-4 Overall Time Point Response per PCWG3 modified RECIST v1.1, Table 8-5 Bone disease response per PCWG3 criteria and Table 8-6 Disease Progression on Bone Scan"
- Section 8.3.1, Radiographic imaging for tumor assessment: PCWG3 guidelines specified as PCWG3 modified RECIST v1.1 guidelines for clarity.
- Section 8.3.1, Radiographic imaging for tumor assessment: Clarification added to indicate that for disease progression by bone scan criteria, the confirmatory scan must be outside the 12-week flare window.
- Section 8.3.1, Radiographic imaging for tumor assessment: Guidance on imaging assessment updated that whole body bone scan with technetium-99m labeled diphosphonates should be performed per study imaging site manual. The text that "per institutional standard of care" was removed
- Section 8.3.3, Clinical progression: Statement indicating participants requiring palliative therapy up to 8 weeks after first study treatment dose deleted as it was redundant and conflicting with earlier bullet in the section describing administration of any radiotherapy as qualifying event for clinical progression. Additionally, criterion regarding need for immediate initiation of new anticancer intervention for complications due to tumor progression was updated from "even in the absence of radiological progression" to even in the absences of confirmed radiological progression"
- Table 8-10, Blood urea nitrogen (BUN) was removed from required assessments and the word "fasting" was remove from "glucose" Additionally Urea was updated to "urea nitrogen"
- Section 8.5.1, Clinical outcome assessments (COAs): "or designee" added to allow appropriately trained personnel other than the Investigator to review complete measures for potential AEs and SAEs.

[redacted]

- Section 9.1.1, Discontinuation of study treatment: "Unequivocal clinical progression" was removed from Section 9.1.1 as it was added in error during protocol amendment 1 update and it was inconsistent with trial design; e.g. Section 3, Treatment period states "In the absence of safety concerns, every effort should be made to keep the participant on the randomized treatment until BICR-determined radiographic progression or completion of the 6 cycles of ^{177}Lu-PSMA-617."
- Section 9.1.1, Discontinuation of study treatment: The following sentence was added "Participants who have delay of treatment due to interruption of study drug supply can restart study treatment if they have recovered from all drug related toxicities per dose modification Table 6-2, do not demonstrate radiographic progression on most recent scheduled or unscheduled imaging, have not started other anticancer therapy, and every effort has been made to reschedule treatment as early as possible to minimize deviations from the treatment schedule."
- Section 9.2, Withdrawal of informed consent / Opposition to use data/biological samples: Section updated in line with the current Novartis protocol template.
- Section 10.1.1 Adverse events and Section 10.1.3 SAE reporting: The following sentence was added- "For participants who received ^{177}Lu-PSMA-617 in the ^{177}Lu-PSMA-617 arm or in crossover, the following SAEs will be captured beyond the 30 day safety period regardless of relationship to study treatment and whether new anticancer therapy has been initiated: hematologic toxicities with primary focus on myelosuppression and thrombocytopenia (including need for transfusion or use of growth factors), renal failure, xerostomia, xerophthalmia, secondary malignancies."

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1 (13-Jan-2022)

The study started on 15-Jun-2021 (FPFV) and as of 19-Dec-2021, 152 patients have received study treatment in 8 countries including US.

Amendment rationale

[redacted]

- Changes in language to selected inclusion/exclusion criteria were made for better clarity and improved definition of the intended study population.
- Updates to the schedule of assessments were made for certain laboratory parameters [redacted] collections.
- Procedures for crossover were revised and clarified.
- Screening period for assessments prior to randomization was expanded.
- Added language on potential drug interactions with ARDT therapy.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- In this protocol, the radiolabeled compound gallium (68Ga) gozetotide (AAA517 / [^{68}Ga]Ga-PSMA-11) is referred to as ^{68}Ga-PSMA-11, and the therapeutic agent lutetium (177Lu) vipivotide tetraxetan (AAA617 / [^{177}Lu]Lu-PSMA-617) is referred to as ^{177}Lu-PSMA-617.
- Throughout the protocol, "Subjects" has been replaced with the term "participants" when referencing study participants. The term "subject" continues to be used for data collection.
- Throughout the protocol, "Withdrawal of consent (WoC)" has been updated to "Withdrawal of consent (WoC) / opposition to use data/biological samples".
- Throughout the protocol, "BIRC" was replaced with "BICR".
- Typographical and grammatical errors addressed throughout the protocol.
- Glossary of terms has been updated as per protocol template version 4.0. Changes are specified below:
  - Definition of "cohort" was revised from "A specific group of participants fulfilling certain criteria and generally treated at the same time" to "A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time"
  - The term "Discontinuation from study" was added to glossary terms and defined as "Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data."

- The term “Study treatment discontinuation” has been changed to “Discontinuation from study treatment” and the definition changed from “When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation” to “Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.”
- Definition of “Electronic Data Capture (EDC)” was revised to clarify that EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care and not only data transcribed from paper source forms used at the point of care.
- Definition of enrolment has been updated from “Point/time of participant entry into the study at which informed consent must be obtained” to ‘Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants.”
- Definition of “Estimand” was updated to indicate the source which is ICH E9(R1) addendum.
- The term “Off-site” was added to the glossary terms and defined as “Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.”
- The term “Off-site healthcare Professional (OHP)” was added to glossary terms and defined as “A qualified healthcare professional, such as those used in the study e.g. nurse, phlebotomist, physician, who perform certain protocol procedures for the participant in an off-site location such as a participant's home."
- The term “Patient-Reported Outcome (PRO)” was added to the glossary and definition provided as “A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else.”
- The term “Remote” was added to the glossary and definition provided as “Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location.”
- “Withdrawal of study consent (WoC)” has been updated to “Withdrawal of study consent (WoC) / Opposition to use of data /biological samples” and definition revised from “Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data” to “Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation.

Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent."

- Protocol Summary was updated in alignment to updates made in protocol sections.
- Section 1.1, Background has been updated with a summary of results from VISION (NCT03511664) study, a phase III trial evaluating best standard care with or without ^{177}Lu-PSMA-617 in men who had metastatic castration-resistant prostate cancer previously treated with at least one androgen-receptor–pathway inhibitor and one or two taxane regimens and who had PSMA-positive gallium-68 (68Ga)–labeled PSMA-11 positron emission tomographic–computed scans.
- Section 2: Section title changed from "Objectives and endpoints" to "Objectives, endpoints and estimands" in line with the recent One CTP protocol template
- Section 3, Study design: Screening period has been revised from "Screening procedures are carried out from day -28 to -14 from randomization in IRT system" to "screening procedures are carried out after ICF signature AND within 28 days of randomization in IRT system" to harmonize screening window for all assessments to 28 days prior to randomization.
- Section 3, Study design: Randomization Period: Timing of randomization has been revised from "randomization at day -14 once eligibility is confirmed" to "randomization should occur within the 28 days screening period once all eligibility criteria are met" to provide better clarity.
- Section 3, Study design: Randomization Period: Biological products and immunotherapy have been added to the list of medications that must not be administered during the study treatment period for consistency with other sections of the protocol.
- Section 3, Study design: Treatment period: Additional guidance provided that, C1D1 can be delayed by up to an additional 3 days for unexpected scheduling delays.
- Section 3, Study design Treatment period: Additional guidance provided that, for participants who are able to complete all planned 6 cycles of ^{177}Lu-PSMA-617, the end of the treatment period is after completion of C6W5 visit and the fourth imaging assessment due at week 37. Guidance provided for better clarity.
- Section 3, Study design, Crossover period:
  - Window for participants randomized to ARDT arm to cross over to start receiving ^{177}Lu-PSMA-617 was clarified to be within 28 days of radiographic disease progression determined by BICR.
  - Additional guidance is provided that, following confirmation of patient eligibility for the crossover, the participant will be registered to Cross over via the IRT system and should start receiving ^{177}Lu-PSMA-617 within 14(+3) days after registration of crossover in IRT system.

- At the time of crossover, the criterion regarding any unresolved toxicity from prior therapy at the start of ^{177}Lu-PSMA-617 was changed from CTCAE grade 1 to CTCAE grade ≤2 or baseline for consistency with inclusion criterion #10.
- Clarified that, Baseline assessments must be performed within 28 days of registration for crossover and are described in Table 8-3. If the EOT1 visit has been performed within prior 28 days of registration for crossover, those results can be used to confirm patient eligibility to the crossover. Revision is to provide consistency with screening period for assessments.
- Clarified that, if a participant has not undergone required assessments within 28 days prior to registration for crossover, then they must complete or repeat the assessments in order to ensure the criteria are met. CT/MRI and bone scan within 28 days prior to registration for crossover must be available as new baseline images.
- Guidance to have ECOG PS, vital signs, hematology, biochemistry and adverse events assessments performed within 7 days prior to commencing treatment in crossover was removed for consistency.

- Section 3, Long term follow-up:
  - Week numbers in which radiographic imaging assessment is to be performed were corrected.
  - Clarified that, patient reported outcomes (PROs) and PSA will be collected during long term follow-up period.
  - Clarified that, radiographic imaging will be collected during long term follow-up only for participants with no rPFS event.
  - PRO has been added to the list of assessments for which if a participant withdraws consent for their collection during long term follow-up, survival information, SAEs related to study treatment and post-treatment antineoplastic therapy will still be collected. The change was made to allow for safety monitoring.
- Section 4.1, Rationale for study design: A statement indicating that VISION (NCT03511664) study is ongoing was deleted as the study is now completed and a summary of results from the study has been provided.
- Section 4.1.1, Rationale for choice of background therapy: addition of biological products and immunotherapy to the list of prohibited medication.
- Section 4.5, Risks and benefits:
  - Reference made to ^{177}Lu-PSMA-617 IB v4.0 was removed as it is no longer the most current IB and updates to the list of events
  - COVID-19 pandemic related risks: Clarified that, a delay in bone scan for more than 4 weeks no longer leads to treatment discontinuation.
  - COVID-19 pandemic related risks: IMP changed to study drug.
- Section 4.6, Rationale for Public Health Emergency mitigation procedures: Section 4.6 was introduced.
- Section 5.1, Inclusion criteria:
  - Inclusion criterion #7 was reworded for clarity from “Participants must have received one prior approved ARDT (for example, abiraterone, enzalutamide, darolutamide, or

apalutamide, etc.) and have documented progression on therapy" to "Participants must have progressed only once on prior second generation ARDT (abiraterone, enzalutamide, darolutamide, or apalutamide).
    - first generation androgen receptor inhibitor therapy (e.g. bicalutamide) is allowed but not considered as prior ARDT therapy
    - second generation ARDT must be the most recent therapy received"
  - Inclusion criterion #8 – In order to align with PCWG3 criteria, PSA progression was changed from requiring 2 consecutive increases in PSA over previous reference value to requiring 2 increases in PSA levels at least a week apart. The minimum start value remains unchanged (2.0 ng/ml). Further clarification provided that, if PSA is the only indication of disease progression, the minimum level of PSA must be 1.0 ng/ml. To align with PCWG3, Criterion for progression of bone disease was also revised from "evaluable disease or one or more new bone lesions(s) by bone scan" to "two new lesions; only positivity on the bone scan defines metastatic disease to bone"
  - Inclusion criterion #9 – 'begining study therapy' was replaced with 'randomization'
  - Inclusion criterion #13 –Added clarification "Participants cannot have previously progressed nor had intolerable toxicity to both enzalutamide and abiraterone" in order to clarify conditions for this criterion.
- Section 5.2, Exclusion criteria
  - Exclusion criterion #3 – Prior treatment that would exclude candidates from participation in the study was updated to include PARP inhibitors. Additional information is provided to indicate that prior treatment with sipuleucel-T is allowed.
  - Exclusion criterion #6 – Concurrent treatment that would exclude candidates from participation in the study was updated to include PARP inhibitors and biological therapy. The update was made to align the criterion with concomitant medication section.
  - Exclusion criterion #11 – For candidates who had active documented COVID-19 infection at time of informed consent and had completely recovered (in accordance with local guidance) to be enrolled only when they had no symptoms for at least 28 days before the first dose of study medication was revised to remove the requirement to have no symptoms for at least 28 days.
  - Exclusion criterion #12 was clarified that for participants with a prior history of other malignancy that has been adequately treated and who are disease and treatment free, the reference point for assessing disease and treatment free condition is randomization.
  - Exclusion #13: The period after stopping study treatment for which sexually active males should agree to continue using condoms was changed from for at least 6 months to for at least 14 weeks after stopping study treatment per guidance document "Guidance Pregnancy Prevention in Clinical Trials, version dated Nov-2021" in line with One CTP V4.0
  - Exclusion criterion #14 was updated to clarify that unmanageable concurrent bladder outflow obstruction or urinary incontinence would exclude a candidate from participation in the study however candidates with bladder outflow obstruction or

urinary incontinence, which is manageable and controlled with best available standard of care (incl. pads, drainage) are allowed. The update is in response to DMC's request to provide more clear definition to investigators.

- Exclusion criterion #17: "as assessed by the investigator" was deleted to remove ambiguous language.

- Section 6.1, Study treatment: addition of biological products and immunotherapy to the list of prohibited medication
- Table 6-1:
  - Dosage form for 177Lu-PSMA-617 was updated from "Radiopharmaceutical solution" to "Radiopharmaceutical solution for infusion/injection"
  - Column header "Supply type" has been changed to "Presentation".
- Section 6.1.2, ^{68}Ga-PSMA-11 Imaging:
  - The read criteria for 68Ga-PSMA-11 eligibility screening assessments were added.
  - Clarification provided that if a potential participant received 68Ga-PSMA-11 as part of a routine local exam prior to signing informed consent for this study, then he must wait at least 3 days prior to repeating 68Ga-PSMA-11 PET imaging as screening for this study.
- Guidance provided on which 68Ga-PSMA-11 products may be used for the study.
- Section 6.1.2, ARDT: Need to also follow local guidelines on contraceptive requirements when using ARDT was added [redacted]
- Section 6.1.3: Partner Radiopharmacy changed to central Radiopharmacy to correct the nomenclature.
- Section 6.1.4, Treatment arms/group:
  - Clarified that prior ARDT use will be determined by the setting (CRPC vs HSPC) when the patient initiated treatment with enzalutamide, abiraterone, apalutamide, or darolutamide then suffered disease progression.
- Section 6.1.6, Treatment duration:
  - Window of +3 days has been introduced at C1D1 to accommodate potential scheduling delays.
  - Clarified that, for participants on the 177Lu-PSMA-617 arm who complete the planned 6 cycle course therapy, the treatment period ends after the week 37 imaging and C6W5 visit is completed.
- Section 6.2.1, Concomitant therapy:
  - Subsection: Palliative radiotherapy:
    - Time-point for first post baseline scan was corrected from 12 weeks to 8 weeks.
    - Guidance provided for better clarity that when the need for palliative radiation to lesions other than bone is seen after the baseline scan, palliative radiation to the target lesion should be possibly avoided, the lesion should be assessed per RECIST 1.1 criteria, and initiation of palliative radiation may result in study discontinuation when radiographic progression is confirmed.

    - Guidance provided for better clarity that if palliative radiation treatment is planned to be initiated during the study in the absence of radiographic progression, the investigator should use best clinical judgement to assess the potential clinical benefit of palliative radiation weighed against the risk of overlapping side effects of radiation and study treatment when considering timing and doses of palliative radiotherapy. Any interruption of study treatment greater than 4 weeks from the next scheduled dose requires permanent discontinuation of study treatment
  - Subsection: Medications for myelosuppression: Clarified that the use of growth factors should follow published guidelines of the ASCO and /or other international/national guidelines at the discretion of the investigator/attending physician.
- Section 6.2.2, Prohibited medication: addition of biological products and immunotherapy to the list of prohibited medication. Guidance provided that enzalutamide has potential drug interactions with medications that are strong CYP3A4 inducers and strong CYP2C8 inhibitors. Abiraterone has potential drug interactions with medications that are strong CYP3A4 inducers or inhibitors. The treating investigator must follow the dose modification recommendations per the labeling for each agent in cases where such medications are unavoidably co-administered with study treatment for ARDT arm participants.
- Section 6.5.2, Dose modification:
  - Information from Table 6-2 regarding dose modification management if central lab results are not available in time to review prior to dosing and discontinuation of treatment with 177Lu-PSMA-617 if any toxicity is determined to be unacceptable to the participant or the investigator was put in the paragraph preceding the table.
  - Clarification was added for dose modification due to casual relationship between 177Lu-PSMA-617 and an adverse event
  - Clarification was added on toxicity management
- Table 6-2:
  - Table header updated from “Dose modifications” to “Toxicity management and dose modifications for 177Lu-PSMA-617 treatment for adverse drug reactions” to clarify that the table is applicable to treatment related events.
  - Serum creatinine: the terms ‘within 24hours’ were changed to ‘before the next administration’
  - Amylase and/or lipase elevation: The term asymptomatic amylase and/or lipase elevation” was changed to “Amylase and/or lipase elevation”. Criteria for dose modification due to elevated amylase/lipase was updated.
  - Electrolyte and metabolic abnormalities: The term used for the abnormality ≥ Grade 2 has been updated from “Electrolyte or metabolic abnormalities that are correctable within a 48 hr period without sequela” to “Electrolyte or metabolic abnormalities that persist for greater than 48 hrs with sequela”
  - Removal of events ‘Any AE that requires drug discontinuation or treatment delay of > 4 weeks’ and ‘Any unacceptable toxicity’

  - Note: updated frequency of hematologic parameters monitoring from 8 to 12 weeks
- Table 6-3: Added to provide guidance for dose reduction for ^{177}Lu-PSMA-617. Subsequent table numbering was impacted
- Section 6.3.2, Wording added clarifying randomization procedures.
- Section 6.5.3.1, Follow up on potential drug-induced liver injury (DILI) cases: A recommendation added that Glutamate Dehydrogenase testing is additionally recommended if available for the assessment of DILI. Updated for better monitoring of DILI.
- Section 6.7, Preparation and administration: Guidance provided that immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the tear-off label from the packaging and affix it to the source document.
- Section 6.7.1, Handling of study treatment and additional treatment updated header to 'Handling of study treatment and other treatment'
- Section 6.7.1.1, Handling of study treatment
  - ^{68}Ga-PSMA-11: the term 'bolus' was updated to 'single intravenous injection'.
  - Guidance provided that technical complaints are to be reported to the respective Novartis contact/associate or 3rd party representative
  - Advised that medication labels will be in the local language and in compliance with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.
  - Clarified that a site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines.
- Section 6.7.2, Instruction for prescribing and taking study treatment
  - Guidance provided that when a participant with manageable bladder outflow/urinary incontinence is randomized to receive treatment with ^{177}Lu-PSMA-617, the investigator should consult local nuclear medicine expert and ensure, that local radiation safety standards can be followed, and there is no additional potential impact of radiation safety (for trial participant, site staff, environment). Guidance provided in response to DMC request for better guidance for sites.
  - Clarified that management of bladder outflow/urinary incontinence is at the discretion of the investigators and may include best available standard of care options which are considered appropriate by the investigator. Guidance provided in response to DMC request for better guidance for sites.
  - Clarification provided that guidelines for administration of ARDT include also contraceptive measures as requested by HA.
  - Additional clarification was provided on management of extravasation or site irritation when administering ^{177}Lu-PSMA-617
  - COVID-19 pandemic was removed and replaced with "Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster"
- Section 7, Informed consent procedures

  - A statement indicating that the main study consent included [redacted]
  - COVID-19 pandemic was removed and replaced with "Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster"
  - Clarified that in situations when per protocol the investigator may conduct consent discussion remotely the investigator may do so only if also allowable by local Health Authority.
- Section 8, Visit schedule and assessments
  - Clarified that participants who discontinue from study are to return for end of treatment visit as soon as possible and attend follow-up visit as indicated in the Assessment Schedule
  - Clarified that participants who withdraw their consent/oppose the use of their data/biological samples should also be scheduled for a final evaluation visit if they agree.
  - Clarified that "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor while "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.
  - Guidance provided that PRO measure(s) must be completed before any clinical assessments are performed at any given visit.
  - COVID-19 pandemic was removed and replaced with "Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster"
  - Clarification provided that if allowable by a local Health Authority and depending on operational capabilities, off-site study visit may replace on-site study visit.
  - Correction made to clarify that a delay in bone scan for more than 4 weeks no longer lead to treatment discontinuation.
- Table 8-1
  - Screening period clarified that it occurs after ICF signature and within 28 days of randomization in IRT
  - Cycle 1 Day 1 has been granted additional 3 days to allow for unexpected schedule delays.
  - All other visits in Cycle 1 (excluding C1D1) have visit window changed from ±7 days to ±3 days.
- Table 8-2
  - For ARDT arm after cycle 6, clarification provided that cycles will occur every 12 weeks.
  - Visit name for EOT period was updated from "End cycle" to EOT1
  - Row for weeks was removed from the table as having it did not add value.

- Start of screening was changed from day -28 to day -42 to allow for enough operational time to complete screening assessments.
- End days of cycles have been removed from C1W2, C1W3, C1W4, C1W5, C1W6, and Cycles 2-6 (C#W1, C#W3, C#W5) as having them did not add value.
- Superscript #5 was added to hematology, clinical chemistry and coagulation panel assessments at C1W1 and C#W1 and for ARDT arm to clinical chemistry and coagulation panel at C#W1 beyond cycle 6, to clarify that results of these laboratory assessments must be reviewed prior to dosing.
- Superscript #6 was removed from hematology, clinical chemistry and coagulation assessments and in so doing, the frequency of their assessments during LTFU was corrected from every 24 weeks to every 12 weeks.
- Superscript #6 has been introduced on ARDT arm beyond cycle 6 to clarify the study cycle in the context of ARDT dosing.
- PSA was added to be assessed during Long term FU for consistency.
- [redacted]
- Superscript 19 added to Survival assessment during Long term FU to provide clarification that as long as the participant remains on study, contact for survival assessments should continue during long term follow-up even if a participant has withdrawn consent for other assessments that require visits to study site such as blood sampling, PROs, and/or imaging.
- Requirement added to assess during the 30 days Safety FU the use of new antineoplastic therapies since study drug discontinuation to better monitor the safety of the participant.
- Symptomatic skeletal events assessment introduced as it is a secondary endpoint.
- Clinical progression assessments introduced as it is a secondary endpoint.
- Footnote #4 updated to include temperature and clarified that temperature needs to be recorded only once approximately 15 minutes prior to study treatment.
- Footnote #5: Clarification that hematology assessment was to be performed every 8 weeks was removed as the frequency has been added in the column header.
- Footnote #5 revised to clarify that, results of hematology, clinical chemistry and coagulation panel assessments at C1W1 and C#W1 and for ARDT arm at C#W1 beyond cycle 6, must be reviewed prior to dosing prior at those visits.
- Footnote #6: Clarification that hematology, clinical chemistry and coagulation assessments during Long term FU was to be performed every 24 weeks was removed as the correct frequency in the column header is every 12 weeks.
- Footnote #6 revised to clarify that though ARDT is administered continuously however, for the purposes of this research study, although unconventional, the visit timepoints are termed “cycles”.

[redacted]

- Footnote #10: Pelvis was added for consistency.
- Footnote #12: Week numbers in which radiographic imaging assessment is to be performed were corrected.
- Footnote #14: Week numbers in which radiographic imaging assessment is to be performed were corrected.
- Footnote #15: Clarified that PRO will be assessed at LTFU2 (168 days after EOT) and LTFU4 (336 days after EOT) for all participants unless, lost to follow-up or withdrawal of consent / opposition to use data/biological samples.
- Footnote #18 added to clarify that if the potential participant received [^{68}Ga]Ga-PSMA-11 as part of a routine local exam prior to signing informed consent for this study, he must wait at least 3 days prior to repeating ^{68}Ga-PSMA-11 PET imaging as screening for this study.
- Footnote #19 added to clarify that as long as the participant remains on study, contact for survival assessments should continue in long term follow up even if a subject has withdrawn consent for other assessments that require visits to study site such as blood sampling, PROs, and/or imaging.
- Footnote #20 added to clarify that clinical progression as assessed by the investigator and referenced in Section 8.3.3.

[redacted]

- Table 8-3
- Column labeled "Baseline" has been added to the table and assessments to be performed specified.
- Row for weeks was removed from the table as having it did not add value.
- End day of Baseline is added as Day -1.
- End days of cycles have been removed from C1W1, C1W2, C1W3, C1W4, C1W5, C1W6, and Cycles 2-6 (C#W1, C#W3, C#W5) as having it did not add value.
- Superscript #5 was removed from hematology, clinical chemistry and coagulation panel assessments and in so doing, the frequency of their assessments during LTFU was corrected from every 24 weeks to every 12 weeks as stated in the column header.
- Superscript #5 was added to hematology, clinical chemistry and coagulation panel assessments at C1W1 and C#W1 to clarify that results of these laboratory assessments must be reviewed prior to dosing.
- PSA was added to be assessed during Long term FU for consistency.

[redacted]

- Survival assessment removed from C#W3 as the patient would still be on active treatment.
- Symptomatic skeletal events assessment introduced as it is a secondary endpoint.
- Clinical progression assessments introduced as it is a secondary endpoint.
- Footnote #4 updated to include temperature and clarified that temperature needs to be recorded only once approximately 15 minutes prior to study treatment.
- Footnote #5 clarification on the hematology, clinical chemistry and coagulation during Long term FU was to be assessed every 24 weeks was removed to correct the frequency of assessment to every 12 weeks as in column header.
- Footnote #5 revised to clarify that, results of hematology, clinical chemistry and coagulation panel assessments at C1W1 and C#W1 and for ARDT arm at C#W1 beyond cycle 6, must be reviewed prior to dosing prior at those visits.
- [redacted]
- Footnote #9: Week numbers in which radiographic imaging assessment is to be performed were corrected.
- Footnote #10 clarified that a new radiographic imaging assessment is required at crossover baseline only if there is none done within 28 days prior to registration for crossover.
- Footnote #11: Week numbers in which radiographic imaging assessment is to be performed were corrected.
- Footnote #12: Clarified that PRO will be assessed at LTFU2 (168 days after EOT) and LTFU4 (336 days after EOT) for all participants unless, lost to follow-up or withdrawal of consent / opposition to use data/biological samples
- Footnote #13: Timing of ^{177}Lu-PSMA-617 Order was additionally clarified that it occurs after confirmation of eligibility and IRT registration for crossover.
- Footnote #14 added that "Assessments from EOT1 may be used if performed within prior 28 days. Assessments may be repeated if necessary to meet eligibility"
- Footnote #15 added to provide clarification that as long as the participant remains on study, contact for survival assessments should continue during Long term FU even if a subject has withdrawn consent for other assessments that require visits to study site such as blood sampling, PROs, and/or imaging.
- Footnote #16 added that clinical progression as assessed by the investigator and referenced to Section 8.3.3.

- Section 8.1, Screening:
  - Clarified that all screening assessments to confirm eligibility should start after signing of ICF and within 28 days prior to randomization.
  - Clarified that if any screening assessment result does not meet eligibility criteria the assessment may be repeated as long as it is performed within the 28 days prior to randomization.
  - Laboratory test changed to screening assessment.

  - Clarified that if the ^{68}Ga-PSMA-11 PET/CT needs to be repeated then a new eligibility read by the central imaging vendor is required. Further that, baseline imaging (CT/MRI and bone scan) must continue to be within window for the new anticipated randomization date, and repeated if necessary.
  - Guidance provided that the investigator should immediately notify the study sponsor and central imaging vendor if any participant is to be rescreened, and whether scans already submitted to the central imaging vendor need to be linked to the new participant identification.
- Section 8.1.1, Eligibility screening:
  - A statement that the key eligibility criteria checklist will be completed prior to the first dose of study drug in the IRT system was removed because no checklist is designed to be completed.
  - A statement that the eligibility check will be embedded in the IRT system was removed because there is no such checklist.
  - Clarified that randomization is performed as per Section 6.3.2.
- Section 8.1.2, Information collected on screening failures: Clarified that the AE eCRF should also be completed for all participants who have received ^{68}Ga-PSMA-11.
- Section 8.2, Participant's demographics/other baseline characteristics:
  - Updated to provide clarification that participant's demographics will include: full date (only if required and permitted) or year of birth or age, sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions until date of signature of informed consent will be recorded in the eCRF. And where possible diagnosis and not symptoms should be recorded.
  - Updated to provide clarification why participant's race/ethnicity data are collected and analyzed. Clarified also that, all prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented.
  - Clarified that prostate cancer history should include also Gleason score at diagnosis, AJCC stage at diagnosis and extent of disease.
- Section 8.3.1, Radiographic imaging for tumor assessment
  - Guidance provided that sites of "soft-tissue" disease will be characterized as either target or non-target lesions based on CT/MRI images and that the distribution of the target and non-target lesions should be representative of the subject's overall disease. Detailed guidance provided on the number of lesions and how they will be chosen for measurement over the course of the study.
  - Guidance provided that sites of bone disease will be recorded based on bone scan, with exception to bone metastasis with soft tissue component which may qualify for target/non-target when detectable at CT/MRI and that for the purpose of the study, bone lesion(s) should be assessed by bone scan only.
  - COVID-19 pandemic removed and replaced with "Public Health emergency as declared by Local or Regional authorities i.e pandemic, epidemic or natural disaster"
- Table 8-4:

- Week numbers in which radiographic and bone scan assessments are to be performed were corrected.
- Repeat instructions regarding procedure for localized bone CT, MRI or X-ray was removed from the table.
- Specified that bone scan should be done with technetium-99m labeled disphosphonate in alignment with other sections of the protocol.
- Guidance on management of contraindication to CT intravenous contrast media was moved from the paragraph below the table and added as a footnote to the table.

- Baseline imaging assessment:
  - Clarified that whole body bone scan is to be performed using technetium-99m labeled diphosphonates.
  - Option for whole body bone MRI, Fluorodeoxyglucose positron emission tomography (FDG-PET) or sodium fluoride (NaF) PET] was removed as technetium-99m labeled diphosphonates must be used. Additionally, statement that "Localized CT, MRI, or X-rays should be acquired for all skeletal lesions identified on the screening whole body bone scan, which are not visible on the chest, abdomen and pelvis CT/MRI" was deleted to remove ambiguity.
  - Clarified also that X-ray should not be used to measure tumor lesions.
- Post-baseline imaging assessment:
  - Clarified that for "soft-tissue" disease, determination of CR or PR requires confirmation by repeat assessments that should be performed at least 4 weeks after the criteria for response are first met.
  - Clarified that investigators may perform FDG-PET scans to corroborate progressive disease per the PCWG3 Guidelines, but will not be used by itself to determine radiographic progression.

- Section 8.3.3, Clinical progression: Duration of palliative therapy not considered potentially indicative of disease progression was corrected from 12 weeks to 8 weeks after first study treatment dose.
- Section 8.3.4, PSA level: The statement that increases and decreases will be tracked to assess PSA responses as per PCWG3 (Section 16.3) removed as is Section 16.3 is no longer applicable to PSA.
- Section 8.4 Safety:
  - COVID-19 pandemic deleted and replaced with "Public Health emergency as declared by Local or Regional authorities i.e pandemic, epidemic or natural disaster"
  - Clarified that following Public Health emergency that limited/prevented onsite visit, onsite visit may resume only when it is safe for the participant to visit the site again.
  - Table 8-5: Clarified that vital signs include temperature and that temperature needs to be recorded only once at the 15 min pre-dose timepoint. Duplicate information that "Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature." was removed.
- Section 8.4.1 Laboratory evaluation

  - Guidance provided that if participants cannot visit the site for safety lab assessments conducted through central labs, local lab collection may be used during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits.
  - Table 8-7 Blood urea nitrogen and glucose was removed. eGFR was added to EOT visit to ensure that it is assessed for participant potentially crossing over.
- Section 8.4.3 Pregnancy and assessment of fertility:
  - The period for which effective birth control should be used following the last dose of ^{177}Lu-PSMA-617 and for which a male participants should not donate sperm following the last dose of ^{177}Lu-PSMA-617 was changed from at least 6 months to at least 14 weeks per guidance document "Guidance Pregnancy Prevention in Clinical Trials, version dated Nov 2021"
  - Recommendation that participants who have been administered ^{68}Ga-PSMA-11 but did not start treatment with ^{177}Lu-PSMA-617, practice an effective barrier method of birth control was changed to contraception not required and reference made to IB for latest guidance on contraception. Guidance also provided that participants receiving ARDT must follow contraceptive requirements as per the local label for the respective drugs.
- Section 8.5.1, Clinical outcome assessments; subsection: Patient Reported Outcomes: The guidance regarding the possibility for Clinical Outcome Assessments data to be collected remotely due to COVID-19 was revised and expanded to include all Public Health Emergencies as declared by Local or Regional authorities and collection would depend on local regulations, technical capabilities, and following any applicable training in the required process.
- Section 8.5.1.4 Trial Feedback: Clarification provided that the completion of Trial Feedback Questionnaire is optional.

- Section 9: Title modified to Discontinuation and completion
- Section 9.1: Title modified to Discontinuation from study treatment and from study
- Section 9.1.1: Title modified to Discontinuation from study treatment.

- Situation when discontinuation of study treatment for a participant is considered to occur was updated for better clarity.
- Circumstances under which study treatment must be discontinued was revised to remove ambiguity and provide better clarity:
  - Clarified that permanently stopping study treatment after completion of the 6 cycles of ^{177}Lu-PSMA-617 per protocol is no longer considered a discontinuation and is removed reasons for study treatment discontinuation.
  - Clarified that use of prohibited medication is a criterion for discontinuation from study treatment irrespective of the reason why the prohibited medication was used.
  - Correction made to indicate that, the time limit of a maximum of 4 weeks of treatment interruption beyond which treatment must be permanently discontinued was made applicable to all interruptions irrespective of reason for interruption.
  - A delay in bone scan for more than 4 weeks was removed from the reasons for treatment discontinuation.
  - Unequivocal clinical progression has been added for consistency.

- Section 9.1.2 Discontinuation from study: A new section "Discontinuation from study" was introduced to define a situation when a participant is considered discontinued from study.
- Section 9.1.2 Withdrawal of consent: Previously in Section 9.1.2 was moved to Section 9.2
- Section 9.1.3 Lost to follow-up: Revised for better clarity and states what the participant did not state the intention to discontinue from or withdraw ie discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples.
- Section 9.1.4, Early study termination by sponsor: Previously in Section 9.1.4 was moved to Section 9.4.
- Section 9.2 Title updated from "Withdrawal of consent" to "Withdrawal of consent / opposition to use data/biological samples"
  - Guidance updated
    from:
    Withdrawal of consent occurs only when a participant Does not want to participate in the study anymore, and Does not want any further visits or assessments and Does not want any further study related contacts and Prohibits further collection and use of their data and samples
    to:
    Withdrawal of consent / opposition to use data/biological samples occurs when a participant explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples) and No longer wishes to receive study treatment and Does not want any further visits or assessments (including further study related contacts)
- This request should be in writing (depending on local regulations) and recorded in the source documentation.

- Use of personal data was updated
  from
  Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.
  to
  Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However they still retain the right to object to the further collection or use of their Personal Data.

- Section 9.3 Study completion and post study treatment: Guidance provided that for participants who are able to complete the planned 6 cycles of ^{177}Lu-PSMA617, the end of the treatment period is upon completion of the C6W5 visit and the response assessment imaging due at week 37.
- Section 9.4 Title "Early study termination by the sponsor" has been moved from section 9.1.4 to Section 9.4.
- Section 10.1.1 Adverse events:
  - Instruction regarding duration was modified to indicate that an outcome is expected for all events whether they ended or are ongoing.
  - Options regarding outcome has been updated to include recovering/resolving.
- Section 10.1.3 SAE reporting:
  - Clarified that SAE must be reported to Novartis Safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events. And noted that, if local regulations regarding reporting timelines are more stringent, then local regulations prevail. And that, detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.
  - Additional clarification provided regarding reporting SAE experienced after the 30-day safety follow-up to indicate that local law/regulation will prevail if different from protocol guidance.
  - Clarified that follow-up to the original episode must be reported immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information. And noted that, if local regulations regarding reporting timelines are more stringent, then local regulations prevail.
- Section 10.2 Additional Safety Monitoring: Phrase "not applicable" was deleted to remove inconsistency.
- Section 12.1, definitions of RECIST Analysis Set and ^{68}Ga-PSMA-11 Full Analysis Set clarified. Addition of ^{177}Lu-PSMA-617 Safety Set to analyze safety in all patients receiving ^{177}Lu-PSMA-617 [redacted]
- Section 12.4 Analysis of the primary endpoint(s)/estimand(s)
  - Header was updated to 'Analysis of the supporting primary objectives'
- Section 12.4.1, Definitions of the primary endpoints(s)/estimand(s): removal of the word 'estimands'

- Section 12.5, Analysis of secondary endpoints/ estimands: Header updated to 'Analysis supporting secondary objectives'
- Section 12.5.1.2:
  - Clarification that ^{177}Lu-PSMA-617 treatment for crossover patients is considered the second line treatment in PFS2 analyses
  - PSA50 response timepoints aligned with PSA collection schedule
- Section 12.5.2:
  - On-treatment period for randomized treatment is defined to take into account the length of ^{177}Lu-PSMA-617 cycles and the crossover
  - Adverse events reported related to ^{68}Ga-PSMA-11 will be considered 'on-treatment' regardless of start of randomized treatment
  - Vital signs: updated, vital signs will be summarized by treatment and Visit/time.
- [redacted]
- Section 15, References: Additional two references below added:
  - Fizazi K, Herrmann K, Krause BJ, et al (2021) Health-related quality of life (HRQoL), pain and safety outcomes in the phase 3 VISION study of ^{177}Lu-PSMA-617 patients with metastatic castration-resistant prostate cancer [abstract]. Ann Oncol; 32 Suppl 5: S626-S677
  - Sartor O, de Bono J, Chi KN, et al (2021) Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med; 385(12): 1091-1103.
- Section 16.2, A note added to emphasize that PCWG3 modified RECIST 1.1 must be adhered to for all local and central response assessments.
- Section 16.3, Appendix 3 PCWG3
  - PSA response assessment was removed from Appendix 16.3 as PSA in not a primary objective.
  - Table 16-6: PCWG3 (2016) guidelines has been added to the protocol for quick access.
- Section 16.4: Appendix 4 has been added to the protocol to provide study-specific adjustments of Response Evaluation Criteria in Solid Tumors, Guideline based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines RECIST Criteria (App. 2)

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CAAA617B12302
Study Title	PSMAfore: A phase III, Open-label, Multi-Center, Randomized Study Comparing ^{177}Lu-PSMA-617 vs. a Change of androgen receptor-directed therapy in the Treatment of Taxane Naïve Men with Progressive Metastatic Castrate Resistant Prostate Cancer
Brief Title	Open-label study comparing ^{177}Lu-PSMA-617 vs. a change of androgen receptor-directed therapy drugs in the treatment of mCRPC
Sponsor and Clinical phase	Novartis, Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine whether ^{177}Lu-PSMA-617, given for 6 cycles at a dose of 7.4 Gigabecquerel (GBq) (200 Millicuries (mCi)) +/- 10%, improves the radiographic progression free survival (rPFS) or death compared to a change in androgen receptor-directed therapy (ARDT) in metastatic castrate resistant prostate cancer (mCRPC) participants that were previously treated with an alternate ARDT and not exposed to a taxane-containing regimen in the castrate resistant prostate cancer (CRPC) or metastatic hormone-sensitive prostate cancer (mHSPC) settings.
Primary Objective	To evaluate whether treatment with ^{177}Lu-PSMA-617 improves the time to radiographic progression by BICR according to Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1 or death in participants with progressive PSMA-positive mCRPC compared to participants treated with ARDT
Key Secondary Objective	To evaluate whether treatment with ^{177}Lu-PSMA-617 improves the overall survival (OS) in participants with progressive PSMA-positive mCRPC compared to participants treated with ARDT treatment
Secondary Objectives	• To estimate the time to radiographic progression by BICR or death in participants treated with ARDT who subsequently crossover to ^{177}Lu-PSMA-617 after radiographic progression (rPFS2) • To evaluate Progression free survival (PFS) by investigator's assessment • To evaluate the second progression Free Survival (PFS2) by investigator's assessment • To evaluate whether treatment with ^{177}Lu-PSMA-617 improves the biochemical response as detected by Prostate specific antigen (PSA) halving compared to participants treated with ARDT • To evaluate whether treatment with ^{177}Lu-PSMA-617 improves the time to first symptomatic skeletal event (TTSE) compared to participants treated with ARDT • To evaluate whether treatment with ^{177}Lu-PSMA-617 improves the time to radiographic soft tissue progression compared to participants treated with ARDT • To evaluate whether treatment with ^{177}Lu-PSMA-617 improves the time to chemotherapy compared to participants treated with ARDT • To evaluate whether treatment with ^{177}Lu-PSMA-617 improves the health-related quality of life (HRQoL) compared to participants treated with ARDT • To evaluate the safety and tolerability of ^{177}Lu-PSMA-617
Exploratory Objectives	[redacted]

	[redacted]
Study Design	This is a phase III, open label, multicenter randomized study for PSMA-positive metastatic CRPC participants previously treated with an ARDT and where it is considered appropriate to delay taxane-based chemotherapy. The study aims at evaluating the superiority of ^{177}Lu-PSMA-617 over a change of ARDT treatment in prolonging rPFS. The primary endpoint of rPFS will be assessed via blinded independent centralized review of radiographic images provided by the treating physician and as outlined in PCWG3 Guidelines. The study will also evaluate whether ^{177}Lu-PSMA-617 improves the overall survival (OS) in participants with progressive PSMA-positive mCRPC compared to participants treated with a change in ARDT treatment. OS is defined as the time from randomization to death due to any cause. **Screening period** Screening procedures are carried out after signature of informed consent and within 28 days prior to randomization in Interactive Response Technology (IRT) system. At screening, the participants will be assessed for eligibility and will undergo a ^{68}Ga-PSMA-11 positron emission tomography (PET)/computed tomography (CT) scan to evaluate PSMA positivity by central review. Only participants with PSMA positive cancer and confirmed eligibility criteria will be randomized. Randomization will be stratified by prior ARDT use in castrate-resistant prostate cancer (CRPC) vs. HSPC setting and by symptomatology i.e. asymptomatic or mildly symptomatic (score on item 3 of the Brief Pain Inventory Short Form (BPI-SF) questionnaire (symptomatic = score >3 on item 3 of the BPI-SF questionnaire). For all participants, the treating physician will make a choice of which ARDT (abiraterone or enzalutamide) will be administered to the participant should they get randomized to the ARDT arm. If the participant gets randomized to receive ^{177}Lu-PSMA-617, the choice of change of ARDT treatment will be discarded. **Randomization period** Randomization occurs within the 28 days screening period once all eligibility criteria are met. The participants will be randomized 1:1 to receive ^{177}Lu-PSMA-617 or a change of the ARDT treatment. The ARDT change will include approved Androgen Receptor (AR) axis targeted therapy (abiraterone or enzalutamide). Supportive care will be allowed in both arms at the discretion of the investigator and includes available care for the eligible participant according to best institutional practice for mCRPC treatment, including androgen deprivation therapy (ADT). Investigational agents, biological products, immunotherapy, cytotoxic chemotherapy, other systemic radioisotopes (e.g. radium-223), Poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors or hemi-body radiotherapy treatment must not be administered during the study treatment period. ARDT must not be administered concomitantly with ^{177}Lu-PSMA-617. **Treatment period** • **^{177}Lu-PSMA-617 treatment arm** Participants randomized to the investigational arm must begin ^{177}Lu-PSMA-617 dosing within 14 days after randomization. Participants will receive 7.4 GBq (200 mCi) +/- 10% ^{177}Lu-PSMA-617 once every 6 weeks for 6 cycles as per Table 8-2. Best supportive care, including ADT, may be used. After the last day of study treatment period of ^{177}Lu-PSMA-617 (i.e. after completion of 6 cycles of treatment OR treatment discontinuation for any reason) [for e.g. upon radiographic progression as assessed by blinded centralized review]) or upon radiographic progression as assessed by blinded centralized review, the participants must have an End of Treatment (EOT) visit performed ≤ 7 days and enter the Post-treatment Follow-up. In the absence of safety concerns, every effort should be made to keep the participant on the randomized treatment until BICR-determined radiographic progression or until the completion of the 6 cycles of ^{177}Lu-PSMA-617. • **ARDT treatment arm** For participants randomized to the ARDT treatment arm, the change of ARDT treatment for each participant will be selected by the treating physician prior to randomization and will be administered per the physician's orders. Best supportive care, including ADT,

may be used. After the last day of study treatment (treatment discontinuation for any reason) or upon radiographic progression as assessed by blinded centralized review, the participants must have an End of Treatment (EOT) visit performed ≤ 7 days and enter the Post-treatment Follow-up.
In absence of safety concerns, every effort should be made to keep the participant on the randomized treatment until BICR-determined radiographic progression.

End of Treatment

Randomized treatment may be discontinued if:

- The participant, sponsor or investigator chooses to discontinue treatment
- Toxicity
- Completion of the 6 cycles of ^{177}Lu-PSMA-617
- Serious non-compliance to the protocol
- BICR-determined progression

It is important that the scheduled imaging assessments continue until BICR-determined progression. PSA progression is strongly discouraged as a criterion for initiation of a new neoplastic therapy prior to BICR-determined progression. PCWG3 guidelines should be followed to guide discontinuation of treatment
End of Treatment visit must be performed ≤ 7 days after the last day of study treatment period. EOT is to occur before the participant is to enter the post-treatment Follow-up period of the study and before the initiation of any subsequent anticancer treatment, outside of what is allowed in the study.
If a participant withdraws consent for the treatment period of the study, an EOT must be done and the participant will enter the Post-treatment Follow-up unless he specifically withdraws post-treatment Follow-up.

Crossover period

Upon confirmation of rPFS by BICR, participants randomized to the ARDT arm will either be allowed to cross over to receive ^{177}Lu-PSMA-617 within 28 days of central confirmation of radiographic disease progression, or may continue to receive any other therapy per the discretion of the treating physician in the Post-treatment Follow-up.
In order for a participant randomized to the change in ARDT arm to cross over to receive ^{177}Lu-PSMA-617, he must meet the following criteria:

- Confirmed radiographical progression as assessed by BICR
- No intervening antineoplastic therapy is administered after the randomized treatment
- Any unresolved toxicity from prior therapy should be controlled and must be no greater than CTCAE grade ≤2 or baseline at the time of registration. for crossover
- ECOG performance status 0-1 at the time of registration for crossover
- Adequate organ function at the time of registration for crossover:
  - Bone Marrow reserve:
    - ANC ≥1.5 x 10^9/L
    - Platelets ≥100 x 10^9/L
    - Hemoglobin ≥9 g/dL
  - Hepatic
    - Total bilirubin (TBIL) ≤ 2 x ULN (upper limit of normal). For participants with known Gilbert's Syndrome ≤3 x ULN is permitted
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤3.0 x ULN OR ≤5.0 x ULN for patients with liver metastases
  - Renal:
    - eGFR ≥ 50 mL/min/1.73m^2 using the Modification of Diet in Renal Disease (MDRD) equation
- Agreement to continue with the study visit schedule

A participant, who is deemed to have disease progression per investigator assessment, but not by BICR, is not eligible to cross over at that time. Such participant should continue to receive randomized study treatment until progression determined by BICR.
Please refer to Section 8 for visit schedule and assessments following crossover.
If crossover to ^{177}Lu-PSMA-617 is selected, then ^{177}Lu-PSMA-617 will be administered with the same dose/schedule as for participants who were initially randomized to receive

	^{177}Lu-PSMA-617 as described above. After the last day of study treatment period of ^{177}Lu-PSMA-617 or upon second radiographic progression (rPFS2), the participants must have a second End of Treatment (EOT2) visit performed ≤ 7 days and enter the Post-treatment Follow-up. The participant can receive any other therapy per the discretion of the treating physician in the Post-treatment Follow-up. **Post-treatment Follow-up period** • **30 day Safety Follow-up** All randomized and/or treated participants should have a safety follow-up conducted approximately 30 days after the EOT visit. • **Long term follow-up** Long term follow-up starts after the 30 Days Safety follow-up and lasts until the accrual of events for the planned OS-based analysis (key secondary endpoint). In long term follow-up safety and efficacy information will be collected: • **Safety**: During the long term follow-up, all medically significant adverse events (all SAEs) deemed to be related to ^{177}Lu-PSMA-617 will be collected. This will include potential late onset radiation toxicity. For participants who received ^{177}Lu-PSMA-617 in the ^{177}Lu-PSMA-617 arm or in crossover, the following adverse events will be captured beyond the 30 day safety period regardless of relationship to study treatment and whether new anticancer therapy has been initiated: hematologic toxicities with primary focus on myelosuppression and thrombocytopenia (including need for transfusion or use of growth factors), renal failure, xerostomia, xerophthalmia, secondary malignancies. • **Efficacy**: In any participant entering long term follow-up discontinuing for reasons other than BICR-determined radiographic progression, tumor assessments must be performed every 8 weeks after first dose of study treatment for the first 24 weeks (week 9, 17, 25) and then every 12 weeks (week 37, 49, etc) until confirmation of radiographic progression by BICR The long-term follow-up period will also include the collection of survival information and other assessments included in Table 8-2 and Table 8-3. **Other**: Other data collected during long-term follow-up includes blood sampling for hematology, chemistry testing, coagulation, [redacted] as per Table 8-2 and Table 8-3. The visits will be carried out every 12 weeks (± 28 days) until death, lost to follow-up, withdrawal of consent (WoC) / opposition to use data/biological samples or accrual of the number of events required for the planned analyses for OS for the study, whichever occurs first. This follow-up will allow to collect information on medically significant long-term toxicities such as long-term radiotoxicity. Duration of long term follow-up is expected to continue till end of study. If the participant withdraws consent for the collection of blood samples, physical exams PROs and imaging assessments during the long-term follow-up, information on survival, AEs related to study treatment and post-treatment antineoplastic therapy will be collected. Participants who have received ^{177}Lu-PSMA-617 and remain in follow-up on the trial at the sponsor's completion of the study will be asked to join a separate study of long-term safety for a duration of up to 10 years.
Study Population	Adult PSMA-positive men previously treated with an ARDT where it is considered appropriate to delay taxane-based chemotherapy. Approximately 450 participants will be randomized (225 per treatment group).
Inclusion Criteria	Participants eligible for inclusion in this study must meet all of the following criteria: 1. Signed informed consent must be obtained prior to participation in the study 2. Participants must be adults ≥ 18 years of age 3. Participants must have an ECOG performance status of 0 to 1 4. Participants must have histological pathological, and/or cytological confirmation of adenocarcinoma of the prostate 5. Participants must be ^{68}Ga-PSMA-11 PET/CT scan positive, and eligible as determined by the sponsor's central reader 6. Participants must have a castrate level of serum/plasma testosterone (< 50 ng/dL or < 1.7 nmol/L) 7a. Participants must have progressed only once on prior second generation ARDT (abiraterone, enzalutamide, darolutamide, or apalutamide).

	first generation androgen receptor inhibitor therapy (e.g. bicalutamide) is allowed but not considered as prior ARDT therapy • second generation ARDT must be the most recent therapy received 8. Participants must have progressive mCRPC. Documented progressive mCRPC will be based on at least 1 of the following criteria: • Serum/plasma PSA progression defined as 2 increases in PSA measured at least 1 week apart. The minimal start value is 2.0 ng/mL; 1.0 ng/mL is the minimal starting value if confirmed rise in PSA is the only indication of progression. • Soft-tissue progression defined [PCWG3-modified RECIST v1.1 (Eisenhauer et al 2009, Scher et al 2016)] • Progression of bone disease: two new lesions; only positivity on the bone scan defines metastatic disease to bone (PCWG3 criteria (Scher et al 2016)) 9a. Participants must have ≥ 1 metastatic lesion that is present on baseline CT, MRI, or bone scan imaging obtained prior to randomization 10. Participants must have recovered to ≤ Grade 2 from all clinically significant toxicities related to prior therapies (i.e. prior chemotherapy, radiation, etc.) except alopecia 11. Participants must have adequate organ function: • Bone marrow reserve: • ANC ≥ 1.5 x 10^9/L • Platelets ≥100 x 10^9/L • Hemoglobin ≥ 9 g/dL • Hepatic: • Total bilirubin < 2 x the institutional upper limit of normal (ULN). For participants with known Gilbert's Syndrome ≤ 3 x ULN is permitted • ALT or AST ≤ 3.0 x ULN OR ≤ 5.0 x ULN for participants with liver metastases • Renal: • eGFR ≥ 50 mL/min/1.73m^2 using the Modification of Diet in Renal Disease (MDRD) equation 12. Albumin ≥ 2.5 g/dL 13a. Candidates for change in ARDT as assessed by the treating physician • Participants cannot have previously progressed nor had intolerable toxicity to both enzalutamide and abiraterone.
Exclusion criteria	Participants meeting any of the following criteria are not eligible for inclusion in this 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 2. Previous PSMA-targeted radioligand therapy 3a. Prior treatment with cytotoxic chemotherapy for castration resistant or castrate sensitive prostate cancer (e.g., taxanes, platinum, estramustine, vincristine, methotrexate, etc.), immunotherapy or biological therapy [including monoclonal antibodies]. [Note: Taxane exposure (maximum 6 cycles) in the adjuvant or neoadjuvant setting is allowed if 12 months have elapsed since completion of this adjuvant or neoadjuvant therapy. Prior treatment with sipuleucel-T is allowed] 4. Any investigational agents within 28 days prior to day of randomization 5. Known hypersensitivity to any of the study treatments or its excipients or to drugs of similar classes 6a. Concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, PARP inhibitor, biological therapy, or investigational therapy 7. Transfusion or use of bone marrow stimulating agents for the sole purpose of making a participant eligible for study inclusion 8a. Participants with a history of CNS metastases who are neurologically unstable, symptomatic, or receiving corticosteroids for the purpose of maintaining neurologic integrity. Participants with CNS metastases are eligible if received therapy (surgery, radiotherapy, gamma knife), asymptomatic and neurologically stable without corticosteroids. Participants with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not

	neurologically impaired. 9. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression 10. History or current diagnosis of the following ECG abnormalities indicating significant risk of safety for study participants: • Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block) • History of familial long QT syndrome or known family history of Torsades de Pointe • Cardiac or cardiac repolarization abnormality, including any of the following: History of myocardial infarction (MI), angina pectoris, or CABG within 6 months prior to starting study treatment 11a. 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. • HIV-infected participants who are at a low risk of AIDS-related outcomes may participate in this trial. • Participants with an active documented COVID-19 infection (any grade of disease severity) at time of informed consent may be included only when completely recovered (in accordance with local guidance). 12a. Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. However, participants with a prior history of malignancy that has been adequately treated and who have been disease free and treatment free for more than 3 years prior to randomization, are eligible, as are participants with adequately treated non-melanoma skin cancer and superficial bladder cancer 13a. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 14 weeks after stopping study treatment. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above. If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF 14a. Unmanageable concurrent bladder outflow obstruction or urinary incontinence. Note: Participant with bladder outflow obstruction or urinary incontinence, which is manageable and controlled with best available standard of care (incl. pads, drainage) are allowed. 15. History of somatic or psychiatric disease/condition that may interfere with the objectives and assessments of the study 16. Any condition that precludes raised arms position 17a. Eligible for treatment(s) other than ARDT based on presence of any mutations or biomarkers that are known as predictors of better response (e.g., AR-V7 or BRCA). 18. Not able to understand and to comply with study instructions and requirements
Study Treatment	^{177}Lu-PSMA-617 or approved ARDT (abiraterone or enzalutamide)
Treatment of interest	^{177}Lu-PSMA-617

Efficacy Assessments	• Radiographic imaging for tumor assessments:
	  • CT with contrast/magnetic resonance imaging (MRI)
	  • Bone scans with technetium-99m labeled diphosphonates
	• PCWG3-modified RECIST v1.1
	• Symptomatic skeletal events
	• Clinical progression
	• PSA levels

Key safety assessments	• Adverse Events (AEs) • Serious Adverse Events (SAEs) • Vital signs, physical examinations • ECGs • Laboratory parameters including hematology, clinical chemistry and coagulation • Concomitant medications and/or therapies
Other assessments	• ECOG Performance Status scale • [redacted] • Health-related quality of life: • European Quality of Life (EuroQol) 5 Domain 5 Level scale questionnaire (EQ-5D-5L) • Functional Assessment of Cancer Therapy - Prostate (FACT-P) • Brief Pain Inventory - Short Form (BPI-SF)
Data analysis	The following data analyses are planned for the study: • **Primary rPFS Analysis** Assuming proportional hazards model for rPFS, the null hypothesis will be tested at one-sided 2.5% level of significance: H01 (null hypotheses): $\Theta \geq 0$ vs. Ha1 (alternative hypotheses): $\Theta < 0$, where Θ is the log hazard ratio of rPFS in the ^{177}Lu-PSMA-617 (investigational) arm vs. a change of ARDT treatment (control) arm. The primary efficacy analysis to test this hypothesis and compare rPFS, the primary efficacy variable, between the two treatment groups will be using a stratified log-rank test at an overall one-sided 2.5% level of significance in favor of the ^{177}Lu-PSMA-617 arm. The stratification will be based on following randomization stratification factors (prior ARDT use: CRPC vs. HSPC setting; and symptomatology: asymptomatic or mildly symptomatic (score of 0-3 on Brief Pain Inventory Short Form (BPI-SF) questionnaire) vs symptomatic (score >3 on BPI-SF questionnaire). Analyses will be based on the FAS population according to the randomized treatment group and strata assigned at randomization. The rPFS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, median and associated 95% confidence intervals will be presented for each treatment group. The hazard ratio for rPFS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test. The primary rPFS analysis will only be carried out after all participants have been randomized and 156 events have been observed. • **OS Interim and Final Analysis** OS, as the key secondary variable, will be formally statistically tested, if the primary variable rPFS is statistically significant. The key secondary efficacy analysis is to compare the two treatment groups and will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance using randomization stratification factors (prior ARDT use: CRPC vs. HSPC setting; and symptomatology: asymptomatic or mildly symptomatic vs symptomatic). The key secondary efficacy variable, OS, will be analyzed at the interim analyses and final analysis of a 4-look group sequential design with a Lan-DeMets (O'Brien-Fleming) alpha spending function using estimated information fractions of (0.135,0.42,0.75, 1). Initially, a 3-look design was planned for OS using estimated information fractions of (0.25, 0.75, 1). However, the first interim occurred when the rPFS primary analysis was performed at which time the actual information fractionwas only 0.135. Therefore, an additional interim analysis was added, with a data cut-off approximately 9 months after the data cut-off for the primary rPFS analysis at which time an information fraction of 0.42 is expected. The third interim OS analysis will be performed at approximately 0.75 information fraction, corresponding to when approximately 223 of the 297 targeted OS events have been observed. The primary intent of the interim analyses is to stop early for superior efficacy. There is no intent to assess futility at these interim analyses. Analyses will be based on the full analysis set (FAS) population according to the randomized treatment group and strata assigned at randomization. The OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, median and associated 95% confidence intervals will be presented for each treatment group. The hazard ratio for OS

	will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test. Other secondary endpoints including time to Symptomatic skeletal events (SSE), Objective Response Rate (ORR), Disease Control Rate (DCR), duration of response, Proportion of participants who have achieved a ≥ 50% decrease from baseline that is confirmed by a second PSA measurement ≥4 weeks (PSA50 response), time to PSA progression, and Health-Related Quality of Life (HRQoL) (FACT-P, BPI-SF, EQ-5D-5L) will also be analyzed. Detailed statistical methodology for these analyses will be provided in the statistical analysis plan.
Key words	^{177}Lu-PSMA-617, ARDT, mCRPC, rPFS, CRPC, HSPC, PSMA

1 Introduction

1.1 Background

Prostate cancer is the second leading cause of cancer mortality in United States (US) and the third leading cause of cancer-related death in Europe in men (Malvezzi et al 2019, Siegel et al 2017). An estimated 1.1 million men worldwide were diagnosed and 307,000 died due to prostate cancer in 2012. Almost 70% of the diagnosed cases are 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 (Bray et al 2012).

There is an urgent need for more effective treatments to improve outcomes for participants with metastatic castration-resistant prostate cancer (mCRPC). The median age at diagnosis of mCRPC is 70 years (Flaig et al 2016). Once participants 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). In addition, there are significant comorbidities associated with mCRPC. Approximately 90% of mCRPC participants develop bone metastases (Kirby et al 2011) and 49% of them will develop a serious skeletal event within 2 years (Saad et al 2004). As a result, 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 participants, can be extremely symptomatic and at risk of serious oncological complications. There can be a considerable challenge in the clinic due to the symptoms of metastatic soft tissue and visceral disease, general frailty and bone marrow impairment.

Four main drug classes have been approved for treatment for prolonging survival in mCRPC participants. These include ARDTs (i.e., abiraterone and enzalutamide), taxanes (docetaxel and cabazitaxel), immunotherapy (sipuleucel-T) and bone-targeted radiopharmaceutical (radium 223 dichloride). With the evolution in the treatment landscape of prostate cancer, some of these life-prolonging therapies (ARDT and docetaxel) are increasingly used in earlier stages (e.g. metastatic hormone sensitive prostate cancer and non-metastatic prostate cancer). This creates an even greater unmet medical need in mCRPC. Among participants who have previously received an ARDT therapy, several mechanisms have been implicated in development of resistance to the treatment (Attard et al 2009). The rPFS for participants that change ARDTs ranges from 3.6 to 15 months and OS from 11 to 23 months (de Bono et al 2020, de Wit et al 2019, Komura et al 2019). On the other hand, many participants do not receive chemotherapy primarily because of preexisting medical conditions or associated toxic effects. (Harris et al 2011, Engel-Nitz et al 2011, Lissbrant et al 2013, Zielinski et al 2014). Sipuleucel-T is best used in mildly asymptomatic small volume disease; and radium 223 is used to treat men with bone-only disease. PARP inhibitors are an emerging drug class in mCRPC, but their use is restricted in a subgroup of mCRPC participants with homologous recombination repair gene mutations [PROfound (de Bono et al 2020, Hussain et al 2019) and TRITON2 (Abida et al 2019) studies].

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 et al 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 (Benesova et al 2015). PSMA-617 was uniquely developed for both imaging and radio ligand 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.

^{177}Lu, the radioactive cargo being delivered by PSMA-617, has physical properties that make it an appropriate radionuclide for the treatment of mCRPC. ^{177}Lu is a medium energy P emitter (490 ke V) with a maximum energy of 0.5 Me V and a maximal tissue penetration of < 2 mm. The shorter p - range of ^{177}Lu provides better irradiation of small tumors, in contrast to the longer P-range of 90Y (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 participants with metastatic prostate cancer (Hillier et al 2009, Kratochwil et al 2015, Kulkarni et al 2018c).

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 participants 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 participants. 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 participants (Ahmadzadehfar et al 2015) treated between Nov-2013 and Jan-2014, with 5.6 GBq/150 mCi (4.1-6.1 GBq/110-165 mCi). PSA decline > 50% occurred in 50% of participants, 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 participants 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 participants, 70% were identified as PSMA-positive via PET imaging and eligible for treatment. Most participants had been exposed to at least 1 taxane chemotherapy and either abiraterone or enzalutamide in the mCRPC setting. In this heavily pre-treated participant population with few therapeutic alternatives, 64% of participants 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 participants with measurable disease, the objective

response rate in measurable disease as defined by 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.

More recently Hofman presented the first randomized prospective open-label Phase-II study of ^{177}Lu-PSMA-617 vs cabazitaxel in 200 docetaxel progressing metastatic castration-resistant prostate cancer. Participants dosed with up to 6 cycles of ^{177}Lu-PSMA-617 (Hofman 2020). The primary endpoint was PSA response, defined as ≥ 50% reduction in PSA from baseline. Secondary endpoints, included PSA progression-free survival, overall survival, and quality of life.

This first ever randomized study, showed that a significantly greater proportion of patients on ^{177}Lu-PSMA-617 (66%) had a PSA decline >=50% compared to cabazitaxel (37%) (P<0.0001).

In summary, over 40 compassionate use publications and prospective Phase 2 clinical trial data describe the use of ^{177}Lu-PSMA-617 in participants who have been exposed to approved agents. In the post-taxane, post-androgen axis inhibitor setting ^{177}Lu-PSMA-617 has demonstrated a well-established, predictable, well tolerated safety profile. Clinical series indicate the most common side effects, predominately Grade 1-2, of ^{177}Lu-PSMA-617 treatment are dry mouth, nausea, vomiting, diarrhea, constipation, fatigue, anemia, thrombocytopenia and neutropenia. The incidence of Grade 3/4 toxicity in the series were very low, and mainly restricted to reversible hematological events. Efficacy has been demonstrated on multiple clinically significant endpoints, including PSA response, soft tissue lesion response measured by RECIST, progression-free survival (PFS), OS, pain and quality of life. No standard dose and schedule have been developed.

The preliminary clinical evidence indicates that ^{177}Lu-PSMA-617 may demonstrate clinical benefit for men with mCRPC, improving rPFS and OS compared with a change in ARDT and there is no recommended standard of care. Data from this study will complement the data from the VISION study for ^{177}Lu-PSMA-617 as a treatment in mCRPC prior to the use of taxanes.

VISION (NCT03511664), a phase III trial evaluating best standard of care with or without ^{177}Lu-PSMA-617 in men who had metastatic castration-resistant prostate cancer previously treated with at least one androgen-receptor–pathway inhibitor and one or two taxane regimens and who had PSMA-positive Gallium (^{68}Ga) gozetotide ([^{68}Ga]Ga-PSMA-11) positron emission tomographic–computed scans. VISION was designed as a registration trial for ^{177}Lu-PSMA-617 with alternate primary endpoints of radiographic progression-free or overall survival. Key secondary endpoints were objective response, disease control, and time to symptomatic skeletal events.

^{177}Lu-PSMA-617 plus standard care significantly prolonged (Sartor et al 2021), as compared with standard care, both imaging-based progression-free survival (median, 8.7 vs. 3.4 months; hazard ratio for progression or death, 0.40; 99.2% confidence interval [CI], 0.29 to 0.57; P<0.001) and overall survival (median, 15.3 vs. 11.3 months; hazard ratio for death, 0.62; 95% CI, 0.52 to 0.74; P<0.001). All the key secondary end points favored ^{177}Lu-PSMA-617. Among the 248 patients who had measurable target lesions according to RECIST, version 1.1, on independent central review at baseline, a complete response was noted in 17 of 184 patients

(9.2%) in the ^{177}Lu-PSMA-617 group and in none of the 64 patients in the control group. A partial response was noted in 77 patients (41.8%) in the ^{177}Lu-PSMA-617 group and in 2 (3%) in the control group.

Treatment with ^{177}Lu-PSMA-617 was associated with a low incidence of adverse events that led to dose reduction, interruption, or discontinuation. As of 27-Jan-2021, patients that received at least one dose of randomized treatment were 734 and included in the safety analysis. Of them, 519 patients (98.1%) and 170 (82.9%) reported at Treatment-emergent adverse events (TEAEs), in the ^{177}Lu-PSMA-617 group and the control group, respectively. The incidence of adverse events of grade 3 or above was higher with ^{177}Lu-PSMA-617 group than control group (52.7% vs. 38.0%), but quality of life was not adversely affected. The most common treatment-emergent adverse events (TEAEs), being reported in ≥ 12% of patients who received at least 1 dose of study therapy were fatigue (43.1% vs. 22.9%), dry mouth (38.8% vs. 0.5%), nausea (35.3% vs. 16.6%), anemia (31.8% vs. 13.2%), back pain (23.4% vs. 14.6%), arthralgia (22.3% vs. 12.7%), decreased appetite (21.2% vs. 14.6%), constipation (20.2% vs. 11.2%), diarrhea (18.9% vs. 2.9%), vomiting (18.9% vs. 6.3%), thrombocytopenia (17.2% vs. 4.4%), lymphopenia (14.2% vs. 3.9%), leukopenia (12.5% vs. 2.0%) in the ^{177}Lu-PSMA-617 group and the control group respectively (Sartor et al 2021)

Additionally, ^{177}Lu-PSMA-617 plus SOC delayed time to worsening in health related quality of life (HRQoL) and pain, and delayed the time to first symptomatic skeletal event versus standard care alone in adults with advanced mCRPC (K. Fizazi et al 2021).

Further details on ^{177}Lu-PSMA-617 can be found in the [Investigator's Brochure].

1.2 Purpose

The purpose of this study is to determine whether ^{177}Lu-PSMA-617, given for 6 cycles at a dose of 7.4 GBq (200 mCi) +/- 10% improves the radiographic progression free survival (rPFS) or death compared to a change in treatment of androgen receptor-directed therapy (ARDT) in metastatic castrate resistant prostate cancer (mCRPC) participants that are previously treated with another ARDT and have not been exposed to a taxane-containing regimen in the CRPC or mHSPC settings. [redacted]

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate whether treatment with ^{177}Lu-PSMA-617 improves the time to radiographic progression by PCWG3-modified RECIST v1.1 or death in participants with progressive PSMA-positive mCRPC compared to participants treated with ARDT	• Radiographic progression-free survival (rPFS) is defined as the time from the date of randomization to the date of first documented radiographic disease progression as assessed by blinded independent central review (BICR) and as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death due to any cause.

Objective(s)	Endpoint(s)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Key Secondary Objective: To evaluate whether treatment with ^{177}Lu-PSMA-617 improves the overall survival (OS) in participants with progressive PSMA-positive mCRPC compared to participants treated with ARDT treatment	• OS: Time from randomization to death due to any cause
• To estimate the time to radiographic progression or death in participants treated with ARDT who subsequently cross over to ^{177}Lu-PSMA-617 after radiographic progression (rPFS2)	• rPFS2 defined as time from the date of crossover (ARDT to ^{177}Lu-PSMA-617) to the date of radiographic disease progression by BICR or death from any cause [rPFS definition as outlined in PCWG3 guidelines]
• To evaluate Progression free survival (PFS) by investigator's assessment	• PFS defined as time from date of randomization to the first documented progression by investigator's assessment (radiographic, clinical, or PSA progression) or death from any cause, whichever occurs first
• To evaluate the second progression Free Survival (PFS2) by investigator's assessment	• PFS2 defined as time from date of randomization to the first documented progression by investigator's assessment (radiographic progression, clinical progression, PSA progression) or death from any cause, whichever occurs first, on next-line of therapy
• To evaluate whether treatment with ^{177}Lu-PSMA-617 improves the biochemical response as detected by Prostate specific antigen (PSA) halving compared to participants treated with ARDT	• PSA50 defined as proportion of participants who achieved a ≥ 50% decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks. PSA50 will be evaluated at 3, 6 and 12 months.
• To evaluate whether treatment with ^{177}Lu-PSMA-617 improves the time to first symptomatic skeletal event (TTSE) compared to participants treated with ARDT	• Time to SSE (TTSSE) defined as date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first
• To evaluate whether treatment with ^{177}Lu-PSMA-617 improves the time to radiographic soft tissue progression compared to participants treated with ARDT	• Time to soft tissue progression (TTSTP) defined as time from randomization to radiographic soft tissue progression per PCWG3-modified RECIST v1.1 (Soft Tissue Rules of Prostate Cancer Working Group modified Response Evaluation Criteria in Solid Tumors Version 1.1) as Assessed by Blinded Independent Central Review (BICR)
• To evaluate whether treatment with ^{177}Lu-PSMA-617 improves the time to chemotherapy compared to participants treated with ARDT	• Time to chemotherapy (TTCT) defined as time from randomization to initiation of the first subsequent chemotherapy or death, whichever occurs first
• To evaluate whether treatment with ^{177}Lu-PSMA-617 improves the health-related quality of life (HRQoL) compared to participants treated with ARDT	• HRQoL as assessed by EQ-5D-5L, FACT-P and BPI-SF
• To evaluate the safety and tolerability of ^{177}Lu-PSMA-617	• Frequency of adverse events, safety laboratory assessments and vital signs
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
[redacted]	[redacted]

Objective(s)	Endpoint(s)
[redacted]	[redacted]

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results.

Primary clinical question of interest: what is the effect of ^{177}Lu-PSMA-617 with best supportive care (BSC) versus ARDT with BSC with regard to time to radiographic progression or death in the treatment of taxane naïve men with Progressive PSMA-positive Metastatic Castrate Resistant Prostate Cancer as defined through inclusion/exclusion criteria, regardless of treatment discontinuations (TD) for any reasons and regardless of change in best supportive care or start of new antineoplastic therapy prior to rPFS event. Further details can be found in Section 12.

The justification for the primary estimand is that it will capture both the effect of the study treatment and the effect of additional medications, mirroring the conditions in clinical practice. Further details can be found in Section 12.

The primary estimand is described by the following attributes:

1. Population: all randomized taxane naïve men with Progressive PSMA-positive Metastatic Castrate Resistant Prostate Cancer, treated with another ARDT as last treatment that are candidates for ARDT change and where it is considered appropriate to delay taxane-based chemotherapy as defined through inclusion/exclusion criteria. Further details about the population are provided in Section 5

2. Variable: rPFS defined as the time from date of randomization to the date of first documented radiographic progression-free survival as assessed by BICR and outlined in PCWG3 guidelines or death due to any cause. Further details on rPFS are provided in Section 12.4.1
3. Treatment of interest: the investigational treatment is ^{177}Lu-PSMA-617 with best supportive care regardless of subsequent anti-neoplastic treatment. The control treatment is ARDT with best supportive care regardless of subsequent anti-neoplastic treatment. Further details about the investigational treatment and control treatment are provided in Section 6.
4. Handling of remaining intercurrent events:
   - Discontinuation of study treatment for any reason
   - Change in best supportive care
   - Start of anti-neoplastic therapy prior to radiographic progression

Details on how to handle intercurrent events are provided in Section 12.4.3.

5. Summary measure: rPFS hazard ratio (^{177}Lu-PSMA-617 with BSC versus ARDT with BSC) along with 95% confidence interval, estimated using a Cox proportional hazard model stratified by the randomization stratification factors. Further details on how the summary measure will be tested are provided in Section 12.4.2

2.2 Secondary estimands

Key secondary clinical question (hypothetical) of interest: what is the effect of ^{177}Lu-PSMA-617 with BSC versus ARDT with BSC with regard to overall survival in the treatment of taxane naïve men with Progressive PSMA-positive Metastatic Castrate Resistant Prostate Cancer as defined through inclusion/exclusion criteria, had crossover not occurred and regardless of treatment discontinuations for any reasons and regardless of change in best supportive care or start of new antineoplastic therapy? Further details can be found in Section 12.

The justification for the key secondary estimand is that it will capture both the effect of the study treatment and the effect of additional medications while accounting for the impact of crossover. Further details can be found in Section 12.

The key secondary estimand (hypothetical) is described by the following attributes:

1. Population: same as that of primary estimand
2. Variable: Overall Survival (OS) defined as the time from randomization to death due to any cause. Further details on OS provided in Section 12.5.1.1
3. Treatment of interest: same as that of primary estimand
4. Handling of remaining intercurrent events:
   - Discontinuation of study treatment for any reason
   - Change in best supportive care
   - Start of new anti-neoplastic therapy
   - Crossover to ^{177}Lu-PSMA-617 arm for participants in the ARDT arm

Details on how to handle the intercurrent events are provided in Section 12.5.1.1

5. Summary measure: OS hazard ratio (^{177}Lu-PSMA-617 with BSC versus ARDT with BSC) along with 95% confidence interval, estimated using a Cox proportional hazard model

stratified by the randomization stratification factors. Further details on how the summary measure will be tested are provided in Section 12.5.1.1

3 Study design

This is a phase III, open label, multicenter randomized study for PSMA-positive mCRPC participants previously treated with an ARDT where it is considered appropriate to delay taxane-based chemotherapy.

The study aims at evaluating the superiority of ^{177}Lu-PSMA-617 over a change of ARDT treatment in prolonging rPFS. The primary endpoint of rPFS will be assessed via blinded centralized review of radiographic images provided by the treating physician and as outlined in PCWG3 Guidelines.

The study will also evaluate whether ^{177}Lu-PSMA-617 improves the overall survival (OS) in participants with progressive PSMA-positive mCRPC compared to participants treated with a change in ARDT treatment. OS is defined as the time from randomization to death due to any cause (Figure 3-1).

Written informed consent form (ICF) must be obtained prior to any screening procedures. Screening procedures are carried out after ICF signature and within 28 days of randomization in IRT system. The participant must be registered in the IRT for screening and ^{177}Lu-PSMA-617 requested. All procedures described in the Assessment Schedule as per Table 8-2 and Table 8-3 must be carried out, prioritizing laboratory and imaging assessments to allow time to obtain the results.

The participants will be assessed for eligibility and will undergo a ^{68}Ga-PSMA-11 PET / CT scan to evaluate PSMA positivity by central review. Only participants with PSMA positive cancer and confirmed eligibility criteria will be randomized. Randomization will be stratified by prior ARDT use in castrate-resistant prostate cancer (CRPC) vs. HSPC setting and by symptomatology i.e. asymptomatic or mildly symptomatic (score on item 3 of the Brief Pain Inventory Short Form (BPI-SF) questionnaire (symptomatic = score >3 on item 3 of the BPI-SF questionnaire).

For all participants, the treating physician will make a choice of which ARDT (abiraterone or enzalutamide) will be administered to the participant should they get randomized to the ARDT arm. If the participant gets randomized to receive ^{177}Lu-PSMA-617, the choice of change of ARDT treatment will be discarded.

Randomization period

Randomization should occur within the 28 days screening period once all eligibility criteria are met. The participants will be randomized 1:1 to receive ^{177}Lu-PSMA-617 or a change of the ARDT treatment.

If the participant is randomized to the ^{177}Lu-PSMA-617 arm, the drug needs to be ordered immediately and allow 2 weeks to reach the site.

For the participants randomized to the ARDT arm, the change of ARDT treatment will include approved AR axis targeted therapy (abiraterone or enzalutamide).

Supportive care will be allowed in both arms and includes available care for the eligible participant according to best institutional practice for mCRPC treatment, including androgen deprivation therapy (ADT) and at the discretion of the investigator. Other Investigational agents, biological products, immunotherapy, cytotoxic chemotherapy, other systemic radioisotopes (e.g. radium-223), Poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors or hemi-body radiotherapy treatment must not be administered during the study treatment period. ARDT must not be administered concomitantly with ^{177}Lu-PSMA-617.

Treatment period

- ^{177}Lu-PSMA-617 treatment arm

Participants randomized to the investigational arm must begin ^{177}Lu-PSMA-617 dosing within 14 days after randomization. C1D1 can be delayed by up to an additional 3 days for unexpected scheduling delays. Participants will receive 7.4 GBq (200 mCi) +/- 10% ^{177}Lu-PSMA-617 once every 6 weeks for 6 cycles as per Table 8-2. Best supportive care, including ADT, may be used.

After the last day of study treatment period of ^{177}Lu-PSMA-617 (i.e. after completion of 6 cycles of treatment OR treatment discontinuation for any reason) [for e.g. upon radiographic progression as assessed by blinded centralized review]), the participants must have an End of Treatment (EOT) visit performed ≤ 7 days and enter the Post-treatment Follow-up. For participants who are able to complete all planned 6 cycles of ^{177}Lu-PSMA-617, the end of the treatment period is after completion of C6W5 visit and the fourth imaging assessment due at week 37.

In the absence of safety concerns, every effort should be made to keep the participant on the randomized treatment until BICR-determined radiographic progression or completion of the 6 cycles of ^{177}Lu-PSMA-617.

- ARDT treatment arm

For participants randomized to the ARDT treatment arm, the change of ARDT treatment for each participant will be selected by the treating physician prior to randomization and will be administered per the physician's orders. Best supportive care, including ADT, may be used. After the last day of study treatment (treatment discontinuation for any reason) or upon radiographic progression as assessed by blinded centralized review, the participants must have an End of Treatment (EOT) visit performed ≤ 7 days and enter the Post-treatment Follow-up.

In absence of safety concerns, every effort should be made to keep the participant on the randomized treatment until BICR-determined radiographic progression.

End of Treatment

Randomized treatment may be discontinued if:

- Completion of the 6 cycles of ^{177}Lu-PSMA-617
- Evidence of tumor progression by central radiological assessment as measured by PCWG3-modified RECIST v1.1 criteria
- Unacceptable toxicity as assessed by Investigator
- Participant non-compliance or voluntary withdrawal from study or from study treatment

- Required ongoing use of a prohibited treatment for participant safety reasons
- Evidence that the participant is no longer clinically benefiting from study treatment
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study
- At the sponsor's or investigator's discretion

It is important that the scheduled imaging assessments continue until BICR-determined progression. PSA progression is strongly discouraged as a criterion for initiation of a new neoplastic therapy prior to BICR-determined progression. PCWG3 guidelines should be followed to guide discontinuation of treatment

EOT visit must be performed ≤ 7 days after the last day of study treatment period. EOT is to occur before the participant is to enter the post-treatment Follow-up period of the study and before the initiation of any subsequent anticancer treatment, outside of what is allowed in the study.

If a participant withdraws consent for the treatment period of the study, an EOT must be done and the participant will enter the Post-treatment Follow-up unless he specifically withdraws consent for post-treatment Follow-up.

Crossover period

Upon confirmation of rPD by BICR, participants randomized to the ARDT arm will either be allowed to cross over to receive ^{177}Lu-PSMA-617 within 28 days of confirmation of radiographic disease progression determined by BICR, or may continue to receive any other therapy per the discretion of the treating physician in the Post-treatment Follow-up and start of new intervening antineoplastic therapies disqualifies patient for crossover. Following confirmation of patient eligibility for the crossover, the participant can be assigned to the crossover via the IRT system. The participant should start receiving ^{177}Lu-PSMA-617 within 14 (+3) days after registration of crossover in IRT system.

In order for a participant randomized to the change in ARDT arm to cross over to receive ^{177}Lu-PSMA-617, he must meet the following criteria:

- Confirmed radiographical progression as assessed by BICR within prior 28 days
- No intervening antineoplastic therapy is administered after the randomized treatment
- Any unresolved toxicity from prior therapy should be controlled and must be no greater than CTCAE grade 2 or baseline at the time of registration for crossover
- ECOG performance status 0-1 at the time of registration for crossover
- Adequate organ function at the time of registration for crossover:
  - Bone marrow reserve:
    - ANC ≥ 1.5 x 10^9/L
    - Platelets ≥100 x 10^9/L
    - Hemoglobin ≥ 9 g/dL
  - Hepatic:

    - Total bilirubin < 2x the institutional upper limit of normal (ULN). For participants with known Gilbert's Syndrome ≤ 3 x ULN is permitted
    - ALT or AST ≤ 3.0 x ULN OR ≤ 5.0 x ULN for participants with liver metastases
  - Renal:
    - eGFR ≥ 50 mL/min/1.73m2 using the Modification of Diet in Renal Disease (MDRD) equation
- Agreement to continue with the study visit schedule

Baseline assessments must be performed within 28 days of registration for crossover and are described in Table 8-3. If the EOT1 visit has been performed within prior 28 days of registration for crossover, those results can be used to confirm patient eligibility to the crossover. If the patient has not undergone specific assessments defined below within 28 days prior to registration for crossover, they must complete or repeat the assessments in order to ensure the above criteria are met. CT/MRI and bone scan within 28 days prior to registration for crossover must be available as new baseline images.

A participant, who is deemed to have disease progression per investigator's assessment, but not by BICR, is not eligible to cross over at that time. Such participant should continue to receive randomized study treatment until progression determined by BICR. Please refer to Section 8 for visit schedule and assessments following crossover.

If crossover to ^{177}Lu-PSMA-617 is selected, then ^{177}Lu-PSMA-617 will be administered with the same dose/schedule as for participants who were initially randomized to receive ^{177}Lu-PSMA-617 as described above.

After the last day of study treatment period of ^{177}Lu-PSMA-617 or upon rPFS2, the participants must have a EOT2 visit performed ≤ 7 days and enter the Post-treatment Follow-up. The participant can receive any other therapy per the discretion of the treating physician in the Post-treatment Follow-up.

Post-treatment Follow-up period

- 30 day Safety Follow-up

All randomized and/or treated participants should have a safety follow-up conducted approximately 30 days after the EOT visit (or EOT2 visit if crossover occurs).

- Long term follow-up

Long term follow-up starts after the 30 Day Safety follow-up and lasts until the accrual of events for the planned OS-based analysis (key secondary endpoint). In long term follow-up safety and efficacy information will be collected:

- Safety: During the long term follow-up, all medically significant adverse events (all SAEs) deemed to be related to study treatment will be collected including potential late onset radiation toxicity. For participants who received ^{177}Lu-PSMA-617 in the ^{177}Lu-PSMA-617 arm or in crossover, the following adverse events will be captured beyond the 30 day safety period regardless of relationship to study treatment and whether new anticancer therapy has been initiated: hematologic toxicities with primary focus on myelosuppression and

thrombocytopenia (including need for transfusion or use of growth factors), renal failure, xerostomia, xerophthalmia, secondary malignancies.

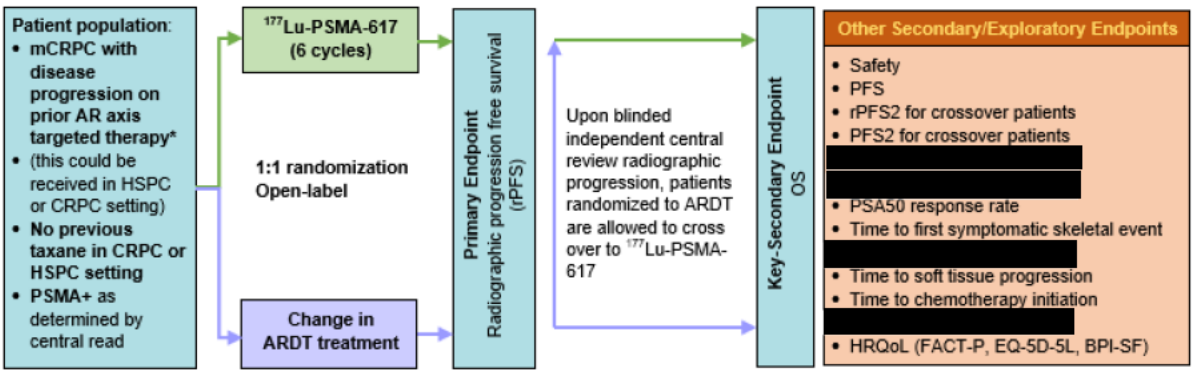
- Efficacy: In any participant entering long term follow-up discontinuing for reasons other than BICR-determined radiographic progression, tumor assessments must be performed every 8 weeks after first dose of study treatment for the first 24 weeks (week 9, 17, 25) and then every 12 weeks (week 37, 49, etc) until confirmation of radiographic progression by BICR.

The long-term follow-up period will also include the collection of physical exam, survival and treatment updates, patient reported outcomes (PROs), as well as blood sampling for hematology, chemistry testing, coagulation, radiographic imaging (only for participants with no rPFS event), PSA, [redacted] as per Table 8-2 and Table 8-3. The visits will be carried out every 12 weeks (± 28 days) until death, lost to follow-up, withdrawal of consent / opposition to use data/biological samples or accrual of the number of events required for the planned analyses for OS for the study, whichever occurs first. This follow-up will allow medically significant long-term toxicities to be captured, such as long-term radiotoxicity. Duration of long term follow-up is expected to continue till end of study.

If the participant withdraws consent for the collection of blood samples, physical exams, PROs, and imaging assessments during the long-term follow-up, information on survival, and AEs per above will be collected.

Participants who have received 177Lu-PSMA-617 and remain in follow-up on the trial at the sponsor's completion of the study will be asked to join a separate study of long-term safety (CAAA617A12402) for a duration of up to 10 years.

Figure 3-1 Study Design



Stratification factor: Prior ARDT use in CRPC vs HSPC; asymptomatic and mildly symptomatic vs symptomatic patients
* Candidates who are considered appropriate for delaying taxane-based chemotherapy

4 Rationale

4.1 Rationale for study design

The purpose of this study is to determine whether ^{177}Lu-PSMA-617, given for 6 cycles at a dose of 7.4 GBq (200 mCi) +/- 10%, improves the rPFS compared to a change in ARDT in mCRPC participants that were previously treated with an alternate ARDT and were not exposed to a taxane-containing regimen in the CRPC or HSPC settings. rPFS is an important endpoint in mCRPC recognized by PCWG3 as well as several other trials conducted in this setting.

After radiographic progression, follow up for survival will continue. The key secondary objective is to evaluate whether ^{177}Lu-PSMA-617 improves the overall survival (OS) compared to participants treated with a change in ARDT treatment.

Eligible participants will be randomized to one of two treatment arms. Randomization will be stratified to avoid bias in treatment selection. Treatment will be open-label. Upon confirmation of rPFS by BICR, participants randomized to the ARDT arm will be allowed to cross over to receive ^{177}Lu-PSMA-617.

The preliminary clinical evidence indicates that ^{177}Lu-PSMA-617 may demonstrate clinical benefit for men with mCRPC, improving rPFS and OS compared with a change in ARDT. [redacted]

4.1.1 Rationale for choice of background therapy

Supportive care will be allowed in both arms and includes available care for the eligible participant according to best institutional practice for mCRPC treatment, including ADT. This is allowed in order to maintain serum testosterone levels, and management of the overall disease symptomatology per discretion of the treating physician.

Investigational agents, biological products, immunotherapy, cytotoxic chemotherapy, other systemic radioisotopes (e.g. radium-223), Poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors or hemi-body radiotherapy treatment must not be administered prior to radiographic progression assessed by blinded centralized review (primary endpoint). ARDT must not be administered concomitantly with ^{177}Lu-PSMA-617.

4.2 Rationale for dose/regimen and duration of treatment

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, 12 dosimetry studies have been conducted in 158 participants. 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 over 53 publications, summarizing the safety and or efficacy information from over 1280 participants.

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. Although the German Society of Nuclear Medicine 2016 recommended a 6.0 GBq dose every 8 weeks for 3 cycles, the majority of these publications have used a regimen of 4 cycles of 6 GBq every 8 weeks. However, efficacy and safety information from a prospective phase 2 study suggested that dosing of 4.0-8.9 (mean 7.5) GBq every 6 weeks for 4 cycles was well tolerated and efficacious (Violet et al 2020). 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 participant (Bräuer et al 2017, Kessel K et al 2019, Kulkarni et al 2018a, Kulkarni et al 2018b, Kulkarni et al 2018c, Maffey Steffan et al 2020, Rahbar et al 2018, Yadav et al 2020, Yordanova et al 2017, van Kalmthout et al 2019).

In the phase II TheraP study (ANZUP protocol 1603, NCT03392428), 200 Australian men with mCRPC were randomly allocated (1:1) to treatment with either ^{177}Lu-PSMA-617 or cabazitaxel. The starting dose for ^{177}Lu-PSMA-617 was 8.5 GBq and was reduced by 0.5 GBq per cycle, i.e. 8.5, 8, 7.5, 7, 6.5, 6, for a maximum of 6 cycles given every 6 weeks. This equates to a cumulative dose of 43.5 GBq, which 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.

Further details on ^{177}Lu-PSMA-617 can be found in the [Investigator's Brochure].

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Four main drug classes have been approved for treatment for prolonging survival in mCRPC participants. These include ARDTs (i.e., abiraterone and enzalutamide), taxanes (docetaxel and cabazitaxel), immunotherapy (sipuleucel-T) and bone-targeted radiopharmaceutical (radium 223 dichloride). With the evolution in the treatment landscape of prostate cancer, some of these life-prolonging therapies (ARDT and docetaxel) are increasingly used in earlier stages (e.g. metastatic hormone sensitive prostate cancer and non-metastatic prostate cancer). This creates an even greater unmet medical need in mCRPC. Among participants who have previously received an ARDT therapy, several mechanisms have been implicated in development of resistance to the treatment (Attard et al 2009). The rPFS for participants that change ARDT treatment ranges from 3.6 to 15 months and OS from 11 to 23 months (de Bono et al 2020,de Wit et al 2019, Komura et al 2019). On the other hand, many participants do not receive chemotherapy primarily because of preexisting medical conditions or associated toxic effects. (Engel-Nitz et al 2011, Harris et al 2011, Lissbrant et al 2013, Zielinski et al 2014). Sipuleucel-T is best used in mildly asymptomatic small volume disease; and radium 223 is used to treat men with bone-only disease. PARP inhibitors are an emerging drug class in mCRPC, but their use is restricted in a subgroup of mCRPC participants with homologous recombination repair gene mutations [PROfound (de Bono et al 2020, Hussain et al 2019) and TRITON2 (Abida et al 2019) ESMO 2019 studies].

ARDTs such as abiraterone and enzalutamide have shown efficacy and are approved for treatment of mCRPC among participants who have not previously been treated with taxane-based chemotherapy, and are a relevant comparator for this study.

4.4 Purpose and timing of interim analyses/design adaptations

No interim analysis is planned for rPFS. The final rPFS analysis will only be carried out after all participants have been randomized.

OS Interim Analysis

A hierarchical testing procedure will be adopted and the statistical tests for OS will be performed only if the primary efficacy endpoint rPFS is statistically significant.

A maximum of three interim analyses are planned. The first interim analysis was performed at the time of the final rPFS analysis. The second interim analysis is not event-driven but instead will be performed at approximately 9 months of additional follow-up from the data cut-off used for the primary analysis, by which time approximately 125 of the 297 targeted OS events (42% information fraction) are expected. This interim analysis is expected to occur around 24 months from the date of first participant randomized in the study.

The third interim analysis is planned after approximately 223 of the approximately 297 targeted OS events (i.e., at approximately 75% information fraction) have been observed. This interim analysis is expected to occur around 38 months from the date of first participant randomized in the study. The primary intent of these interim analyses is to stop early for superior efficacy. There is no intent to assess futility at these interim analyses.

More details on OS interim analyses can be found in Section 12.5.1.1 and Section 12.7.

4.5 Risks and benefits

PSMA is over-expressed in prostate cancer, and this over-expression increases further in cases of de-differentiated, metastatic or hormone-refractory disease (Israeli et al 1993, Sweat et al 1998, Wright et al 1995, Wright et al 1996). This study will enroll participants with mCRPC who have progressed on ARDT and taxane naïve for advance stage. These participants have very limited treatment options. Participants who are determined by ^{68}Ga-PSMA-11 as PSMA-positive will be administered ^{177}Lu-PSMA-617.

The use of ^{68}Ga-PSMA-11 for PET scanning of prostate cancer participants has been ongoing since 2011 to assess disease burden in the setting of both biochemical recurrence (BCR); rising PSA in advanced/metastatic disease. Publications that report clinical use have demonstrated better sensitivity and specificity than choline-based imaging for prostate cancer, with a very low rate of adverse events. ^{68}Ga-PSMA-11 has also been the most commonly used radioactive imaging agent to evaluate PSMA-expressing mCRPC in participants being considered for ^{177}Lu-PSMA-617 radioligand therapy. ^{68}Ga-PSMA-11 has been shown to be well tolerated with no adverse events following infusion in a retrospective analysis of 1007 participants (Afshar-Oromieh et al 2017). ^{68}Ga-PSMA-11 is approved in the US under the trademark of LOCAMETZ® as a radioactive diagnostic agent indicated for PET imaging of PSMA-positive lesions in men with prostate cancer with suspected metastasis who are candidates for initial

definitive therapy, with suspected recurrence based on elevated serum PSA level and for selection of patients with metastatic prostate cancer for whom ^{177}Lu-PSMA-617 PSMA-directed therapy is indicated. It has demonstrated a favorable safety profile with about 1% of patients experiencing mild reactions such as fatigue, nausea, constipation, and vomiting. Further details can be found in the ^{68}Ga-PSMA-11 Investigator's Brochure. ^{177}Lu-PSMA-617 is approved in the US under the brand name of PLUVICTO™ for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

Preclinical work, dosimetry studies, and clinical experience with ^{177}Lu-PSMA-617 since 2013, suggest positive response rates and a favorable safety profile in participants with mCRPC (Ahmadzadehfar et al 2016, Fendler et al 2017, Ferdinandus et al 2017, Haug et al 2016, Kratochwil et al 2016, Kulkarni et al 2016, Rahbar et al 2016a, Rahbar et al 2016b, Rahbar et al 2018, Rathke et al 2017, Yadav et al 2017).

Dosimetry studies have confirmed that ^{177}Lu-PSMA-617 is targeted and some 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 clinical studies so far. There has been evidence of reversible hematological toxicity. No significant diarrhea or renal impairment was reported from a retrospective review of doctors' reports (Rahbar et al 2017). In the prospective studies sponsored by Endocyte (VISION study and RESIST-PC study), the commonly reported adverse events (> 10% of participants) to date include: anemia, dry mouth, constipation, diarrhea, nausea, vomiting, fatigue, decreased appetite, arthralgia and back pain (Refer to [^{177}Lu-PSMA-617 IB]). A small number of hematological events (thrombocytopenia, anemia and pancytopenia) have been reported as fatal (Refer to [^{177}Lu-PSMA-617 IB]).

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 participants 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 nonhematological toxicities attributed to 177Lu-PS^{MA-}617 occurring in > 25% of participants included transient Gl-2 dry mouth (66%), Gl-2 nausea (48%), Gl-3 fatigue (38%), and Gl-2 vomiting (26%). The most common hematological toxicities attributed to 177Lu-PSM^{A-6}17 occurring in > 25% of participants included Gl-3 lymphocytopenia (72%), Gl-4 thrombocytopenia (38%), Gl-3 neutropenia (30%) and G 1-3 anemia (28%). G3-4 toxicities attributed to 177Lu-PSM^{A-6}17 were infrequent with lymphocytopenia (32%), thrombocytopenia (10%), anemia (10%), neutropenia (6%) and fatigue (2%). In a subsequent open labeled Phase-II randomized study of 177Lu-PSM^{A-6}17 vs cabazitaxel in 200 docetaxel progressing metastatic castration-resistant prostate cancer, Hofman 2020 showed that a significantly greater proportion of patients on ^{177}Lu-PSMA-617 (66%) had a PSA decline >=50% compared to cabazitaxel (37%) (P<0.0001). Cabazitaxel was associated with more Grade 3/4 neutropenia, febrile neutropenia, diarrhea, change in taste, and neuropathy than LuPSMA, whereas more thrombocytopenia, dry mouth, and dry eye occurred in LuPSMA-treated patients.

Potential risks of ^{177}Lu-PSMA-617 include the effects of radiological toxicity (such as increased risk of carcinogenicity, risk of infertility), late renal toxicity and bleeding events.

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. Appropriate eligibility criteria and stopping rules are included in this protocol. Guidance of toxicity risk reduction and supportive care for ^{177}Lu-PSMA-617 and toxicity management and dose modification for ^{177}Lu-PSMA-617 are provided in Table 6-2.

Sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if their female partner were to become pregnant during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

The risk-benefit ratio is expected to be favorable to the ^{68}Ga-PSMA-11 imaging agent and ^{177}Lu-PSMA-617 therapy.

Additional details of the nonclinical and clinical experience with ^{177}Lu-PSMA-617 are provided in the [Investigator's Brochure].

COVID-19 pandemic related risks

If the COVID-19 pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented with approval from Novartis. The investigator and sponsor might consider:

- The Investigator may conduct the informed consent discussion remotely as described in Section 7.
- Sending the study participant to another imaging center (when feasible) and performing local labs or visits by site staff/home nursing service to the participant's home depending on local regulations and capabilities as described in Section 8. If visits by site staff to a participant’s home are not feasible the collection of samples may be modified by Novartis and will be communicated to the Investigator. If the treatment (with ^{177}Lu-PSMA-617 or ARDT) is interrupted for more than 4 weeks due to COVID-19 pandemic, the participant must have an EOT visit performed in ≤ 7 days and enter the Post-treatment Follow-up
- For safety monitoring, to arrange phone calls, virtual contacts (e.g. teleconsult) to replace on-site study visits, for the duration of the pandemic until it is safe for the participant to visit the site again as described in Section 8.4
- Delivery of study drug directly to a participant’s home, as described in Section 6.7.2
- Clinical Outcome Assessments may be collected remotely (e.g. web portal) if data cannot be obtained due to COVID-19 pandemic, depending on local regulations, technical capabilities, and following any applicable training in the required process, as described in Section 8.5.1

The site must communicate immediately to Novartis any COVID-19 related issues that could impact the performance of the study to assess potential mitigation measures.

4.6 Rationale for Public Health Emergency mitigation procedures

In the event of a Public Health emergency as declared by local or regional authorities i.e. "pandemic, epidemic or natural disaster", mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by local or regional health authorities and ethics committees as appropriate.

5 Study Population

In this study, the participant population will consist of male participants ≥ 18 years of age, with mCRPC cancer who were previously treated with another ARDT as last treatment and have not been exposed to a taxane-containing regimen in the CRPC or HSPC settings and who are considered appropriate for delaying taxane-based chemotherapy.

Approximately 450 participants will be randomized (225 per treatment group).

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Participants must be adults ≥ 18 years of age
3. Participants must have an ECOG performance status of 0 to 1
4. Participants must have histological pathological, and/or cytological confirmation of adenocarcinoma of the prostate
5. Participants must be ^{68}Ga-PSMA-11 PET/CT scan positive, and eligible as determined by the sponsor's central reader
6. Participants must have a castrate level of serum/plasma testosterone (< 50 ng/dL or < 1.7 nmol/L)

7a. Participants must have progressed only once on prior second generation ARDT (abiraterone, enzalutamide, darolutamide, or apalutamide).

- first generation androgen receptor inhibitor therapy (e.g. bicalutamide) is allowed but not considered as prior ARDT therapy
- second generation ARDT must be the most recent therapy received

8. Participants must have progressive mCRPC. Documented progressive mCRPC will be based on at least 1 of the following criteria:
   - Serum/plasma PSA progression defined as 2 increases in PSA measured at least 1 week apart. The minimal start value is 2.0 ng/mL; 1.0 ng/mL is the minimal starting value if confirmed rise in PSA is the only indication of progression
   - Soft-tissue progression defined [PCWG3-modified RECIST v1.1 (Eisenhauer et al 2009, Scher et al 2016)]
   - Progression of bone disease: two new lesions; only positivity on the bone scan defines metastatic disease to bone (PCWG3 criteria (Scher et al 2016))

9a. Participants must have ≥ 1 metastatic lesion that is present on screening/baseline CT, MRI, or bone scan imaging obtained ≤ 28 days prior to randomization

10. Participants must have recovered to ≤ Grade 2 from all clinically significant toxicities related to prior therapies (i.e. prior chemotherapy, radiation, etc.) except alopecia

11. Participants must have adequate organ function:
    - Bone marrow reserve:
        - ANC ≥ 1.5 x 10^9/L
        - Platelets ≥100 x 10^9/L
        - Hemoglobin ≥ 9 g/dL
    - Hepatic:
        - Total bilirubin < 2 x the institutional upper limit of normal (ULN). For participants with known Gilbert's Syndrome ≤ 3 x ULN is permitted
        - ALT or AST ≤ 3.0 x ULN OR ≤ 5.0 x ULN for participants with liver metastases
    - Renal:
        - eGFR ≥ 50 mL/min/1.73m^2 using the Modification of Diet in Renal Disease (MDRD) equation

12. Albumin ≥ 2.5 g/dL

13a. Candidates for change in ARDT as assessed by the treating physician
    - Participants cannot have previously progressed nor had intolerable toxicity to both enzalutamide and abiraterone

5.2 Exclusion criteria

Participants meeting **any** of the following criteria are **not** eligible for inclusion in this 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
2. Previous PSMA-targeted radioligand therapy

3a. Prior treatment with cytotoxic chemotherapy for castration resistant or castrate sensitive prostate cancer (e.g., taxanes, platinum, estramustine, vincristine, methotrexate, etc.), immunotherapy or biological therapy [including monoclonal antibodies]. [Note: Taxane exposure (maximum 6 cycles) in the adjuvant or neoadjuvant setting is allowed if 12 months have elapsed since completion of this adjuvant or neoadjuvant therapy. Prior treatment with sipuleucel-T is allowed].

4.Any investigational agents within 28 days prior to day of randomization

5. Known hypersensitivity to any of the study treatments or its excipients or to drugs of similar classes

6a. Concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, PARP inhibitor, biological, or investigational therapy

7. Transfusion or use of bone marrow stimulating agents for the sole purpose of making a participant eligible for study inclusion

8a. Participants with a history of CNS metastases who are neurologically unstable, symptomatic, or receiving corticosteroids for the purpose of maintaining neurologic integrity. Participants with CNS metastases are eligible if received therapy (surgery, radiotherapy, gamma knife), asymptomatic and neurologically stable without corticosteroids. Participants with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired.

9. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression

10. History or current diagnosis of the following ECG abnormalities indicating significant risk of safety for study participants:
    - Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
    - History of familial long QT syndrome or known family history of Torsades de Pointe
    - Cardiac or cardiac repolarization abnormality, including any of the following: History of myocardial infarction (MI), angina pectoris, or CABG within 6 months prior to starting study treatment

11a. 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
    - HIV-infected participants who are at a low risk of AIDS-related outcomes may participate in this trial.
    - Participants with an active documented COVID-19 infection (any grade of disease severity) at time of informed consent may be included only when completely recovered (in accordance with local guidance).

12a. Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. Participants with a prior history of malignancy that has been adequately treated and who have been disease free and treatment free for more than 3 years prior to randomization are eligible, as are participants with adequately treated non-melanoma skin cancer and superficial bladder cancer

13a. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 14 weeks after stopping study treatment. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above. If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF

14a. Unmanageable concurrent bladder outflow obstruction or urinary incontinence. Note: Participants with bladder outflow obstruction or urinary incontinence, which is manageable and controlled with best available standard of care (incl. pads, drainage) are allowed.

15. History of somatic or psychiatric disease/condition that may interfere with the objectives and assessments of the study
16. Any condition that precludes raised arms position
17a. Eligible for treatments other than ARDT based on presence of any mutations or biomarkers that are known as predictors of better response (e.g., AR-V7 or BRCA)
18. Not able to understand and to comply with study instructions and requirements

6 Treatment

6.1 Study treatment

In this study, the term "study treatment" indicates the randomized assignment of either ^{177}Lu-PSMA-617 or a change in the approved ARDT treatment. The investigational product radioligand imaging compound ^{68}Ga-PSMA-11 is used as imaging agent during screening. Participants will be administered ^{177}Lu-PSMA-617 intravenously as per best practice and Investigator's decision. (Refer to Section 6.7 for study drug preparation and dispensation).

Study participants will be randomized at a 1:1 ratio to receive either ^{177}Lu-PSMA-617 or a change in the approved ARDT treatment (abiraterone or enzalutamide). Supportive care will be allowed in both arms and includes available care for the eligible participant according to best institutional practice for mCRPC treatment, including androgen deprivation therapy (ADT) and at the discretion of the investigator. Changes to Concomitant Medications will be captured in the CRF. Investigational agents, biological products, immunotherapy, cytotoxic chemotherapy, other systemic radioisotopes (e.g. radium-223), Poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors or hemi-body radiotherapy treatment must not be administered while on study treatment.

The general doses of the study treatment are listed in Table 6-1. ARDT treatment are approved drugs and will be provided locally by the study site, subsidiary or designee as commercially available, or locally by Novartis, according to local clinical practices and local regulations. Please refer to the Package Insert for complete guidelines for administration and for safety monitoring guidelines.

6.1.1 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.2 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
^{177}Lu-PSMA-617 (1 GBq/mL at End of Production)	Radiopharmaceutical solution for infusion/injection	Intravenous use	Open label, vial	Sponsor (global)
^{68}Ga-PSMA-11 (25 µg)	Either provided as Kit for the radiopharmaceutical preparation of ^{68}Ga-PSMA-11 or as ready to use radiopharmaceutical solution for injection	Intravenous use	Open label, vial or syringe	Sponsor (global)
ARDT	See package insert	Oral Use	Locally by the study site, subsidiary or designee as commercially available, or locally by Novartis, according to local clinical practices and local regulations	

^{68}Ga-PSMA-11 Imaging

During screening, all participants will undergo imaging with the investigational product ^{68}Ga-PSMA-11 for the purpose of eligibility determination. Participants must have disease that expresses PSMA as seen on a ^{68}Ga-PSMA-11 PET/CT scan by central review.

For subjects with soft tissue disease (with or without bone disease), the following five (5) requirements must be met in order for a subject to be deemed eligible:

- There must be at least one (1) ^{68}Ga-PSMA-11 PET positive lesion (osseous or extraosseous), irrespective of size.
- All lymph nodes that measure ≥ 25 mm in short axis must be 68Ga-PSMA-11 PET positive.
- All bone metastases with a soft tissue component ≥ 10 mm in the longest diameter must be 68Ga-PSMA-11 PET positive (PSMA-negative bone metastases without a soft tissue component, do not exclude patients).
- All solid organ metastases (e.g. lung, liver, adrenal glands, etc.) ≥ 10 mm in the longest diameter must be 68Ga-PSMA-11 PET positive.
- All intraprostatic lesions, regardless of size, must be 68Ga-PSMA-11 PET positive.

For subjects with bone only disease, at least one (1) site of bone involvement must be ^{68}Ga-PSMA-11 PET positive.

If the potential participant received ^{68}Ga-PSMA-11 as part of a routine local exam prior to signing informed consent for this study, he must wait at least 3 days prior to repeating ^{68}Ga-PSMA-11 PET imaging as screening for this study.

For background and additional details on ^{68}Ga-PSMA-11, refer to Section 6.7 for study drug preparation and dispensation and to the ^{68}Ga-PSMA-11 Investigator's Brochure. The ^{68}Ga-PSMA-11 will be administered as a single intravenous (i.v.) dose of approximately 150 MBq.

Administered dose must not be lower than 111 MBq or higher than 185 MBq (Refer to Pharmacy Manual for details on dose preparation and administration).

Imaging assessment must be performed only with use of Sponsor supplied kits for the radiopharmaceutical preparation of ^{68}Ga-PSMA-11 or with ready to use ^{68}Ga-PSMA-11 radiopharmaceutical solution for injection supplied by the Sponsor's central radiopharmacy. Other Ga-containing PSMA-targeting radiopharmaceuticals must not be used for imaging at screening to evaluate PSMA-positivity. When such imaging assessments are performed locally at investigator's discretion during the study, they will be considered an exposure to investigational medicinal product (with exception when use is approved and administered according to the local label), their results must not be used to make decisions related to response assessment and/or study treatment.

Treatment with ^{177}Lu-PSMA-617

Study participants randomized to the investigational drug will receive a dose of 7.4 GBq (200 mCi) +/- 10% of ^{177}Lu-PSMA-617 which will be administered once every 6 weeks (1 cycle) for 6 cycles. (Refer to Section 6.7 for study drug preparation and dispensation).

ARDT

The change of ARDT treatment will include approved AR-axis targeted therapy abiraterone or enzalutamide for participants randomized on ARDT arm. ARDT treatment should be dosed as per approved local labels and guidelines including contraceptive requirements.

6.1.3 Supply of study treatment

^{177}Lu-PSMA-617 will be provided as a single dose ready to use radiopharmaceutical solution, with a volumetric activity of 1 GBq/mL at the reference date and time (calibration time (tc), that corresponds to the End of Production (EOP)). The volume of the solution dispensed varies between 7.6 mL and 12.3 mL in order to provide the required amount of radioactivity at the date and time of administration. The shelf life of the product is defined as 120 hours (5 days) after calibration time.

The Investigational Product ^{68}Ga-PSMA-11 will be provided:

- as a kit for radiopharmaceutical preparation: single vial with a white lyophilized powder to be locally reconstituted with a solution of gallium-68 chloride (^{68}GaCl3) in HCl eluted from an approved ^{68}Ge/^{68}Ga generator (for the clinical sites equipped with an approved ^{68}Ge/^{68}Ga generator).
- as a single dose ready to use radiopharmaceutical solution: vial or syringe with the radiopharmaceutical solution supplied by the central radiopharmacy (for the clinical sites not equipped with an approved ^{68}Ge/^{68}Ga generator).

The volume of ^{68}Ga-PSMA-11 solution for injection, corresponding to the radioactive dose to be administered, is calculated according to the estimated time of injection, on the basis of the current activity provided by the generator and of physical decay of the radionuclide (half-life = 68 min). After reconstitution, the ^{68}Ga-PSMA-11 solution must be used within 6 hours.

The process of ordering and delivery, as well as the procedure for ^{68}Ga-PSMA-11 solution preparation is described in the Pharmacy Manual.

Both products must be handled and administered by qualified/authorized personnel only and must be prepared in accordance with pharmaceutical quality requirements and radiation safety regulations.

ARDT should be administered orally on a continuous basis, as per package insert and guidelines to the participants randomised to the ARDT arm.

6.1.4 Treatment arms/group

During screening, potential participants will be assessed for eligibility and will undergo a ^{68}Ga-PSMA-11 PET / CT scan to evaluate PSMA positivity by central review. Only participants with PSMA- positive cancer and confirmed eligibility will be randomized. Randomization will be stratified by prior ARDT use and by symptomatology. Prior ARDT use will be determined by the setting (CRPC vs HSPC) when the patient initiated treatment with enzalutamide, abiraterone, apalutamide, or darolutamide then suffered disease progression. Symptomatology (asymptomatic or mildly symptomatic vs symptomatic) will be determined by score on item 3 of the Brief Pain Inventory Short Form (BPI-SF) questionnaire (symptomatic = score >3 on item 3 of the BPI-SF questionnaire).

Once eligibility criteria are confirmed, participants will be randomized to one of the following 2 treatment arms in a ratio of 1:1

- Study treatment: ^{177}Lu-PSMA-617
- Comparator Approved change in ARDT (abiraterone or enzalutamide)

The change of ARDT treatment for each participant will be selected by the treating physician prior to randomization. If the participant gets randomized to receive ^{177}Lu-PSMA-617, the choice of change of ARDT treatment will be discarded.

Supportive care will be allowed in both arms and includes available care for the eligible participants according to best institutional practice and at the discretion of the investigator.

6.1.5 Guidelines for continuation of treatment

Refer to Section 3 for study treatment and Section 6.5 for dose modifications.

6.1.6 Treatment duration

Participants randomized to the investigational arm must begin ^{177}Lu-PSMA-617 dosing within 14 days after randomization. Up to an additional 3 days are allowed to accommodate other scheduling delays for C1D1. Participants will receive best supportive care and a dose of 7.4 GBq (± 10%) of ^{177}Lu-PSMA-617 once every 6 weeks for 6 cycles as per Table 8-2. After the last day of study treatment period of ^{177}Lu-PSMA-617 or upon radiographic progression, the participants must have an End of Treatment (EOT) visit performed ≤ 7 days and enter the Post-treatment Follow-up period. For participants on the ^{177}Lu-PSMA-617 arm who complete the planned 6 cycle course therapy, the treatment period ends after the week 37 imaging and C6W5 visit is completed.

For both arms, upon EOT visit, participants might be treated with any other medications per discretion of the treating physician.

Please refer to Section 9.2, Table 8-2 and Table 8-3 for further details.

The change of ARDT treatment for each participant will be selected by the treating physician prior to randomization and will be administered per the physician's orders and continued until the participant comes off the treatment period of the study.

Participants may be discontinued from treatment earlier due to unacceptable toxicity (refer to Table 6-2), or disease progression and/or at the discretion of the investigator or the participant. While the participant and/or at the physician's discretion may decide prematurely to cease taking randomized therapy at any time, full follow-up of all randomized participants for the intended duration of the trial is planned by design for the collection of rPFS and OS data.

6.1.6.1 Treatment beyond disease progression

Upon occurrence of radiographic progression as assessed by blinded centralized review, participants randomized to ^{177}Lu-PSMA-617 should stop study treatment and receive any other therapy per the discretion of the treating physician and local regulations in the long-term follow-up period. However, if the investigator determines that the participant is still benefiting from continuation of study treatment, the participant may continue ^{177}Lu-PSMA-617 treatment for up to 6 cycles.

Upon the occurrence of radiographic progression, as assessed by BICR, participants randomized to the ARDT treatment arm will be allowed to cross over to receive ^{177}Lu-PSMA-617 treatment or may continue to receive any other therapy per the discretion of the treating physician in the Post-treatment Follow-up. If crossover to ^{177}Lu-PSMA-617 is selected, then ^{177}Lu-PSMA-617 will be administered with the same dose/schedule as for participants who were initially randomized to receive ^{177}Lu-PSMA-617 as described above in Section 6.1.6.

Please refer to Section 9.1.1 for reasons for treatment discontinuation.

6.2 Other treatment(s)

Supportive care will be allowed in both arms and includes available care for the eligible participants according to best institutional practice and at the discretion of the investigator.

6.2.1 Concomitant therapy

Supportive Care

Participants should receive full supportive care while on study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions.

Within the first few days of treatment with ^{177}Lu-PSMA-617, the most common adverse events (AEs) are general fatigue and an increase in bone pain. The treatment-related bone pain is transient in nature, often occurring within the first 24-48 hours post the initial 1-2 cycles of administration of ^{177}Lu-PSMA-617 and may be managed by administering narcotic analgesics.

Antiemetics may be used at the discretion of the attending physician. Diarrhea management is per the discretion of the treating physician. Diarrhea could be managed conservatively with medications such as loperamide. Participants with severe diarrhea should be assessed for intravenous hydration and correction of electrolyte imbalances.

ADT treatment may be modified for reasons of intolerance at the discretion of the investigator throughout the study. It is discouraged to change ADT treatment in both arms based solely on PSA changes.

Bone Health Agents

Consideration should be given to using concomitant bone health agents such as bisphosphonates and RANKL inhibitors on either arm of the study. Participants receiving bisphosphonates (for example zoledronic acid), RANKL inhibitors (for example denosumab), or similar therapy prior to randomization may be maintained on this therapy during the study. These may be stopped or started at the discretion of the investigator throughout the study.

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

Medications for myelosuppression

Blood and/or blood component transfusion or erythropoiesis stimulation agents are allowed throughout the study after randomization.

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology Clinical Practice Guideline Update (Smith et al 2015) and American Society of Clinical Oncology – American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer (Rizzo et al 2010), and/or other international/national guidelines at the discretion of the investigator/attending physician.

Epoetin (EPO): Use of epoetin in this protocol is permitted at the discretion of the treating physician.

Anticoagulants and platelet aggregation inhibitors are allowed, and for participants who experience thrombocytopenia is to be used with caution.

Palliative radiotherapy

Palliative radiation therapy may be administered to symptomatic bone disease and it is not considered as prohibited medication. The need for palliative radiation may not be counted as an rPFS (i.e., radiographic progression) event, however, it will be listed as clinical progression and meet criteria for a Symptomatic Skeletal Event.

After the 1st post-baseline scan, the need for palliative radiation may indicate radiographic disease progression and should be assessed per the PCWG3 modified RECIST v1.1 criteria, and may result in study treatment discontinuation. When the need for palliative radiation to lesions other than bone is seen after the baseline scan, palliative radiation to the target lesion

should be possibly avoided, the lesion should be assessed per RECIST 1.1 criteria, and initiation of palliative radiation may result in study treatment discontinuation when radiographic progression is confirmed.

If palliative radiation treatment is planned to be initiated during the study in the absence of radiographic progression, the investigator should use best clinical judgement to assess the potential clinical benefit of palliative radiation weighed against the risk of overlapping side effects of radiation and study treatment when considering timing and doses of palliative radiotherapy. Any interruption of study treatment greater than 4 weeks from the next scheduled dose due to administration of radiation or recovery from effects of radiation will require permanent discontinuation of study treatment. All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant enter the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.2 Prohibited medication

Other investigational agents, biological products, immunotherapy, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g., radium-223), Poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors or hemi-body radiotherapy treatment must not be administered on study. ARDT must not be administered concomitantly with ^{177}Lu-PSMA-617.

ARDT drugs have potential drug interactions with medications that include but not limited to CYP3A4 strong inducers or inhibitors. Concomitant use of restricted drugs should be avoided. The treating investigator must review the local full prescribing information regarding potential drug interactions and follow restrictions to drug use or dose modification recommendations per the labeling for each agent in cases where such medications are unavoidably co-administered with ARDT.

Refer to the Exclusion criteria (Section 5.2) for the list with prohibited medications or treatment which makes a potential participant not eligible to enter the study.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening through the clinical data management interface and is retained for the participant throughout his participation in the trial**.** A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

6.3.2 Treatment assignment, randomization

During screening period at day -14, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms in a 1:1 ratio: ^{177}Lu-PSMA-617 or a change in a Comparator Approved ARDT (abiraterone or enzalutamide). The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm.

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider, or by a delegate under Novartis supervision, using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

The investigator or his/her delegate will order each ^{177}Lu-PSMA-617 dose within 10 working days prior to the scheduled cycle. Each administration will be tracked by the investigator or his/her delegate via IRT. Detailed instructions of IMP ordering and IRT use will be provided in the Pharmacy Manual.

The change of ARDT treatment for each participant will be selected by the treating physician prior to randomization. If the participant gets randomized to receive ^{177}Lu-PSMA-617, the choice of change of ARDT treatment will be discarded.

6.4 Treatment blinding

Treatment assignment will be open to participants, investigator staff, persons performing the assessments, and the Novartis study team. In order to minimize the potential impact on the integrity of the study, until the primary analysis is conducted, no aggregate statistical analyses (efficacy or safety across the study) shall be performed by treatment. BICR will remain blinded to the identity of the treatment.

6.5 Dose escalation and dose modification

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

Dose modifications are summarized in Table 6-2.

Dose escalation and modification for ARDT should be managed as per the local label for the respective drug and/or local clinical practice guidelines.

6.5.1 Definitions of dose limiting toxicities (DLTs)

Not applicable.

6.5.2 Dose modifications

For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions, and/or reductions are either recommended or mandated in order to allow participants to continue the study treatment.

These dose modifications are summarized in Table 6-2. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2.

These dose changes must be recorded on the appropriate eCRF.

For ARDT treatment and any supportive care medication, please refer to the medication label for drug interactions and toxicities.

For ^{177}Lu-PSMA-617, the most common adverse events (AEs) within the first few days of treatment 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 central labs for hematology, chemistry and coagulation results must all be assessed prior to dosing with ^{177}Lu-PSMA-617. If central lab results are not available in time to review prior to dosing, local labs may be additionally sent to expedite clearing the patient for treatment. In case of adverse events determined not related to ^{177}Lu-PSMA-617, a dose of ^{177}Lu-PSMA-617 may be delayed or reduced according to dose management guidance at the discretion of the investigator. Table 6-2 provides dose modification criteria and guidance on dose management which must be followed when a causal relationship between ^{177}Lu-PSMA-617 and an adverse event is confirmed by the investigator. Only one reduction in administered activity is permitted. If a participant has further toxicity that would require an additional reduction in administered activity, treatment with ^{177}Lu-PSMA-617 must be discontinued. Once a dose is reduced, treatment with ^{177}Lu-PSMA-617 should not be re-escalated.

If the treatment is delayed due to an AE for more than 4 weeks, or any toxicity is determined to be unacceptable to the participant or the investigator, then 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 participant has not radiographically progressed as measured by PCWG3 criteria.

Table 6-2 Toxicity management and dose modifications for ^{177}Lu-PSMA-617 treatment for adverse drug reactions

Laboratory finding / event	Grade (lab values)[a]	Dose management
Anemia, leukopenia, or neutropenia	Grade 1	Recommendation: maintain dose and administration schedule.
	Grade 2 Hemoglobin < 10.0 – 8.0 g/dL WBC count < 3.0 – 2.0 × 10^9/L ANC < 1.5 – 1.0 × 10^9/L	Management recommendation: hold ^{177}Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Recommendation: Manage clinically as appropriate. The use of growth factors is permitted but should be discontinued

Laboratory finding / event	Grade (lab values)[a]	Dose management
		once the event resolves to Grade 1 or baseline. Check hematinic levels (iron, B12, and folate) and provide supplementation as required. Transfusions may be given as clinically indicated for anemia.
	≥ Grade 3 Hemoglobin < 8.0 g/dL WBC count < 2.0 × 10^9/L ANC < 1.0 × 10^9/L Or other non-platelet hematological values ≥ Grade 3	Mandatory: hold ^{177}Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle (except lymphocytopenia that responds to medical intervention). Recommendation as for grade 2.
Thrombocytopenia	Grade 1	Recommendation: maintain dose and administration schedule.
	≥ Grade 2 (platelet count of < 75 × 10^9/L)	Mandatory: hold ^{177}Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle. Recommendation: platelet transfusions may be given as clinically indicated.
Serum creatinine	Grade 1 (> ULN - 1.5 x ULN)	Recommendation: maintain dose and administration schedule.
	Grade 2 (> 1.5 - 3.0 x baseline, or > 1.5 - 3.0 x ULN)	Mandatory: hold ^{177}Lu-PSMA-617 until resolved to ≤ Grade 1 or baseline, then maintain dose level.
	Increased ≥ 40% from baseline AND calculated creatinine clearance decreased > 40% from baseline	Mandatory: Reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle.
	Grade 3 (> 3.0 x baseline, > 3.0 – 6.0 x ULN)	Mandatory: discontinue ^{177}Lu-PSMA-617. If corrected to grade 1 by supportive care measures (i.e., fluid hydration) before the next administration and continue but reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle.
	Grade 4 (> 6.0 x ULN)	Mandatory: discontinue ^{177}Lu-PSMA-617.
Isolated total bilirubin elevation	> ULN - 1.5 x ULN	Recommendation: maintain dose and administration schedule.
	> 1.5 - 3.0 x ULN	Recommendation: maintain dose and administration schedule. Repeat liver function tests (LFTs)[b] within 48-72 hours, then monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or to baseline.
	> 3.0 - 10.0 x ULN	Mandatory: Hold treatment Repeat LFTs[b] within 48-72 hours, then monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or to baseline: treatment re-initiation is possible if clinically indicated. Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated)

Laboratory finding / event	Grade (lab values)[a]	Dose management
		component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination), then earlier treatment re-initiation is possible at the discretion of the investigator.
	> 10.0 x ULN	Mandatory: Discontinue participant from treatment. The participant should be monitored weekly (including LFTs[b]), or as clinically indicated, until total bilirubin has resolved to baseline.
Isolated AST or ALT elevation	> ULN – 3 x ULN	Recommendation: maintain dose and administration schedule.
	If normal at baseline: > 5.0 x ULN for more than 2 weeks, OR >10xULN If elevated at baseline: > 3.0x baseline AND > 10x ULN	Mandatory: Hold ^{177}Lu-PSMA-617. Repeat LFTs[b] within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ULN or to baseline. If resolved, reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle.
	> 20.0 x ULN	Mandatory: Permanently discontinue ^{177}Lu-PSMA-617. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks.
Combined[c] elevations of AST or ALT and total bilirubin	For participants with normal baseline ALT and AST and total bilirubin value: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN without evidence of cholestasis[d] OR For participants with elevated baseline AST or ALT or total bilirubin value: AST or ALT > 3x baseline OR > 8.0 x ULN, whichever is lower, combined with total bilirubin > 2x baseline AND > 2.0 xULN* *Note: For participants with Gilbert's syndrome, at least 2-fold increase in direct bilirubin.	Mandatory: Hold ^{177}Lu-PSMA-617 and assess for DILI: Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b], or as clinically indicated, until AST, ALT, or total bilirubin have resolved ≤ ULN or to baseline. (Refer to the Section 6.5.3.1 for additional follow-up evaluations as applicable). If causality assessment indicates that DILI is probable: Permanently discontinue participant from treatment. If not DILI: Treat the identified cause according to institutional guidelines. Once resolved, reduce by one dose level.
Amylase and/or lipase elevation	≤ Grade 2 (> 1.5 - 2.0 x ULN)	Recommendation: maintain dose and administration schedule.
	Grade 3 (> 2.0 - 5.0 x ULN with signs or symptoms)	Recommendation: Hold ^{177}Lu-PSMA-617 until resolved to Grade ≤,1 or baseline then:

Laboratory finding / event	Grade (lab values)[a]	Dose management
	OR (> 5.0 x ULN and asymptomatic)	If resolved in ≤ 7 days, then maintain dose level. If resolved in > 7 days, reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle. Perform imaging**.
	Grade 4 (> 5.0 x ULN and with signs or symptoms)	Mandatory: Discontinue ^{177}Lu-PSMA-617. Perform imaging**.
Pancreatitis	Grade 2	Mandatory: Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 1 or baseline.
	Grade ≥ 3	Mandatory: Discontinue ^{177}Lu-PSMA-617.
Gastrointestinal toxicity	≤ Grade 2	Recommendation: maintain dose and administration schedule.
	≥ Grade 3	Mandatory: Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 2 or baseline.
Salivary gland toxicity	≥ Grade 2	Mandatory: Reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle.
Electrolyte or metabolic abnormalities that persist for greater than 48 hrs with sequela	≥ Grade 2	Mandatory: Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 1 or baseline.
Fatigue/ Asthenia	≤ Grade 2	Recommendation: maintain dose and administration schedule.
	≥ Grade 3	Mandatory: Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 2 or baseline.
Pain	≥ Grade 3 Persistent G3 pain not amenable to medical therapy.	Mandatory: Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 2 or baseline.
Spinal cord compression	Any grade	Mandatory: 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	Any grade	Mandatory: 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.
Non-hematological, clinically significant toxicity not otherwise stated	≥ Grade 2	Recommendation: Hold ^{177}Lu-PSMA-617 administration until resolved to Grade 1 or baseline.
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. All dose modifications should be based on the worst preceding toxicity.		

Laboratory finding / event	Grade (lab values)[a]	Dose management
[a] Common Toxicity Criteria for Adverse Events (CTCAE Version 5.0) [b] Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (ALP) (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN) [c] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction [d] "Cholestasis" defined as ALP elevation (>2.0 xULN and R value <2) in participants without bone metastasis or elevation of ALP liver fraction in participants with bone metastasis Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury * Note: For participants with Gilbert's syndrome, at least 2-fold increase in direct bilirubin. ** Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, participants will be discontinued permanently from study treatment.		

Table 6-3 Dose reduction steps for ^{177}Lu-PSMA-617

Dose reduction for ^{177}Lu-PSMA-617			
	Starting dose level – 0	Dose level – 1 (-20%)	Dose level – 2
^{177}Lu-PSMA-617	7.4 GBq (200mCi)	5.9 GBq (160mCi)	Not applicable
*Dose reduction should be based on the worst toxicity demonstrated at the last dose. **Refer to pharmacy manual for practical details in on dose reduction.			

6.5.3 Follow-up for toxicities

Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary. All participants must be followed up for adverse events and serious adverse events for 30 days following end of treatment visit and long term follow up period as described in Table 8-2 and Table 8-3. Long term follow up starts after 30 Day Safety follow-up and lasts until death, loss to follow up, withdrawal of consent / opposition to use data/biological samples or accrual of the pre-specified number of events for the OS-based (key secondary endpoint) analysis, whichever occurs first. All medically significant adverse events (all SAEs) deemed to be related to ^{177}Lu-PSMA-617, including potential late onset radiation toxicity, will be collected during this period.

6.5.3.1 Follow up on potential drug-induced liver injury (DILI) cases

Participants with transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI, and should be considered as clinically important events

and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the participant's baseline AST/ALT and total bilirubin value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT >3.0 x baseline] OR [ALT or AST > 8.0 x ULN], whichever occurs first, combined with [total bilirubin > 2.0 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, Gamma-glutamyl transferase (GGT), prothrombin time (PT)/International Normalized Ratio (INR), alkaline phosphatase, albumin, and creatine kinase. If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended.

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion – e.g. using CT, MRI, or duplex sonography.

Perform relevant examinations (Ultrasound or MRI, Endoscopic retrograde Cholangiopancreatography (ERCP)) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis (is defined as an ALP elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis).

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury (//livertox.nih.gov/rucam.html).

Table 6-4 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Table 6-4 Guidance on specific clinical and diagnostic assessments

Disease	Assessment
Hepatitis A, B, C, E	• immunoglobulin M (IgM), Serum antibody to hepatitis A virus (anti-HAV); Hepatitis B surface antigen (HBsAg), immunoglobulin M & Immunoglobulin G antibody to hepatitis B core antigen (IgM & IgG anti-HBc), Hepatitis B Virus (HBV) DNA; anti Hepatitis C Virus (anti-HCV), Hepatitis C Virus (HCV) RNA, IgM & IgG anti Hepatitis E Virus (anti-HEV), Hepatitis E Virus (HEV) RNA
cytomegalovirus (CMV), HSV (Herpes simplex virus), Epstein-Barr virus (EBV) infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• antinuclear antibodies (ANA) and antismooth muscle antibody (ASMA) titers, total IgM, Immunoglobulin G (IgG), Immunoglobulin E (IgE), Immunoglobulin A (IgA)
Alcoholic hepatitis	• Ethanol history, GGT, Mean corpuscular volume (MCV), Carbohydrate-Deficient-Transferrin (CD-transferrin)
Nonalcoholic steatohepatitis	• Ultrasound or Magnetic resonance imaging (MRI)
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, Endoscopic retrograde cholangiopancreatography (ERCP) as appropriate.
Wilson disease (if <40 yrs old)	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – Triiodothyronine (T3), Thyroxin (T4), thyroid stimulating hormone (TSH); cardiovascular disease (CVD) / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 Diabetes (T1D) / glycogenic hepatitis).

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" i.e. >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates *probably caused* by the treatment, not by something else, and only such a case can be considered a Drug-induced liver injury (DILI) case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

For the participants on ARDT arm the investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he is unable for any reason to take the study treatment

as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log and in the corresponding eCRF pages.

Participants on ^{177}Lu-PSMA-617 arm will have the treatment administered during site visits as per schedule of events, Table 8-2 and Table 8-3. All study treatment must be recorded in the Drug Accountability Log and in the corresponding eCRF pages.

6.6.2 Treatment of overdose

In the event of administration of a radiation overdose with ^{177}Lu-PSMA-617, the radiation absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding.

Follow standard clinical practice for overdose of systemically administered radionuclidetherapy with radioligands. For overdose of ARDT, follow the guidance per product label.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section (Section 6.1.2).

For ^{177}Lu-PSMA-617 and ^{68}Ga-PSMA-11 preparation and administration, please refer to procedure and instructions contained in the Pharmacy Manual.

For ARDT, please refer to package insert.

As per the treatment assigned to the participant by the IRT, investigator staff will identify the study treatment to dispense to the participant.For ^{177}Lu-PSMA-617 and ^{68}Ga-PSMA-11, immediately after administration to the participant, site personnel will complete the accountability logs for traceability purposes. For more detailed instructions please refer to the Pharmacy Manual.

6.7.1 Handling of study treatment and other treatment

6.7.1.1 Handling of study treatment

Investigational study treatment ^{177}Lu-PSMA-617 must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the label and the Investigator's Brochure.

Clinical supplies are to be dispensed only in accordance with the protocol.Technical complaints are to be reported to the respective Novartis contact/associate or 3rd party representative.

^{177}Lu-PSMA-617

The packaging ^{177}Lu-PSMA-617 consists in a white glass vial (Type I of the Eu. Ph.) containing a maximum of 12.3 mL of radioactive solution. The vial is inserted into a lead shielded container (secondary packaging) closed in a Type A box (according to ADR and IATA regulations).

^{177}Lu-PSMA-617 solution should be handled by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken, complying with the requirements of Good Manufacturing Practice for pharmaceuticals.

Since ^{177}Lu-PSMA-617 is a ready-to-use solution, no manipulation of the investigational product is intended at the clinical site. The only quality control (QC) tests that must be performed at the clinical site are; 1) confirm correct product certificate of release; 2) measure radioactivity in the vial before and after administration using a calibrated radioactivity measurement system; 3) control the appearance of the solution (clear, colorless to slightly yellow solution, free from visible particles).

Once received, ^{177}Lu-PSMA-617 has to be stored upright according to storage conditions as described on the medication label, in the original package to protect from ionizing radiation (lead shielding).

Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials. In these conditions the product has a shelf life of 120 hours after the end of production.

The radioactive ^{177}Lu-PSMA-617 will be locally discarded according to all disposal requirements and local regulations for radioactive materials. The disposal of all study medication will be documented appropriately: copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

^{177}Lu-PSMA-617 labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions, expiry date and participant ID.

^{68}Ga-PSMA-11

The packaging of ^{68}Ga-PSMA-11 consists in a box (secondary packaging) and one 10 mL glass vials (primary packaging).

^{68}Ga-PSMA-11 will be supplied by Sponsor as a sterile, one-vial kit for reconstitution with ^{68}Ga solution eluted from approved commercial GMP ^{68}Ge/^{68}Ga generator to:

1. the clinical site, in case of the kit's reconstitution and radiolabelling will be performed at hospital's radiopharmacy
2. the radiopharmacy appointed by the sponsor, in case of an external radiopharmacy will be in charge of the kit's reconstitution and radiolabeling

In the second case, the clinical site will order the ^{68}Ga-PSMA-11 single dose ready to use solution for injection following the instructions described in the Pharmacy manual.

^{68}Ga-PSMA-11 must be prepared and administered as a single intravenous injection at the investigational site by appropriately trained personnel. The instruction for radiolabeling

procedure and dispensing ^{68}Ga-PSMA-11, cautionary notes, analytical controls and stability of the radiolabeled product will be provided to each site (please refer to the Pharmacy Manual).

After reconstitution with ^{68}Ga solution eluted from GMP ^{68}Ge/^{68}Ga generator, the investigational product is a radioactive substance which must be used within 6 hours; it must be handled and administered by qualified/authorized personnel only and must be prepared in accordance with pharmaceutical quality requirements and radiation safety regulations.

The kit for the preparation of ^{68}Ga-PSMA-11 should be stored upon receipt according to storage conditions as described in the medication label.

Kit labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions, expiry date.

^{68}Ga-PSMA-11 labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions, expiry date and participant ID.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 ARDT

ARDT should be handled as per package insert and guidelines.

6.7.2 Instruction for prescribing and taking study treatment

^{177}Lu-PSMA-617

- **Preparation**

^{177}Lu-PSMA-617 is a ready-to-use single-dose vial. The solution should be inspected visually prior to use, and only clear colorless to yellowish solutions free of visible particles should be used. The visual inspection of the solution should be performed under a shielded screen for radioprotection purposes. ^{177}Lu-PSMA-617 is not to be used before receipt of the batch release certificate. The amount of radioactivity in the radiopharmaceutical vial must be measured with an appropriate and calibrated device prior to administration in order to confirm that the actual amount of radioactivity to be administered is equal to the planned amount at the time of administration.

- **Administration**

Treatment with ^{177}Lu-PSMA-617 must be performed in accordance with national and/or local radiation and safety requirements. When a participant with manageable bladder outflow/urinary incontinence is randomized to receive treatment with ^{177}Lu-PSMA-617, the investigator should consult local nuclear medicine expert and ensure, that local radiation safety standards can be followed, and there is no additional potential impact of radiation safety (for trial participant, site staff, environment)

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

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

^{177}Lu-PSMA-617 will be administered intravenously as per best practice and Investigator's decision.

The total activity administered must be recorded (GBq, mCi or MBq) by measuring the residual radioactivity in the vial or in the syringe before and after administration. To guarantee a reliable measure, the dose calibrator (or activimeter) must be previously calibrated with a source equivalent to the dose that will be provided for the participants. Such calibration should be performed at least yearly and before the administration of the first participant first cycle, using a dose supplied for the participant (before the administration).

A saline flush of ≥10 mL NS (normal saline) should be administered after administration of ^{177}Lu-PSMA-617 to assure that there isn’t any residual drug in the intravenous line.

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

Participants should also be monitored for any evidence of pain or burning sensation during ^{177}Lu-PSMA-617 administration. Participants should be encouraged to maintain a good fluid intake on the day of treatment and following therapy.

To minimize irradiation of the urinary bladder, participants will be encouraged to increase fluid intake and to void frequently through the first days after administration. Participants should be advised to observe rigorous hygiene to avoid contamination risk of others using the same toilet facility. Management of bladder outflow/urinary incontinence is at the discretion of the investigators. Management may include best available standard of care options which are considered appropriate by the investigator. Use of pads, catheters, other drainage is allowed to control these conditions. As a precaution, participants may be kept in radiation isolation following administration as per local recommendations, and should be allowed to urinate during this time, and before release. General rules for bathroom use and hygiene (i.e. flush tissue paper and anything from your body) in the Therapy Discharge Instructions should be followed for at least 2 days after treatment.

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

It is not known if ^{177}Lu-PSMA-617 is a vesicant. Extravasation of ^{177}Lu-PSMA-617 may lead to localized tissue retention of the radiopharmaceutical agent and prolonged local exposure to ionizing radiation resulting in tissue damage and necrosis. In order to minimize the risk of extravasation or site irritation when administering ^{177}Lu-PSMA-617, the solution should only be infused through a confirmed free-flowing (i.e., patent) intravenous line. If extravasation of ^{177}Lu-PSMA-617 solution occurs, management should follow institutional guidelines, and may include, but not be limited to, dispersive intervention on the affected arm such as warming the extravasation area to increase blood flow and lymphatic drainage.

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.

^{68}Ga-PSMA-11

- **Preparation**

In case of the kit's reconstitution and radiolabelling will be performed at hospital's radiopharmacy.

The instruction for radiolabeling procedure, cautionary notes, analytical controls and stability of the radiolabeled product will be provided to each site (please refer to the Pharmacy Manual).

In case of an external radiopharmacy will be in charge of the kit's reconstitution and radiolabeling, the clinical site will receive the ^{68}Ga-PSMA-11 single dose ready to use solution for injection.

- **Administration**

^{68}Ga-PSMA-11 must be administered as a single intravenous injection at the investigational site by appropriately trained personnel. The instruction for radiolabeling procedure and dispensing ^{68}Ga-PSMA-11, cautionary notes, analytical controls and stability of the radiolabeled product will be provided to each site (please refer to the Pharmacy Manual).

After reconstitution with ^{68}Ga solution eluted from GMP ^{68}Ge/^{68}Ga generator, the investigational product is a radioactive substance which must be used within 6 hours: it must be handled and administered by qualified/authorized personnel only and must be prepared in accordance with pharmaceutical quality requirements and radiation safety regulations. The total activity administered must be recorded (GBq, mCi or MBq) by measuring the residual radioactivity in the vial or in the syringe before and after administration with the dose calibrator (or activimeter).

ARDT

ARDT should be administered orally on a continuous basis, as per package insert and guidelines including contraceptive measures.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, delivery of IMP directly to a participant's home is generally permitted in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or

possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. Implementation will need to be discussed with Novartis. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 3-months' supply. In this case, regular phone calls or virtual contacts (as close as possible to the visits as per schedule) will occur between the site and the participant for instructional purposes, safety monitoring, and discussion of the participant´s health status until the participants can again visit the site.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his level of understanding. If the participant is capable of doing so, he must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council for Harmonisation Good Clinical Practice (ICH E6 GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

Main study consent, which also included:

- A subsection that requires a separate signature for the 'Additional Research on your personal data' to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for the female partners of any male participants who took study treatment

[redacted]

[redacted]

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

[redacted]

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc).

A copy of the approved version of all consent forms must be provided to Novartis/Sponsor after IRB/IEC approval.

Participants might be asked to complete an optional questionnaire (Trial Feedback Questionnaire) to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

The Assessment Schedule Table 8-2 and Table 8-3 lists all of the assessments when they are performed. Assessment schedule lists all of the assessments and indicates with an 'X' or 'S', the visits when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The table indicates which assessments produce data to be entered into the clinical database or received electronically from a vendor 'X' or remain in source documents only 'S'. No eCRF will be used as a source document.

Participants should be seen for all visits/assessments as outlined in the assessment schedule Table 8-2 and Table 8-3 or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study are to return for end of treatment visit as soon as possible and attend follow-up visit as indicated in the Assessment Schedule.

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the eCRF.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

PRO measure(s) must be completed before any clinical assessments are performed at any given visit.

As per Section 4.6, during a Public Health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, or sending the participant to another imaging center (when feasible) can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

For participants randomized to the ^{177}Lu-PSMA-617 treatment where COVID-19 pandemic limits or prevents on-site study visits, any alternative methods as described above may be used with approval from Novartis to carry out the study assessments as outlined in Table 8-2. If the treatment with ^{177}Lu-PSMA-617 is interrupted for more than 4 weeks due to COVID-19 pandemic, treatment must be discontinued and the participant must have an EOT (or EOT2 if is a crossover participant) visit performed in ≤ 7 days and enter the Post-treatment Follow-up.

For participants randomized to the ARDT treatment where COVID-19 pandemic limits or prevents on-site study visits, delivery of IMP (as described in Section 6.7.2) and any alternative methods as described above may be used with approval from Novartis to continue with the study assessments as per Table 8-2 and Table 8-3. If the treatment with ARDT is interrupted for more than 4 weeks due to COVID-19 pandemic, the participant must have an EOT visit performed in ≤ 7 days and enter the Post-treatment Follow-up. The participant can continue with the ARDT treatment till the EOT visit.

Table 8-1 Window periods for Visit Schedule

Screening	After ICF signature and within 28 days of randomization in IRT system
Cycle 1 Day 1	Within 14 days after randomization in IRT system - (Maximum time needed to provide ^{177}Lu-PSMA-617 to the site) up to an additional 3 days to allow for unexpected schedule delays
Cycle 1 (all visits excluding C1D1 visit)	±3 days
Cycle 2-6 (all visits) of all subsequent cycles	±7 days
Imaging evaluations	±7 days
EOT	≤ 7 days
30-Day Safety FUP	+7 days
Long-term follow-up	± 28 days

Table 8-2 Assessment Schedule, ^{177}Lu-PSMA-617 and ARDT treatment arms

Period	**Screening**		**Treatment Period - Cycle 1**						**Treatment Period - Cycles 2-6 (6 week cycles, no assessments on weeks 2, 4, 6)[1]**			**Treatment period – Cycle 7 onward for ARDT arm (12 week cycles)[6]**	**EOT**	**Post-Treatment FU**	
Visit Name	**Screening**	**Randomization**	**C1W1**	**C1W2**	**C1W3**	**C1W4**	**C1W5**	**C1W6**	**C#W1**	**C#W3**	**C#W5**	**C7W1, C8W1, etc.**	**EOT1/EOT 2**	**30 day Safety FU**	**Long term FU (every 12 Weeks)**
Days	**-42 to -14**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**1**	**≤ 7 days**	**+ 7 days**	**+/- 28 days**
Informed consent	X														
Order of [^{68}Ga]Ga-PSMA-11[18]	X														
Perform [^{68}Ga]Ga-PSMA-11 PET/CT scan[18]	X														
Demography	X														
Inclusion / Exclusion criteria	X														
Relevant medical history/current medical history	X														
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X		

Period	**Screening**		**Treatment Period - Cycle 1**						**Treatment Period - Cycles 2-6 (6 week cycles, no assessments on weeks 2, 4, 6)[1]**			**Treatment period – Cycle 7 onward for ARDT arm (12 week cycles)[6]**	**EOT**	**Post-Treatment FU**	
Visit Name	**Screening**	**Randomization**	**C1W1**	**C1W2**	**C1W3**	**C1W4**	**C1W5**	**C1W6**	**C#W1**	**C#W3**	**C#W5**	**C7W1, C8W1, etc.**	**EOT1/EOT 2**	**30 day Safety FU**	**Long term FU (every 12 Weeks)**
Days	**-42 to -14**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**1**	**≤ 7 days**	**+ 7 days**	**+/- 28 days**
End of period Disposition	X												X		X (at end of FU)
Physical Exam	S (full)[3]		S (short)[3]						S (short)[3]				S (short)[3]	S (short)[3]	S (short)[3]
Height	X														
Weight	X												X	X	
ECOG	X		X										X	X	
Vital Signs[4]	X		X						X			X	X	X	
ECG	X	As clinically indicated											X		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X[23]	X[23]
SAEs related to study treatment															X[23]
Hematology	X		X[5]	X	X	X	X	X	X[5]	X	X	X[5]	X	X	X
Clinical Chemistry	X		X[5]	X	X	X	X	X	X[5]	X	X	X[5]	X	X	X
Coagulation Panel	X		X[5]	X	X	X	X	X	X[5]	X	X	X[5]	X	X	X
Urinalysis	X												X	X	

Period	Screening		Treatment Period - Cycle 1						Treatment Period - Cycles 2-6 (6 week cycles, no assessments on weeks 2, 4, 6)[1]			Treatment period – Cycle 7 onward for ARDT arm (12 week cycles)[6]	EOT	Post-Treatment FU	
Visit Name	**Screening**	**Randomization**	**C1W1**	**C1W2**	**C1W3**	**C1W4**	**C1W5**	**C1W6**	**C#W1**	**C#W3**	**C#W5**	**C7W1, C8W1, etc.**	**EOT1/EOT 2**	**30 day Safety FU**	**Long term FU (every 12 Weeks)**
Days	**-42 to -14**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**1**	**≤ 7 days**	**+ 7 days**	**+/- 28 days**
Serum/plasma testosterone	X								X			X[5]	X	X	
PSA	X								X			X[5]	X	X	X
[redacted]															
Radiographic Imaging (CT with I.V. contrast/MRI	X[11]	X[12]											X[13]		X[14]

Period	**Screening**		**Treatment Period - Cycle 1**						**Treatment Period - Cycles 2-6 (6 week cycles, no assessments on weeks 2, 4, 6)[1]**			**Treatment period – Cycle 7 onward for ARDT arm (12 week cycles)[6]**	**EOT**	**Post-Treatment FU**	
Visit Name	**Screening**	**Randomization**	**C1W1**	**C1W2**	**C1W3**	**C1W4**	**C1W5**	**C1W6**	**C#W1**	**C#W3**	**C#W5**	**C7W1, C8W1, etc.**	**EOT1/EOT 2**	**30 day Safety FU**	**Long term FU (every 12 Weeks)**
Days	**-42 to -14**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**1**	**≤ 7 days**	**+ 7 days**	**+/- 28 days**
and bone scan)[10]															
EQ-5D-5L			X						X			X	X	X	X[15]
FACT-P			X						X			X	X	X	X[15]
BPI-SF	X		X						X			X	X	X	X[15]
Trial Feedback Questionnaire			X						X			X	X	X	
IRT participant registration	X														
IRT arm randomization		X													
IRT drug administration			X						X			X			
IRT arm crossover													X[22]	X[22]	X[22]
Order ^{177}Lu-PSMA-617		X[16]					X[16]				X[16]		X[17]		
Administer ^{177}Lu-PSMA-617			X						X						
[redacted]															

Period	**Screening**		**Treatment Period - Cycle 1**						**Treatment Period - Cycles 2-6 (6 week cycles, no assessments on weeks 2, 4, 6)[1]**			**Treatment period – Cycle 7 onward for ARDT arm (12 week cycles)[6]**	**EOT**	**Post-Treatment FU**	
Visit Name	**Screening**	**Randomization**	**C1W1**	**C1W2**	**C1W3**	**C1W4**	**C1W5**	**C1W6**	**C#W1**	**C#W3**	**C#W5**	**C7W1, C8W1, etc.**	**EOT1/EOT 2**	**30 day Safety FU**	**Long term FU (every 12 Weeks)**
Days	**-42 to -14**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**1**	**≤ 7 days**	**+ 7 days**	**+/- 28 days**
Administer ARDT			AS per label. For ARDT treatment arm only												
Best supportive care			X												
Survival															X[19]
New antineoplastic therapies since study drug discontinuation														X	X
Symptomatic skeletal events	X														X
Clinical Progression			X[20]												

X Assessment to be recorded in the clinical database or received electronically from a vendor
[1] 6 cycles of ^{177}Lu-PSMA-617 therapy
[2] EOT visit must be performed ≤ 7 days after the last day of study treatment period
[3] S = assessment to be recorded in the source documentation only
[4] Blood pressure, pulse and respiratory rate to be assessed approximately 15 mins before study treatment and also approximately 30 mins and 60 mins post ^{177}Lu-PSMA-617 administration. Temperature only needs to be recorded once approximately 15 minutes prior to study treatment.
[5]Central labs for hematology, chemistry and coagulation results must all be assessed prior to dosing. If central lab results are not available in time to review prior to dosing, local labs may be additionally sent to expedite clearing the patient for treatment.

Period	Screening		Treatment Period - Cycle 1						Treatment Period - Cycles 2-6 (6 week cycles, no assessments on weeks 2, 4, 6)[1]			Treatment period – Cycle 7 onward for ARDT arm (12 week cycles)[6]	EOT	Post-Treatment FU	
Visit Name	Screening	Randomization	C1W1	C1W2	C1W3	C1W4	C1W5	C1W6	C#W1	C#W3	C#W5	C7W1, C8W1, etc.	EOT1/EOT 2	30 day Safety FU	Long term FU (every 12 Weeks)
Days	-42 to -14	-14 to -1	1	8	15	22	29	36	1	15	29	1	≤ 7 days	+ 7 days	+/- 28 days

[6]ARDT is administered continuously. From Cycle 7 onward, the visit frequency changes from every 6 weeks to every 12 weeks (i.e., C7 starts 6 weeks after C6D1, C8 starts 12 weeks after C7D1). For the purposes of this research study, although unconventional, the visit timepoints are termed "cycles".

[redacted]

[10] CT with contrast/MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis. Brain CT or MRI if clinically indicated as per Imaging Assessment Collection Plan, Table 8-7

[11] Radiographic Imaging (CT with contrast / MRI and bone scan) to be done within 28 days of randomization

[12] Every 8 weeks after first dose of study treatment for the first 24 weeks (week 9, 17, 25) and then every 12 weeks (week 37, 49, etc.) until confirmation of radiographic progression by BICR

[13] If not done within 28 days prior to EOT

[14] Only for participants with no rPFS event. For participants discontinuing for reasons other than radiographic progression: every 8 weeks after first dose of study treatment for the first 24 weeks (week 9, 17, 25) and then every 12 weeks (week 37, 49, etc) until confirmation of radiographic progression by BICR

[15] Assessments will be collected during post treatment follow up at LTFU2 (168 days after 30 day Safety FU) and LTFU4 (336 days after 30 day Safety FU) for all participants unless, lost to follow-up or withdrawal of consent / opposition to use data/biological samples

[16] Order 2 weeks prior dosing

[17] For crossover only, 2 weeks prior dosing

[18] If the potential participant received [^{68}Ga]Ga-PSMA-11 as part of a routine local exam prior to signing informed consent for this study, he must wait at least3 days prior to repeating [68Ga]Ga-PSMA-11 PET imaging as screening for this study.

[19] As long as the participant remains on study, contact for survival assessments should continue in long term follow up even if a subject has withdrawn consent for other assessments that require visits to study site such as blood sampling, PROs, and/or imaging.

[20] Clinical progression as assessed by the investigator. Refer to Section 8.3.3.

[redacted]

[22] ARDT arm patients are potential candidates for crossover at any stage during the study (i.e. on treatment or in follow-up) upon central confirmation of rPFS. See protocol "Section 3- Crossover period" for all crossover requirements. Start of new intervening antineoplastic therapies disqualifies patient for crossover.

Period	**Screening**		**Treatment Period - Cycle 1**						**Treatment Period - Cycles 2-6 (6 week cycles, no assessments on weeks 2, 4, 6)[1]**			**Treatment period – Cycle 7 onward for ARDT arm (12 week cycles)[6]**	**EOT**	**Post-Treatment FU**	
Visit Name	**Screening**	**Randomization**	**C1W1**	**C1W2**	**C1W3**	**C1W4**	**C1W5**	**C1W6**	**C#W1**	**C#W3**	**C#W5**	**C7W1, C8W1, etc.**	**EOT1/EOT 2**	**30 day Safety FU**	**Long term FU (every 12 Weeks)**
Days	**-42 to -14**	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**1**	**≤ 7 days**	**+ 7 days**	**+/- 28 days**
[23] For participants who received ^{177}Lu-PSMA-617 in the ^{177}Lu-PSMA-617 arm or in crossover, the following adverse events will be captured beyond the 30 day safety period regardless of relationship to study treatment and whether new anticancer therapy has been initiated: hematologic toxicities (including need for transfusion or use of growth factors), renal failure, xerostomia, xerophthalmia, secondary malignancies.															

Table 8-3 Assessment Schedule, crossover of ARDT arm participants to ^{177}Lu-PSMA-617 treatment

Period	**Baseline[14]**	**Treatment Period - Cycle 1**						**Treatment Period - Cycles 2-6 (6 week cycles, no assessments on weeks 2, 4, 6)[1]**			**EOT2**	**Post-Treatment Follow-Up**	
Visit Name	**Baseline[14]**	**C1W1**	**C1W2**	**C1W3**	**C1W4**	**C1W5**	**C1W6**	**C#W1**	**C#W3**	**C#W5**	**EOT2[2]**	**30 Day Safety FU**	**Long term FU (every 12 weeks)**
Days	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**≤ 7 days**	**+ 7 days**	**+/- 28 days**
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	
End of period disposition	X										X		X (at end of FU)
Physical Exam	S	S (short)[3]						S (short)[3]			S (short)[3]	S (short)[3]	S (short)[3]
Height													
Weight	X										X	X	
ECOG	X	X									X	X	
Vital Signs	X	X[4]						X[4]			X	X	
ECG		As clinically indicated									X		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X[18]
SAEs related to study treatment													X[18]
Hematology	X	X[5]	X	X	X	X	X	X[5]	X	X	X	X	X
Clinical Chemistry	X	X[5]	X	X	X	X	X	X[5]	X	X	X	X	X
Coagulation Panel		X[5]	X	X	X	X	X	X[5]	X	X	X	X	X
Urinalysis											X	X	
Serum/plasma testosterone								X			X	X	
PSA	X							X			X	X	X
[redacted]													

Period	Baseline[14]	Treatment Period - Cycle 1						Treatment Period - Cycles 2-6 (6 week cycles, no assessments on weeks 2, 4, 6)[1]			EOT2	Post-Treatment Follow-Up	
Visit Name	Baseline[14]	C1W1	C1W2	C1W3	C1W4	C1W5	C1W6	C#W1	C#W3	C#W5	EOT2[2]	30 Day Safety FU	Long term FU (every 12 weeks)
Days	-28 to -1	1	8	15	22	29	36	1	15	29	≤ 7 days	+ 7 days	+/- 28 days
[redacted]													
Radiographic Imaging (CT with I.V. contrast/MRI and bone scan)[8]	X[10]	X[9]									X[10]		X[11]
EQ-5D-5L		X						X			X	X	X[12]
FACT-P		X						X			X	X	X[12]
BPI-SF		X						X			X	X	X[12]
Trial Feedback Questionnaire		X						X			X	X	
IRT drug administration		X						X					
Order 177Lu-PSMA-617	X[13]					X[13]				X[13]			
Administer 177Lu-PSMA-617		X						X					

Period	**Baseline[14]**	**Treatment Period - Cycle 1**						**Treatment Period - Cycles 2-6 (6 week cycles, no assessments on weeks 2, 4, 6)[1]**			**EOT2**	**Post-Treatment Follow-Up**	
Visit Name	**Baseline[14]**	**C1W1**	**C1W2**	**C1W3**	**C1W4**	**C1W5**	**C1W6**	**C#W1**	**C#W3**	**C#W5**	**EOT2[2]**	**30 Day Safety FU**	**Long term FU (every 12 weeks)**
Days	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**≤ 7 days**	**+ 7 days**	**+/- 28 days**
[redacted]													
Best supportive care		X											
Survival													X[15]
New antineoplastic therapies since study drug discontinuation													X
Symptomatic skeletal events		X											
Clinical Progression			X[16]										

X Assessment to be recorded in the clinical database or received electronically from a vendor
[1] 6 cycles of 177Lu-PSMA-617 therapy
[2] EOT visit must be performed ≤ 7 days after the last day of study treatment period
[3] S = assessment to be recorded in the source documentation only
[4] Blood pressure, pulse and respiratory rate to be assessed approximately 15 mins before study treatment and also approximately 30 mins and 60 mins post ^{177}Lu-PSMA-617 administration.
Body temperature needs to be recorded only once, approximately 15 mins before study treatment.
[5]Central labs for hematology, chemistry and coagulation results must all be assessed prior to dosing. If central lab results are not available in time to review prior to dosing, local labs may be additionally sent to expedite clearing the patient for treatment.

Period	Baseline[14]	Treatment Period - Cycle 1						Treatment Period - Cycles 2-6 (6 week cycles, no assessments on weeks 2, 4, 6)[1]			EOT2	Post-Treatment Follow-Up	
Visit Name	Baseline[14]	C1W1	C1W2	C1W3	C1W4	C1W5	C1W6	C#W1	C#W3	C#W5	EOT2[2]	30 Day Safety FU	Long term FU (every 12 weeks)
Days	-28 to -1	1	8	15	22	29	36	1	15	29	≤ 7 days	+ 7 days	+/- 28 days

[redacted]

[8] CT with contrast/MRI tumor assessments should include evaluations of the chest, abdomen and pelvis. Brain CT or MRI if clinically indicated as per Imaging Assessment Collection Plan, Table 8-7

[9] Every 8 weeks after first dose of study treatment for the first 24 weeks (week 9, 17, 25) and then every 12 weeks (week 37, 49, etc) until confirmation of radiographic progression by BICR

[10] If not done within 28 days prior to registration for crossover

[11] Only for participants with no rPFS event. For participants discontinuing for reasons other than radiographic progression: every 8 weeks after first dose of study treatment for the first 24 weeks (week 9, 17, 25) and then every 12 weeks (week 37, 49, etc) until confirmation of radiographic progression by BICR

[12] Assessments will be collected during post treatment follow up at LTFU2 (168 days after 30 day Safety FU) and LTFU4 (336 days after 30 day Safety FU) for all participants unless lost to follow-up or withdrawal of consent / opposition to use data/biological samples

[13] Order 2 weeks prior dosing after confirmation of eligibility and IRT registration for crossover

[14] Assessments from EOT1 may be used if performed within prior 28 days. Assessments may be repeated if necessary to meet eligibility.

[15] As long as the participant remains on study, contact for survival assessments should continue in long term follow up even if a subject has withdrawn consent for other assessments that require visits to study site such as blood sampling, PROs, and/or imaging.

[16] Clinical progression as assessed by the investigator. Refer to Section 8.3.3.

[redacted]

[18] For participants who received ^{177}Lu-PSMA-617 in the ^{177}Lu-PSMA-617 arm or in crossover, the following adverse events will be captured beyond the 30 day safety period regardless of relationship to study treatment and whether new anticancer therapy has been initiated: hematologic toxicities (including need for transfusion or use of growth factors), renal failure, xerostomia, xerophthalmia, secondary malignancies.

8.1 Screening

Screening

Written informed consent must be obtained prior to any screening procedures. Please refer to Section 7 for the Informed Consent procedures. After informed consent is collected, the participant must be registered in IRT and [^{68}Ga]Ga-PSMA-11 requested for the PET / CT scan to evaluate PSMA positivity by central review. Only participants with PSMA- positive cancer will be randomized after eligibility is confirmed. Randomization will be stratified by prior ARDT use in castrate-resistant prostate cancer (CRPC) vs. HSPC setting and by symptomatology.

Laboratory assessments are carried out as priority to allow the necessary time to obtain the results prior to randomization. All Screening assessments to confirm eligibility into the study should be performed after ICF signature and within 28 days prior to randomization. (Table 8-2).

During the screening visit, inclusion and exclusion criteria will be assessed. Screening assessments to confirm eligibility must be performed prior to randomization.

The central reading of PET/computed tomography (CT) scan to evaluate PSMA positivity as well as the results of the hematology and chemistry screen must be available prior to randomization to evaluate eligibility.

A participant who has any screening assessment results that do not satisfy eligibility criteria may have the tests repeated as long as all required assessments are performed within 28 days of randomization. In this case, the participant will not be required to sign a new ICF, and the original participant identification (ID) number assigned by the investigator will be used.

In the event that screening assessments cannot be performed within the screening visit window, or the re-tests do not meet eligibility criteria, or eligibility criteria have changed and therefore not met anymore, the participant is considered a screening failure, and must be discontinued from the study. It is permissible to re-screen a participant if he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis. A new ICF will have to be signed if the investigator chooses to re-screen the participant thereafter, and the participant will be assigned a new participant ID number. All required screening activities, except the ^{68}Ga-PSMA-11 requested for the PET/computed tomography (CT) scan if the previous was done during the last 6 weeks, must be performed when the participant is re-screened for participation in the study. Only in the case when a new [^{68}Ga]Ga-PSMA-11 PET/CT needs to be repeated, will a new eligibility read by the central imaging vendor be required. Baseline imaging (CT/MRI and bone scan) must continue to be within window for the new anticipated randomization date, and should be repeated if necessary. The study sponsor and central imaging vendor should be simultaneously notified immediately of any participant to be rescreened, and whether scans already submitted to the central imaging vendor need to be linked to the new participant identification number.

A participant may only be re-screened once for the study. Once the number of participants screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to

further screening. In this case, the participants who screen failed will not be permitted to re-screen.

8.1.1 Eligibility screening

When all screening procedures are completed and once the participant's eligibility has been checked and confirmed (i.e., all inclusion/exclusion criteria have been verified, including [^{68}Ga]Ga-PSMA-11 positivity confirmed by central review) the investigator or designee may proceed with randomization per Section 6.3.2.

Please refer as well as to the detailed guidelines in the IRT Manual.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form (CRF). The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. The AE eCRF should also be completed for all participants who have received [^{68}Ga]Ga-PSMA-11. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening period (see SAE section for reporting details). **If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized**.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

Country specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

Participant demographics: full date (only if required and permitted) or year of birth or age, sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent will be recorded in the eCRF. Where possible diagnosis and not symptoms should be recorded. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, these data are necessary to assess the diversity of the study population as required by health authorities. All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the protocol Section 6.2.1 Concomitant Therapy for further details on what information must be recorded page of the eCRF.

Participant demographic and baseline characteristic data to be assessed on all participants include:

- Demographic information: age, gender, ECOG PS, height and weight, body temperature, blood pressure and pulse measurements

- Laboratory evaluations: hematology, chemistry, coagulation, urinalysis test, PSA and serum testosterone
- [redacted]

Medical history:

- Prostate cancer prior history including date of initial diagnosis, Gleason score at diagnosis, AJCC stage at diagnosis, extent of disease, and PSMA result with [^{68}Ga]Ga-PSMA-11 PET/CT scan
- Prior and current concomitant medications which related to the prostate therapy and best supportive care/ standard of care
- Date and type of progression (e.g. PSA, radiological, bone, soft tissue or no clinical benefit) and date of disease progression
- Site of progression (new lesions, existing lesions, or both) when available
- Ongoing medical conditions, symptoms and diseases which are recorded on the Medical History eCRF should include the toxicity grade when applicable
- Other all important medical, surgical, and allergic conditions that could have an impact on the participant's evaluation) / current medical conditions (e.g. all relevant current medical conditions which are present at the time of signing informed consent).

8.3 Efficacy

For the timing of efficacy assessments, refer to the schedule of assessments provided in Table 8-2 and Table 8-3.

8.3.1 Radiographic imaging for tumor assessment

Radiologic assessment to monitor radiographic progression should follow PCWG3 modified RECIST v1.1 guidelines. Periodic radiographic imaging will include both:

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

Table 8-4 Overall Time Point Response per PCWG3 modified RECIST v1.1

Soft Tissue (PCWG3-modified RECIST 1.1) TPR	Bone Lesion (PCWG-modified RECIST) TPR	Combined Overall PCWG-modified RECIST 1.1 TPR
PD	Any	PD
Any	PD	PD
Any (except PD)	PDu	PDu
Any (except PD)	UNK*	UNK
UNK	Non-PD or NED	UNK
NED[1]	Non-PD	Non-CR/Non-PD
NED[1]	NED	NED
SD	Non-PD or NED	SD
Non-CR/Non-PD	Non-PD or NED	Non-CR/Non-PD
PR	Non-PD or NED	PR
CR	Non-PD	PR[2]

		Non-CR/Non-PD[3]
CR	NED	CR
* If the bone scan is entirely missing or was not done, then the combined overall TPR is UNK. (1) NED for soft tissue, defined as no target or non-target soft tissue lesions identified at Screening/Baseline and no new soft tissue lesions identified. (2) The combined overall TPR will be PR if target lesions were present at Screening/Baseline. (3) The combined overall TPR will be Non-CR/Non-PD if no targets lesions were present at Screening/Baseline.		

CT with contrast/MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis. Sites of "soft-tissue" disease will be characterized as either target or non-target lesions based on CT/MRI images. The distribution of the target and non-target lesions should be representative of the subject's overall disease. Note, that for the purpose of the study a maximum of five (5) target lesions per site of metastatic spread (e.g., lung, liver, adrenal glands, lymph nodes, etc.) will be chosen for measurement over the course of the study.

- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs/sites of metastatic spread, but in addition should be those that lend themselves to reproducible repeated measurements.
- Target lesion must be measurable at screening/baseline
- The number of target lesions representing one (1) site of metastatic spread may be up to five (5).The total number of target lesions may be more than five (5) in order to represent all sites of metastatic spread.
- Lesion(s) in a prostate should not be selected as target or non-target
- Lesion(s) in a prostate bed in the participants with a history of prostatectomy should not be selected as target or non-target
- Lymph nodes (pelvic, extra pelvic) may be selected as target or non-target when qualifying criteria met
- Lesions/areas of tumor spread located in pelvis, which are extraosseous and other than prostate/prostate bed/lymph nodes (e.g. pelvic masses, invaded bladder, seminal vesicles) may be selected as target or non-target

Sites of bone disease will be recorded based on bone scan, with exception to bone metastasis with soft tissue component which may qualify for target/non-target when detectable at CT/MRI as described above. Note, that for the purpose of the study, bone lesion(s) should be assessed by Bone scan only

Disease progression by bone scan criteria will be met if at least 2 new bone lesions at the first "post treatment" scan that persist, with at least two additional lesions on the next (confirmatory) scan outside the 12-week flare window (2 + 2 PCWG3 criteria), (Scher et al 2016) by BICR.

For scans after the 12-week flare window, the first observation of at least two new lesions relative to the baseline scan must be confirmed on a subsequent scan at least 6 weeks later (2 + 2 PCWG3 criteria).

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

Table 8-5 Bone disease response per PCWG3 criteria

Terms	Definition
No Evidence of Disease (NED)	No bone lesions present.
Non-Progression (Non-PD)	Bone lesions present but requirements for NED, PDu, or PD are not met
Progressive Disease Unconfirmed (PDu)	Temporary designation when 2 or more new bone lesions are 1st observed
Progressive Disease Confirmed (PDc)	2 more new bone lesions have been confirmed
Flare Window	Considered the 1st Post-Treatment Scan. May be performed up to Week 12.
Outside Flare Window	Any time points after the 1st Post-Treatment Scan

Table 8-6 Disease Progression on Bone Scan

Date Progression Detected	Criteria for Progression	Criteria for Confirmation of Progression (Timing)	Criteria for Documentation of PD on Subsequent Scan
<12 weeks of treatment	Two (2) or more new lesions within the flare window	At least six (6) weeks after progression is initially identified	Two (2) or more additional new lesions outside the flare window compared to the prior scan
>12 weeks of treatment	Two (2) or more new lesions outside the flare window	At least six (6) weeks after progression is initially identified	Persistence of bone lesions compared to prior scan

The disease progression will be assessed via blinded centralized review of radiographic images provided by the treating physician for participants randomized in either arm according to PCWG3-modified RECIST v1.1.

For rPFS (defined as the time from the date of randomization to the date of first documented radiographic disease progression confirmed by BICR or death from any cause) upon the occurrence of radiographic progression confirmed by BICR, participants randomized to ^{177}Lu-PSMA-617 may enter the long-term follow up period and continue to receive any other therapy per the discretion of the treating physician. Upon confirmation of rPFS by BICR, participants randomized to ARDT treatment will be allowed to cross over to receive ^{177}Lu-PSMA-617 or may enter the long-term follow up period and continue to receive any other therapy per the discretion of the treating physician.

For rPFS2 defined as the time from the date of crossover (ARDT to ^{177}Lu-PSMA-617) to the date of radiographic disease progression by BICR or death from any cause) upon the occurrence of radiographic progression confirmed by BICR, crossover participants on ^{177}Lu-PSMA-617 may enter the long-term follow up period and continue to receive any other therapy per the discretion of the treating physician. Tumor response of soft tissue, lymph node, and visceral lesions to treatment will be assessed locally and centrally using the PCWG3-modified RECIST v1.1 criteria (Eisenhauer et al 2009, Scher et al 2016) with caveats outlined in the PCWG3 recommendations (Section 16.2 and Section 16.3). Details of the central review process will be described in the Independent Review Charter.

Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. The results of the central evaluations will be used to screen the study participants for eligibility (PET imaging with ^{68}Ga-PSMA-11)

and for study endpoints analysis (BICR for CT with contrast / MRI and bone scan) purposes. The local investigator's assessment will be used for treatment decision making.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, the investigator and sponsor might consider sending the participant to another imaging center, when feasible. Those visits might be scheduled as close as possible to study schedule. If the treatment (with ^{177}Lu-PSMA-617 or ARDT) is interrupted for more than 4 weeks due to COVID-19 pandemic, the participant must have an EOT visit performed in ≤ 7 days and enter the Post-treatment Follow-up.

Table 8-7 Imaging Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement*)	Mandated	Mandated, every 8 weeks after first dose of study treatment for the first 24 weeks (week 9, 17, 25) and then every 12 weeks (week 37, 49, etc) until confirmation of radiographic progression by BICR
Brain CT or MRI*	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Whole body bone scan with technetium-99m labeled diphosphonate	Mandated	Mandated, every 8 weeks after first dose of study treatment for the first 24 weeks (week 9, 17, 25) and then every 12 weeks (week 37, 49, etc) until confirmation of radiographic progression by BICR
CT or MRI of other metastatic sites (e.g. neck)	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis

*If a participant is known to have a contraindication to CT intravenous (IV) contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts; however, if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

Baseline imaging assessments

Imaging assessments will be performed at screening/baseline within 28 days of randomization.

Any imaging assessments already completed during the regular work-up of the participant within 28 days prior to randomization, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after randomization cannot be considered baseline images. The following assessments are required at screening/baseline:

- Chest, abdomen, and pelvis CT or MRI
- Brain CT or MRI, if clinically indicated
- Whole body bone scan, with technetium-99m labeled diphosphonates
- CT or MRI of other metastatic sites (e.g. neck), if clinically indicated

Participants 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 purpose of maintaining neurologic integrity. Participants with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated,

are stable, and not neurologically impaired. For participants 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).

Whole body bone scan with technetium-99m labeled diphosphonates should be performed per study imaging site manual. If clinically indicated, CT or MRI of other areas (e.g. spinal column) of disease as appropriate should be performed.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

X-rays and ultrasound should not be used to measure tumor lesions.

Post-baseline imaging assessments

Imaging assessments as described in Table 8-2 and Table 8-3 should be performed using the same imaging modality used at baseline. Imaging assessments are to be performed every 8 weeks after first dose of ^{177}Lu-PSMA-617 or ARDT for the first 24 weeks (independent of dose delays), then every 12 weeks and at End of Treatment Visit (if not done within 28 days of EOT).

For participants who completed 6 cycles/treatment periods and did not have radiographic progression confirmed by BICR or participants in either arm who discontinue treatment for reasons other than documented radiographic progression, death, lost to follow-up, or withdrawal of consent/ opposition to use data/biological samples, tumor assessments must continue to be performed every 8 weeks from first dose of study treatment for the first 24 weeks, then every 12 weeks until documented radiographic progression, death, lost to follow-up, or withdrawal of consent / opposition to use data/biological samples.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a participant, as necessary. For "soft-tissue" disease, determination of CR or PR requires confirmation by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Each lesion that is measured at baseline must be measured by the same method (either same imaging method) and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of IV contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to corroborate progressive disease per the Prostate Cancer Working Group 3 (PCWG3) Guidelines, but will not be used by itself to determine radiographic progression.

All study imaging (including any off-schedule imaging studies) should be submitted to the designated imaging CRO for quality control and central review.

Time points at which progression is determined locally

All participants who have disease progression determined by the local investigator require an expedited central review by BICR. Rapid image transmission to the imaging CRO may be accomplished by transferring the images electronically, e.g. via the Internet. In all instances, the process at the imaging CRO will ensure that the central reviewers remain blinded to the results of the local assessment and the expedited nature of the review. The investigator seeking an expedited review must indicate "progressive disease is suspected" to the imaging CRO on a designated form or by alternative means, please refer to the imaging vendor site manual for details. The imaging will undergo expedited central review (within 5 business days from the time of image receipt at the imaging CRO and once all applicable queries are resolved) and the results of the central review will be communicated to the site. While the investigator is awaiting the results of the central review, it is preferable that the participant continue on study treatment. However, during this time, the investigator should do whatever is medically necessary for his participant.

If the central review determines disease progression, then the participant will discontinue study treatment and subsequent tumor assessments are no longer required.

If the central review does not determine disease progression, the participant should continue receiving the study treatment unless there is a medical need (i.e., rapid progression or clinical deterioration) for an immediate change in therapy.

Participants will continue to have imaging performed as per protocol (Table 8-2 and Table 8-3) until the central review determines disease progression.

The imaging vendor will ensure that the central reviewers involved are blinded to the expedited status of the reading.

Time points without locally determined progression

All imaging time points without locally determined progression will be read on an ongoing, non-expedited basis as detailed in the imaging manual to be provided by the designated imaging CRO and independent review charter. Results of these readings will not be communicated to the sites.

For participants who cross over to ^{177}Lu-PSMA-617 after their first rPFS event confirmed by BICR, participants will continue to have imaging performed as per protocol (Table 8-3) until the BICR determines second radiographic disease progression.

8.3.2 Symptomatic skeletal events

The time to the first symptomatic skeletal events (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.

8.3.3 Clinical progression

Clinical progression will be assessed by the investigator. The following criteria should be used to determine when a participant 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 confirmed radiological progression
- Deterioration in ECOG performance status to Grade 3 or higher 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 participant to discontinue treatment due to clinical progression.

8.3.4 PSA levels

Central labs will measure PSA levels (Section 8.4.1).

As per Section 4.6, during the COVID-19 pandemic that limits or prevents on-site study visits regular, home nursing visits might be considered (as close as possible to the visits as per schedule), blood samples collection might be done at home and sent to the central lab, until the participant can again visit the site. Local labs might be used if needed.

8.3.5 Appropriateness of efficacy assessments

The measurements are standard based on the PCWG3-modified RECIST v1.1 (Eisenhauer et al 2009), (Scher et al 2016). PCWG3 is an international working group of clinical and translational experts in prostate cancer who developed internationally recognized recommendations.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits regular phone or virtual calls will occur (as close as possible to the visits as per schedule) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

For details on AE collection and reporting, refer to the AE section.

Table 8-8 Assessments & Specifications

Assessment		Specification
Physical examination		A complete physical examination will be carried out during screening. This will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. A short physical exam will include the examination of general appearance and vital signs (blood pressure [systolic blood pressure (SBP) and diastolic blood pressure (DBP)] and pulse). A short physical exam will be carried out as described in Table 8-2 and Table 8-3. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs		Vital signs include temperature, BP, pulse and respiratory rate measurements. After the participant has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Temperature needs to be recorded only once at the 15 min pre-dose timepoint.
Height and weight		Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-2 and Table 8-3.
ECOG Performance status		ECOG Performance status scale will be used as described in Table 8-2 and Table 8-3.

ECOG Performance status scale will be used as described in Table 8-9

Table 8-9 ECOG performance status scale

Score	Performance Status
0	Fully active, able to carry on all pre disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, light housework, office work
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

8.4.1 Laboratory evaluations

Central laboratory will be used for analysis of hematology, chemistry, coagulation, urinalysis, serum/plasma testosterone and PSA testing (safety monitoring) according to the schedule of assessments as described in Table 8-2 and Table 8-3. Local laboratory assessments will be allowed in specific cases where central laboratory analysis is not possible according to local regulations or central laboratory capabilities considering the radioactive nature of the study treatment. Additionally, lab tests may be performed at local labs instead of central labs when medically indicated or in case a visit is done at the end of the week preceding the following cycle and hematology/chemistry results are needed in less than 48 hours to confirm a dose reduction or a dose delay. The samples need to be taken prior to the administration of the Investigational Product. Details on the collections, shipment of the samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. If local laboratory is used for the analysis of samples, the local procedures will be followed.

Local laboratories may be used during the screening period to determine the eligibility criteria for a patient or during study treatment, if necessary, although the use of the central laboratory is recommended.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria: 1) they induce clinical signs or symptoms, 2) they are considered clinically significant, or 3) they require concomitant therapy or procedures. Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from screening or the previous visit.

Unscheduled local laboratory assessments may be performed if medically indicated to assess a (potential) adverse event or when the treating physician cannot wait for central laboratory results for decision making (e.g. therapeutic intervention, interruption of study treatment). In this particular situation, if possible, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis. The results of the local laboratory will be recorded in the eCRF if any of the following criteria are met:

- A treatment decision was made based on the local results, or
- Local lab results document an adverse event not reported by the central laboratory, or
- Local lab results document an adverse event severity is worse than the one reported by the central laboratory, or

- There are no concomitant central results available

At any time during the study, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. Laboratory data will be summarized using the CTCAE version 5 (Section 16.1). Additional analyses are left to the discretion of the investigator.

Novartis must be provided with a copy of the local laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the date of revalidation. Additionally, if at any time a participant has laboratory parameters obtained from a different laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for participants in the study and evaluating any abnormalities for clinical significance.

If participants cannot visit the site for safety lab assessments conducted through central labs, local lab collection may be used during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits.

Table 8-10 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)
Chemistry	Albumin, Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphate, Chloride, Sodium, Potassium, Creatinine, eGFR (at screening and EOT only), Creatine kinase (CK), Direct Bilirubin,Total Bilirubin, Urea nitrogen, Uric Acid, Amylase, Lipase, Glucose
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) If needed Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) will be added
Coagulation	International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Others	Testosterone, PSA

8.4.2 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECG on non-heat-sensitive paper or a certified copy on non heat sensitive paper, appropriately signed must be collected and archived at the study site.

For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding and the investigator should document the clinical evaluation in the

source. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment.

Interpretation of the tracing must be made by a qualified physician and documented on the appropriate eCRF. Any identifier details must be redacted e.g. participant initials, date of birth (where regulations permit), participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate eCRF. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

8.4.3 Pregnancy and assessments of fertility

A condom is required for all male participants who are sexually active with women of child-bearing potential to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants should not donate sperm for at least 14 weeks following the last dose of ^{177}Lu-PSMA-617.

Effective birth control methods should be used from the day of ^{68}Ga-PSMA-11 dose administration, throughout study treatment and for at least 14 weeks following the last dose of ^{177}Lu-PSMA-617.

Contraception methods are not required for the participants and their partners, who have been administered ^{68}Ga-PSMA-11 but did not start treatment with ^{177}Lu-PSMA-617, due to the microdose nature of this single administration. However, due to the potential radiation exposure/ contamination to partners, it is recommended that study patients refrain from sexual activity/ intercourse for 12 hours following administration of ^{68}Ga-PSMA-11. (Please refer to latest IB).

Participants receiving ARDT must follow contraceptive requirements as per the local label for the respective drugs.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Patient reported outcomes (PRO)

A PRO is a measurement based on a report that comes from the study participant about the status of a participant's health condition without interpretation of the participant's report by a

Medical Lead or anyone else. Symptoms or other unobservable concepts known only to the participant (e.g. pain severity or fatigue) can only be assessed using PRO measures.

PROs will be collected on an electronic tablet device at the clinic. Web portal will also be available in case of technical faults with the tablet.

The participant must be given the PRO measure(s) to be completed at the scheduled visit before any clinical assessments are conducted. Participant's refusal to complete all or any part of a PRO measure should be documented in the study data capture system and should not be captured as a protocol deviation. Handling of protocol deviations can be modified if needed per study protocol.

Participant questionnaires should be completed in the language most familiar to the participant.

The participant should be given sufficient space and time to complete the PRO measure(s).

The site personnel should check PRO measure(s) for completeness and ask the participant to complete any missing responses. The responses stored electronically in the database will be considered the source file.

Completed measure must be reviewed and assessed by the investigator or designee for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the participant to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 10 of the study protocol.

The PRO measures used in this study will be the BPI-SF, FACT-P and the EQ-5D-5L. PRO measures will be assessed as described in Table 8-2 and Table 8-3. Assessments will be collected during post treatment follow-up at week 24 and week 48 for patients who prematurely discontinued for any other reasons than disease progression, lost to follow-up or withdrawal of consent / opposition to use data/biological samples at the same time point as the radiographic assessments.

HRQoL will be periodically assessed at baseline, prior to administration of study treatment, at predefined timepoints, at the End of Treatment visit and during post treatment follow up period.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, COA data may be collected remotely (e.g. web portal) depending on local regulations, technical capabilities, and following any applicable training in the required process.

8.5.1.1 Pain Score

Pain will be assessed using the Brief Pain Inventory- Short Form. 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 et al 2009).

8.5.1.2 Health-related quality of life

The ECOG Performance Status scale will be used to assess participants' ability to perform daily living tasks and their range of basic physical ability.

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 et al 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 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 2015). Full details regarding the EQ-5D-5L questionnaire, including references, are available at the EQ-5D website: //euroqol.org/eq-5d-instruments/eq-5d-51-about.

8.5.1.3 FACT-P Questionnaire

The FACT-P questionnaire will also be administered as part of this study to specifically assess the HRQoL of prostate cancer participants. 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 participants' 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 participant 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: //facit.org/FACIT0rg/0uestionnaires.

8.5.1.4 Trial Feedback

This study includes an optional questionnaire, "Trial Feedback Questionnaire" for participants to provide feedback on their clinical trial experience. Individual trial participant responses will not be reviewed by investigators. Responses may be used by the sponsor (Novartis) to understand where improvements can be made in the clinical trial process. This questionnaire does not ask questions about the trial participant's disease, symptoms, treatment effect or adverse events and therefore responses are not considered trial data. Should any spontaneous information be collected about AEs, this would be transferred to the safety database. For more information about the Trial Feedback Questionnaire, contact your Health Economics & Outcomes Research (HEOR) representative.

[redacted]

[redacted]

[redacted]

9 Discontinuation and completion

9.1 Discontinuation from study treatment and discontinuation from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the participant or the investigator.

In addition to mandatory discontinuation of study treatment for toxicity listed in Table 6-2, study treatment must also be discontinued under the following circumstances:

- Evidence of tumor progression by central radiological assessment as measured by PCWG3-modified RECIST v1.1 criteria
- Unacceptable toxicity as assessed by Investigator
- Participant non-compliance or voluntary withdrawal from study or from study treatment
- Required use of a prohibited treatment
- Evidence that the participant is no longer clinically benefiting from study treatment
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study
- At the sponsor's or investigator's discretion
- If the treatment (with ^{177}Lu-PSMA-617 or ARDT) is interrupted for more than 4 weeks for any reason.
    - Participants who have delay of treatment due to interruption of study drug supply can restart study treatment if they have recovered from all drug related toxicities per dose modification Table 6-2, do not demonstrate radiographic progression on most recent scheduled or unscheduled imaging, have not started other anticancer therapy, and every effort has been made to reschedule treatment as early as possible to minimize deviations from the treatment schedule.

Study participants for whom study treatment is discontinued should return to the clinic for the End of Treatment visit.

If a study participant discontinues the treatment period of the study for any reason other than death, radiographic progression or withdrawal of consent / opposition to use data/biological samples, 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.

The investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information in the source and corresponding eCRF pages. The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

Participants who discontinue from study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS the

participants withdraw their consent (see withdraw of informed consent section). Where possible, they should return for the assessments indicated in the assessment schedule (Table 8-2 and Table 8-3). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact person as specified in the lost to follow-up section. This contact should be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

These information should be collected for a period of 30 days after study drug discontinuation, or longer for the SAEs where the Investigator considers that there is a possible relationship in between the SAEs and study treatment.

For participants who discontinue from study treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent/ opposition to use data/biological samples, assessments must continue to be performed as per Table 8-2 and Table 8-3. The visits will be carried out every 12 weeks (± 28 days) until death, lost to follow-up, withdrawal of consent / opposition to use data/biological samples or accrual of the number of events required for the planned analyses for OS for the study, whichever occurs first.

9.1.1.1 Replacement policy

Participants will not be replaced on study.

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason. If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2 Withdrawal of informed consent and exercise of participants' data privacy rights

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent / opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)
  and
- No longer wishes to receive study treatment
  and
- Does not want any further visits or assessments (including further study related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his consent/ opposition to use data/biological samples and record this information. The Investigator shall clearly document if the participant has withdrawn his consent for the use of data in addition to a study discontinuation.

Where consent to the use of Personal and Coded Data is not required in a certain' country's legal framework, the participant therefore cannot withdraw consent. However they still retain the right to object to the further collection or use of their Personal Data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.3 Study completion and post-study treatment

Study completion is defined as when the last participant finishes the last visit for the study or, in the event of an early study termination decision, the date of that decision.

All randomized and/or treated participants should have a safety follow-up conducted approximately 30 days after the EOT visit, followed by the long-term follow-up visits carried

out every 12 weeks (± 28 days) until death, lost to follow-up, withdrawal of consent / opposition to use data/biological samples or accrual of the number of events required for the planned analyses for OS for the study, whichever occurs first. Please refer to Table 8-2 and Table 8-3 for the required assessments at these visits.

Participants randomized on the ^{177}Lu-PSMA-617 arm will reach the end of study treatment after the last day of study treatment period of ^{177}Lu-PSMA-617 or upon radiographic progression. The participants must have an EOT visit performed ≤ 7 days and enter the Post-treatment Follow-up. For participants who are able to complete the planned 6 cycles of ^{177}Lu-PSMA617, the end of the treatment period is upon completion of the C6W5 visit and the response assessment imaging due at week 37.

Participants randomized on the ARDT arm will reach the end of study treatment upon the occurrence of radiographic progression by BICR. The participants will have a choice of crossover to the ^{177}Lu-PSMA-617 arm. If this option is selected, they will reach the end of study treatment after the last day of study treatment period of ^{177}Lu-PSMA-617 or upon second radiographic progression (rPFS2) by BICR. The participants will have a EOT2 visit performed ≤ 7 days and enter the Post-treatment Follow-up.

For participants discontinuing for reasons other than radiographic progression for both arms, tumor assessments must be performed every 8 weeks (± 7 days) after first dose of study treatment for the first 24 weeks, then every 12 weeks (± 7 days) until documented radiographic progression confirmed by BICR.

Post treatment Access

In case of termination of the study by the sponsor due to attainment of the rPFS and OS thresholds for success as cited in Section 12 (Data Analysis and Statistical Methods), strategy decision on ^{177}Lu-PSMA-617 development/launch or reimbursement (as applicable), post study treatment access to ^{177}Lu-PSMA-617 may be provided as per protocol and as permitted by local legislation to all participants remaining at the time of study termination, and will be administered at the discretion of the investigating physician.

9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

In the situation where the primary rPFS analysis is statistically not significant, the decision to continue or stop the trial will be made following discussions between the sponsor, the Steering Committee and the DMC.

In the situation where the primary rPFS analysis is statistically significant, the study will continue as initially planned, in order to collect further survival information and perform planned interim and final OS analyses.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments. The Participant-Reported Outcomes are considered as assessments to detect (Section 8.5.1).

Adverse events will be assessed and graded according to the CTCAE version 5.0.

Grade 1 to 5 will be used to characterize the severity of the Adverse Event. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening and death due to the AE, corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade according to the Common Toxicity Criteria (CTC) AE grade version 5.0
2. Its relationship to the investigational product ^{68}Ga-PSMA-11, or the study treatment ^{177}Lu-PSMA-617 or ARDT. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of

its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant

3. Its duration (start and end dates or ongoing)and the outcome must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Drug interrupted/withdrawn
   - Dose Reduced/increased
   - Dose not changed
6. Its outcome
   - not recovered/not resolved
   - recovering/resolving
   - recovered/resolved
   - recovered/resolved with sequelae
   - fatal
   - unknown

If the event worsens the event should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the EOT visit (or EOT2 visit if crossover occurs). For participants who received ^{177}Lu-PSMA-617 in the ^{177}Lu-PSMA-617 arm or in crossover, the following adverse events will be captured beyond the 30 day safety period regardless of relationship to study treatment and whether new anticancer therapy has been initiated: hematologic toxicities with primary focus on myelosuppression and thrombocytopenia (including need for transfusion or use of growth factors), renal failure, xerostomia, xerophthalmia, secondary malignancies.

For participants that are not randomized, AE monitoring will continue up to and including 14 days after administration of ^{68}Ga-PSMA-11.

For all AEs sufficient information will be obtained to permit an adequate determination of the outcome of the event and an assessment of the causal relationship between the AE and ^{68}Ga-PSMA-11, ^{177}Lu-PSMA-617, ARDT and/or supportive care.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each

visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event, except if the investigator considers that progression of malignancy is related to study treatment.

Adverse events separate from the progression of malignancy (for example deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

  Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines 2020).
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (i.e. exceptional hospitalization for any study specific procedure)
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study has not worsened since signing the informed consent

- social reasons and respite care in the absence of any deterioration in the participant's general condition
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical even has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after EOT (or EOT2 visit if crossover occurs) visit must be reported to Novartis Safety immediately, without undue delay, and under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If local regulations regarding reporting timelines are more stringent, then local regulations prevail. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Any SAEs experienced after the 30-day safety evaluation follow-up assessment, should be reported to Novartis if the investigator suspects a causal relationship to the study treatment (either ARDT or ^{177}Lu-PSMA-617), unless otherwise specified by local law/regulations. For participants who received ^{177}Lu-PSMA-617 in the ^{177}Lu-PSMA-617 arm or in crossover, the following SAEs will be captured beyond the 30 day safety period regardless of relationship to study treatment and whether new anticancer therapy has been initiated: hematologic toxicities with primary focus on myelosuppression and thrombocytopenia (including need for transfusion or use of growth factors), renal failure, xerostomia, xerophthalmia, secondary malignancies.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report

Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, and under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If local regulations regarding reporting timelines are more stringent, then local regulations prevail). The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the participant continued or withdrew from study participation. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and participant Safety (CMO&PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.1.4 Pregnancy reporting

Pregnancies

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother. Follow-up will be made after the Expected Delivery Date for information regarding the outcome of the pregnancy, the health of the newborn at birth and infant health status and development up to 12 (twelve) months after delivery, and for any other relevant information.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to

Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

10.2.2 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial, i.e., not being members of the DMC and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR part 11 requirements, Investigator site staff will not be given access to the EDC system

until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment(s) dispensed to the participant and all dosage and treatment changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by Novartis, who will also manage the database.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after the lock, can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or

assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

12 Data analysis and statistical methods

The primary efficacy and safety analyses will be performed after observing approximately 156 rPFS events as per BICR assessment. The primary Clinical Study Report (CSR) will be produced after the primary rPFS analysis and once all patients randomized to ^{177}Lu-PSMA-617 arm have had the opportunity to complete the full course of treatment. Any additional data for participants continuing to receive study treatment past this time and for participants continuing for efficacy follow-up (rPFS, OS), as allowed by the protocol, will be further summarized in a study report at the time of the final OS analysis after observing approximately 297 deaths, or when statistical significance is reached at any interim OS analysis.

It is planned that the data from all centers participating in the study will be combined, so that an adequate number of participants are available for analysis. Novartis and/or a designated CRO will perform all analyses.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Full Analysis Set comprises all participants to whom study treatment has been assigned by randomization. According to the intent to treat principle (ITT), participants will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure. The FAS will be the primary population for all efficacy analyses.

The Safety Set includes all participants who received at least one dose of study treatment (i.e. at least one dose ^{177}Lu-PSMA-617 or ARDTs). Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

The Crossover Analysis Set (CAS) consists of participants randomized to the ARDT arm who crossed over after BICR-confirmed radiographic progression to receive at least one dose of ^{177}Lu-PSMA-617. This analysis set will be used for all analyses (rPFS2) pertaining to rPFS evaluations collected after participants crossed over in to ^{177}Lu-PSMA-617.

The RECIST Analysis Set (RAS) consists of subset of participants in the FAS with evaluable soft tissue disease by PCWG3-modified RECIST v1.1 at baseline, defined as having at least one lesion (target or non-target) identified at baseline in soft tissue. Participants will be included in the treatment arm to which they were randomized. This analysis set will be used for the analysis of RECIST-based endpoints (e.g, TTSTP [redacted] etc.).

The Ga-PSMA-11 Full Analysis set (Ga-FAS) includes all participants who received the administration of [^{68}Ga]Ga-PSMA-11. This analysis set will be the basis of the safety and imaging summaries for the [^{68}Ga]Ga-PSMA-11 specific analyses. This includes all screened participants who received [^{68}Ga]Ga-PSMA-11 and were randomized, and those who received [^{68}Ga]Ga-PSMA-11 but not randomized.

The Lu-PSMA-617 Safety Set includes all participants who received at least one dose of study ^{177}Lu-PSMA-617, during the randomized part of the protocol or after crossover. This analysis set will be used to provide safety analyses.

[redacted]

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS and Safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term and by treatment group.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure to ^{177}Lu-PSMA-617 and ARDT (as described in Section 6.1) as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

12.4 Analysis supporting primary objectives

The primary objective of the study is described in Table 2-1.

12.4.1 Definition of primary endpoint(s)

The primary estimand is defined in Section 2.1. The primary endpoint (variable attribute of the primary estimand) of the study is radiographic progression-free survival (rPFS), defined as the time from the date of randomization to the date of the first documented radiographic progression as outlined in PCWG3 or death due to any cause. rPFS will be assessed via blinded independent central review (BICR) of radiographic images provided by the treating physician.

Participants 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. Clinical deterioration without objective radiographic evidence will not be considered as documented radiographic progression.

Handling of missing data are provided in Section 12.4.4.

12.4.2 Statistical model, hypothesis, and method of analysis

Assuming proportional hazards for rPFS, the following statistical hypotheses will be tested to address the primary efficacy objective:

$H_{01}:\theta_1 \geq 1$ vs. $H_{A1}:\theta_1 < 1$

where θ_1 is the rPFS hazard ratio (^{177}Lu-PSMA-617 with BSC arm versus ARDT with BSC arm).

The primary efficacy analysis to test these hypotheses and compare the two treatment groups will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance. The stratification will be based on the randomization stratification factors, i.e. prior ARDT use in CRPC vs HSPC; asymptomatic and mildly symptomatic vs symptomatic participants (score of 0-3 on item 3 of the Brief Pain Inventory Short Form (BPI-SF) questionnaire) vs symptomatic (score >3 on item 3 of the BPI-SF questionnaire).

The primary efficacy variable, rPFS, will be analyzed when 156 rPFS events are observed. Analyses will be based on the FAS population according to the randomized treatment group and strata assigned at randomization (strata formed using the randomization factor as obtained via IRT). The rPFS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each

treatment group. The hazard ratio for rPFS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test. The time of the second interim OS analysis will be after approximately 9 months of additional follow-up from the data cut-off used for the primary analysis. [redacted]

12.4.3 Handling of intercurrent events of primary estimand

The primary analysis will account for different intercurrent events as explained in the following:

1. Discontinuation of study treatment for any reason: Tumor assessment data collected irrespective of discontinuation of study treatment will be used for the analysis (treatment policy strategy)
2. Change in supportive care: Tumor assessment data collected irrespective of change in supportive care will be used for the analysis (treatment policy strategy)
3. Start of a new anti-neoplastic therapy prior to radiographic progression or death: rPFS events documented irrespective of initiation of new anti-neoplastic therapy will be used for the primary analysis (treatment policy strategy).

12.4.4 Handling of missing values not related to intercurrent event

If rPFS event is observed after two or more missing or non-adequate tumor assessments, then rPFS will be censored at the last adequate tumor assessment before the rPFS event. If rPFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used.

12.4.5 Sensitivity analyses

Sensitivity analysis performed in the FAS, will obtain the hazard ratio and 95% CI for rPFS per Blinded independent central review (BICR) review from a stratified and covariate unadjusted Cox model with stratification factors derived from the clinical database, in case at least 5% of the participants have discrepancies between strata at randomization (using IRT data) and strata derived from the eCRF data. This analysis will also include Kaplan-Meier median with its 95% CI.

As a sensitivity analysis, rPFS as per investigator review will be analyzed using a stratified Cox model, with the same analysis conventions as the primary efficacy analysis, and the treatment effect will be summarized by the hazard ratio with its 95% confidence interval. Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group.

12.4.6 Supplementary analysis

As supplementary analyses performed in the FAS, the hazard ratio and 95% confidence interval for rPFS per BICR review will be obtained from a stratified and covariate adjusted Cox model. Important covariates will be specified in the Statistical Analysis Plan (SAP).

Analyses may be also performed in the FAS for rPFS per BICR censoring for initiation of new anti-neoplastic therapy using the same analysis conventions as the primary efficacy analysis.

Subgroup analyses for rPFS

If the primary endpoint analyses for rPFS (per BICR) is statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed. Important subgroups will be specified in the Statistical Analysis Plan (SAP).

Further supplementary analyses will be specified in the SAP.

12.5 Analysis supporting secondary objectives

The secondary objectives are described in Table 2-1 and the key secondary estimand is defined in Section 2.2.

OS is identified as the key secondary endpoint (primary variable attribute of the secondary estimand). A hierarchical testing strategy will be used to control the overall type I error rate, where OS will only be formally tested and interpreted if the primary analysis of PFS is statistically significant.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

12.5.1.1 Key secondary estimand

Assuming proportional hazards model for OS, the following statistical hypotheses will be tested only if rPFS is statistically significant:

$H_{02}:\theta_2 \geq 1$ vs. $H_{A2}:\theta_2 < 1$

where θ_2 is the OS hazard ratio (^{177}Lu-PSMA-617 + BSC arm versus ARDT + BSC arm).

The analysis to test these hypotheses will consist of a

stratified log-rank test at an overall one-sided 2.5% level of significance.

The final OS analysis will not be performed at the time point of the final rPFS analysis, but after additional follow-up. Therefore, a four-look group sequential design is considered for OS.

OS will be hierarchically tested in the following way:

- The time point for the first OS interim analysis was at the same time as the rPFS analysis at which point a very limited information fraction was observed.
- The time point for the second OS interim analysis will be after approximately 9 months of additional follow-up from the data cut-off used for the primary analysis, at which time approximately 42% of deaths (125 deaths) are expected to have been recorded in the clinical database. This interim analysis will not be event driven.
- If OS is not statistically significant at the second interim analysis, the time point for the third OS interim analysis will be after approximately 75% of deaths (223 deaths) are expected to have been recorded in the clinical database.

- If OS is not statistically significant at the interim analyses, a final analysis is planned at the time approximately 297 deaths have been recorded.

The type I error probability will be controlled by using a Lan-DeMets (O'Brien-Fleming) alpha spending function for OS which is independent of the one used for rPFS. This guarantees the protection of the overall type I error ($\alpha = 2.5\%$) across all hypotheses and the repeated testing of the OS hypotheses at the interim and the final analyses (Glimm et al 2010).

OS will be analyzed in the FAS population according to the treatment group and strata assigned at randomization. The OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for OS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test.

The OS primary analysis will account for different intercurrent events as explained in the following:

1. discontinuation of study treatment for any reason: OS data collected irrespective of discontinuation of study treatment will be used for the analysis (treatment policy strategy)
2. change in best supportive care: OS data collected irrespective of change in best supportive care will be used for the analysis (treatment policy strategy)
3. start of a new anti-neoplastic therapy: OS data collected irrespective of initiation of new anti-neoplastic therapy will be used for the analysis (treatment policy strategy)
4. crossover to ^{177}Lu-PSMA-617 arm for participants in the ARDT : survival time will be re-calculated based on time spent on ^{177}Lu-PSMA-617 based on appropriate methods as described below(hypothetical strategy).

Restricted Mean Survival Time (RMST) method may be conducted for OS to account for the possible non-proportional hazards effect.

Since participants in the ARDT arm are allowed to cross over to ^{177}Lu-PSMA-617 arm upon confirmation of rPFS by BICR, adjustment for the effect of crossover on OS may be performed based on recognized methods, e.g., a two-stage method or the Rank Preserving Structural Failure Time (RPSFT) model proposed by (Robins et al 1991). RPFST is intended to be used as a primary analysis, however other methods will also be used based on an examination of the appropriateness of the data to the assumptions required by the methods. Further details of sensitivity analyses will be described in the SAP as needed.

Supplementary OS analyses based on FAS will be performed without accounting for crossover.

12.5.1.2 Other secondary efficacy endpoints

PFS is defined as time from date of randomization to the first documented progression by investigator's assessment (radiographic, clinical, or PSA progression) or death from any cause, whichever occurs first.

PFS2 is defined as time from date of randomization to the first documented progression (radiographic progression, clinical progression, PSA progression) on next-line therapy or death from any cause, whichever occurs first. The first documented progression on next-line treatment is based on investigator's assessment of progression disease (PD) (i.e. as captured on the anti-

neoplastic therapy after discontinuation from study treatment CRF page); it is not necessary to continue to collect tumor assessments data for subsequent anti-neoplastic therapies for the purpose of PFS2.

- Next-line therapy is defined as the first new (systemic) anti-neoplastic therapy initiated after discontinuation of study treatment regardless of EoT reason. Drugs given as part of the same regimen should be considered as first line (i.e. part of the next-line therapy).
- New anti-neoplastic therapies after EoT will be collected in the anti-neoplastic therapy after discontinuation from study treatment eCRF page including start/end date, reason for discontinuation, date and type of progression («clinical» vs «radiologic»).
- PFS2 will be censored if no PFS2 event (progression or death) is observed during next-line therapy before the analysis cut-off date; the censoring date will be the last contact date.
- However, in case a second new anti-neoplastic therapy is introduced without prior PFS2 event, then PFS2 will be censored at the end date of the first new anti-neoplastic therapy (i.e. next line therapy).
- Any death prior to initiation of next-line therapy will be considered as an event for PFS2. Any death occurring following end of next line therapy will be considered as an event if no second new anti-neoplastic therapy has been introduced.
- PFS and PFS2 may be identical if a participant did not experience an event (i.e. progression) prior to initiation of next-line therapy, and adequate tumor assessments continue until documented disease progression after initiation of next-line therapy.
- Note: for patients in ARDT arm who cross over, the ^{177}Lu-PSMA-617 treatment is considered the next line therapy, therefore data on progressive disease will be collected from the RECIST/PCWG3/PSA/Clinical progression respective CRF pages for the crossover.

PFS2 will be analyzed in the FAS population according to the randomized treatment group and strata assigned at randomization. The PFS2 distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for PFS2 will be calculated, along with its 95% confidence interval, in the targeted population had crossover not occurred, estimated using Cox proportional hazard model stratified by the randomization stratification factors.

Restricted Mean Survival Time (RMST) method may be conducted for PFS2 to account for the possible non-proportional hazards effect. Since participants in the ARDT arm are allowed to crossover to ^{177}Lu-PSMA-617 after progressive disease, adjustment for the effect of crossover on PFS2 may be performed based on recognized methods, e.g., a two-stage method or the Rank Preserving Structural Failure Time (RPSFT) model proposed by (Robins et al 1991), based on an examination of the appropriateness of the data to the assumptions required by the methods. Further details of sensitivity analyses will be described in the SAP as needed.

Time to SSE (TTSSE) is defined as the time from the date of randomization to the date of the first SSE or death from any cause. SSE date is date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain, or death due to any cause, whichever occurs first.

SSE data for this endpoint is collected up through EOT visit. Censoring date is date of the last study visit (on or before EOT visit).

TTSSE will be analyzed in the FAS population according to the randomized treatment group and strata assigned at randomization. The TTSSE distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for TTSSE will be calculated, along with its 95% confidence interval, using a stratified Cox model. Restricted Mean Survival Time (RMST) method may be conducted for TTSSE to account for the possible non-proportional hazards effect.

PSA50 response will be calculated at 12, 24 and 48 weeks based on the FAS and according to the ITT principle. PSA will be measured every 6 weeks for the first 6 cycles of treatment and then every 12 weeks during long term FUP or continued ARDT cycles. Any PSA measurement included in the above timepoints +/- 2 weeks will be included in the analyses, whether scheduled or unscheduled. PSA response at 12, 24 and 48 months, and along with 95% confidence intervals will be presented by treatment group. Waterfall graphs, which display the best percent change from baseline in maximum decline in PSA for each participant may be used to depict the antitumor activity for each treatment group.

Time to chemotherapy (TTCT) defined as time from randomization to initiation of the first subsequent chemotherapy or death, whichever occurs first. TTCT will be summarized with the same analysis conventions as TTSSE, except it will be censored at the last contact date.

Time to soft tissue progression (TTSTP) defined as time from randomization to radiographic soft tissue progression per PCWG3-modified RECIST v1.1 assessed by BICR. TTSTP will be summarized with the same analysis conventions as TTSSE, except it will be censored at the last scan date and based on RAS.

rPFS2 defined as the time from the date of crossover (ARDT to ^{177}Lu-PSMA-617) to the date of radiographic disease progression assessed via blinded independent central review or death from any cause on the next line of therapy based on the Crossover Analysis Set.

The rPFS2 distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curve, medians and 95% confidence intervals of the medians will be presented.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of participant's informed consent to the day before first dose of study medication

2. On-treatment period: from day of first dose of study medication to 30 days after EOT/EOT2 or (last ^{177}Lu-PSMA-617 dose date + 41 days, last dose date of ARDT + 30 days), whichever is later, or the day before crossover date, if applicable
3. Post-treatment period: starting at day 31 after EOT/EOT2 or (last ^{177}Lu-PSMA-617 dose date + 42 days, last dose date of ARDT + 31 days), whichever is later.

Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study treatment related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment. The study treatments for this study are ^{177}Lu-PSMA-617 or ARDT.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Adverse events which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period.

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths, and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

The number (and proportion) of participants with AESI will be summarized by treatment. AESI consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s). AESI will be defined at the project level and may be regularly updated. The grouping of AEs in AESI

according to project standards will be specified in the Case-Retrieval Sheet and/or the SAP. For each specified AESI, the number and percentage of participants with at least one event part of the AESI will be reported by dose cohort in the safety run-in part and by treatment group in the study.

^{68}Ga-PSMA-11 treatment emergent adverse events (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 14 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 control arm. Adverse events reported related to ^{68}Ga-PSMA-11 are also ^{68}Ga-PSMA-11 TEAEs, irrespective of time of onset or start of randomized treatment. Summary tables for ^{68}Ga-PSMA-11 TEAEs using the Ga-PSMA-11 Full Analysis Set including the number of participants with at least one event, and the total number of events will be presented.

During long-term follow-up, serious adverse events related to ^{177}Lu-PSMA-617 will be collected. Summary tables will be provided in the Safety Set.

Vital signs

All vital signs data will be summarized by treatment and visit/time.

12-lead ECG

1. PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted locally
2. Categorical Analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented.

All ECG data will be listed by treatment group, participant and visit/time, abnormalities will be flagged. Summary statistics of notable ECG values will be provided by treatment.

Clinical laboratory evaluations

All laboratory data will be summarized by treatment group. and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Grading of laboratory values will be assigned programmatically as per NCI CTCAE version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE version 5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

The following listings/summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE version 5.0 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE version 5.0:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE version 5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE version 5.0:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

In addition to the above mentioned tables and listings, other exploratory analyses, for example, figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the analysis plan.

During long-term follow-up, blood collection will continue. Summary tables will be provided in the Safety Set.

[redacted]

[redacted]

12.5.4 Patient reported outcomes

Three participant-reported outcomes (PRO) questionnaires will be assessed in the study: EQ-5D-5L, FACT-P and BPI-SF.

The FAS will be used for analyzing PRO data. Utilities derived from EQ-5D-5L together with FACT-P and BPI-SF are the secondary PRO variables of interest.

Aspects of HRQoL will be self-reported by participants (or via interview format) using the EQ-5D-5L and FACT-P questionnaires, and pain will be assessed by participants using the BPI-SF.

[redacted]

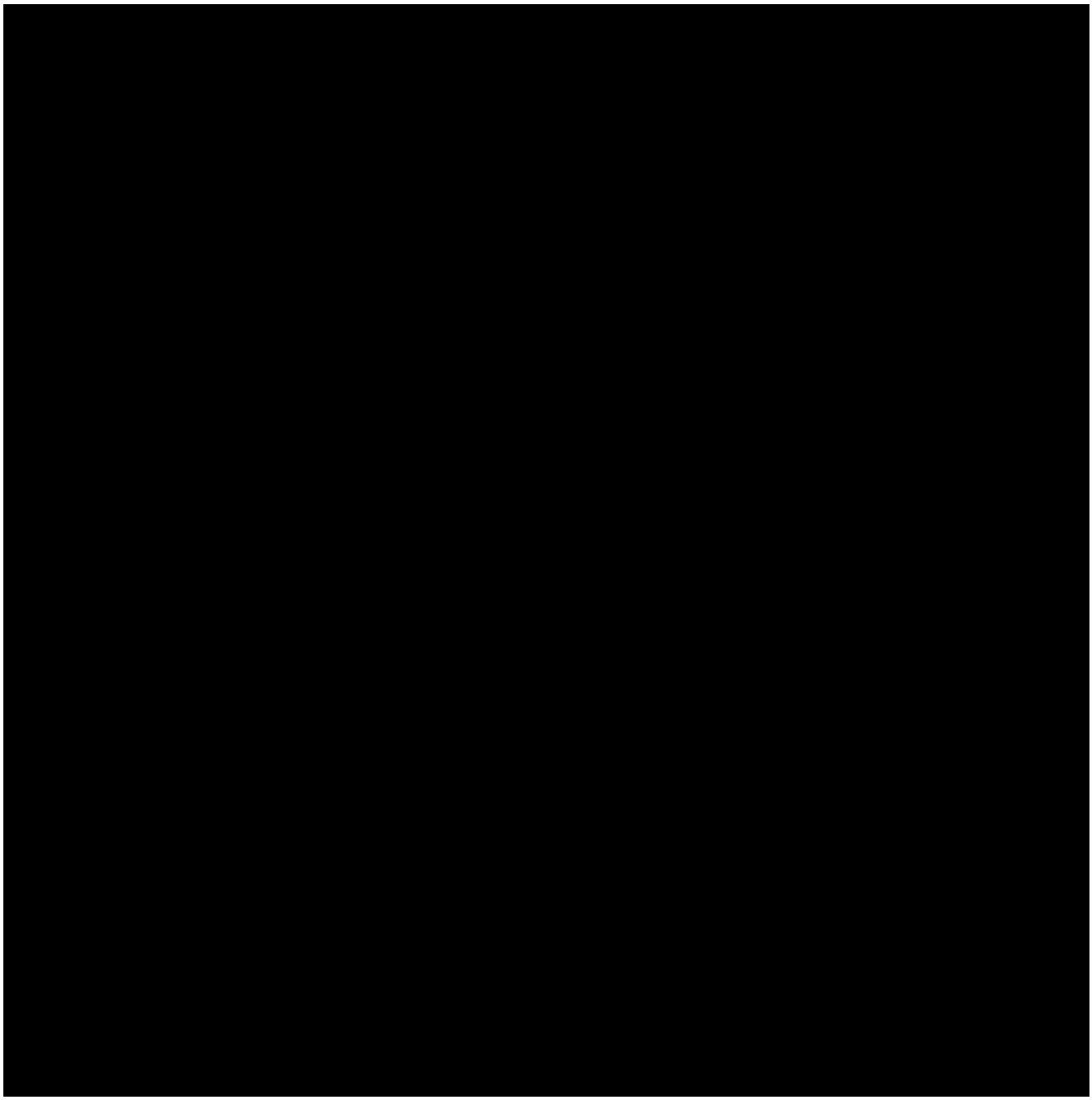
Time to pain improvement response after initial pain worsening will be analyzed using mixture distribution methodology akin to that described by Ellis et al 2008.

Descriptive statistics will be used to summarize the original scores, as well as change from baseline, of the EQ-5D-5L, FACT-P and BPI-SF at each scheduled assessment timepoint for each treatment group. Additionally, change from baseline in the scale and subscale values at

the time of each assessment will be summarized. participants with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

The number of participants completing each questionnaire and the number of missing or incomplete assessments will be summarized by treatment group for each scheduled assessment timepoint. No formal statistical tests will be performed for PRO data and hence no multiplicity adjustment will be applied.

In addition, a repeated measurement analysis model for longitudinal data will be used to estimate differences in utility scores of the EQ-5D-5L, FACT-P and BPI-SF between treatment arms. The differences in least square means between the treatment arms and corresponding 95% confidence interval at selected timepoints will be presented. Details, including handling of missing data, will be specified in the SAP.



12.7 Interim analyses

No interim analysis is planned for rPFS. The primary rPFS analysis was carried out after 167 rPFS events had been observed. [redacted] The first interim OS analysis was performed at the time of the primary rPFS analysis.

Key secondary endpoint: Overall survival (OS)

A hierarchical testing procedure will be adopted and the statistical tests for OS will be performed only if the primary efficacy endpoint rPFS is statistically significant.

A maximum of four analyses (three interims and one final) is planned for OS:

- The first interim OS was performed at the time of the primary rPFS analysis
- The second interim analysis will not be event-driven and will be performed after approximately 9 months of additional follow-up from the data cut-off used for the primary rPFS analysis. Approximately 125 of the approximately 297 targeted OS events (~42% information fraction) are expected to be observed at this predetermined time. This interim analysis is expected to occur around 24 months from the date of first participant randomized in the study.
- The third interim analysis is planned at approximately 75% information fraction (223 deaths) and is expected to occur around 38 months from the date of first participant randomized in the study.
- The final analysis for OS is planned when approximately 297 deaths are expected.

An α-spending function according to (Lan et al 1983) (O'Brien-Fleming) as implemented in East 6.4 (Lan et al 1983), along with the testing strategy outlined below will be used to maintain the overall type I error probability. This guarantees the protection of the 2.5% overall level of significance across the two hypotheses and the repeated testing of the OS hypotheses in the interim and the final analyses (Glimm et al 2010).

The trial allows for the stopping of the study for a superior OS result, provided the primary endpoint rPFS has already been shown to be statistically significant favoring the test treatment arm. Further, the exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and the α already spent for OS at the time of earlier analyses.

An α-spending function according to a four-look (Lan et al 1983) group sequential design with (O'Brien-Fleming) type stopping boundary (as implemented in East 6.4) will be used to construct the efficacy stopping boundaries (Lan et al 1983). Based on the choice of α-spending function described above and if the interim analyses are performed exactly after 40, 125, and 223 OS events, the efficacy boundaries in terms of p-value scale (or equivalently Z-statistic scale) at the interim are calculated as p=0.000000001, 0.00055 and p = 0.01 (or Z = -5.996, Z = -3.263 and Z = -2.345). The observed (i.e. nominal) p-value has to be smaller than 0.000000001, 0.00055 and 0.01 (or equivalently the observed Z-statistic has to be < Z-statistic scale boundary = -5.996, -3.263and -2.345) to conclude superior efficacy at the interim analyses.

Since the observed number of events at the interim analyses may not be exactly equal to the planned 40, 125 and 223 OS events, the efficacy boundary will need to be recalculated using the pre-specified α-spending function and based on the actual number of observed events at interim and the total number of targeted events to calculate the exact information fraction. The observed p-value (or Z-test statistic) at the interim analysis will then be compared against the re-calculated efficacy boundary.

If the study continues to the final OS analysis, the final OS analysis will be performed when approximately 297 OS events have been observed. In practice, the final analysis will be based on the actual number of OS events observed at the cut-off date for the final OS analysis and α already spent at the interim analyses. The boundary for the final analysis will be derived accordingly from the pre-specified α-spending function such that the overall significance level across all analyses is maintained at 0.025.

12.8 Sample size calculation

The sample size calculation is based on the primary variable rPFS and key secondary variable OS.

Overall, a total study sample size of approximately 450 participants will be randomly assigned to each treatment arm in a 1:1 ratio (225 participants in ^{177}Lu-PSMA-617 with BSC arm and 225 participants in ARDT with BSC arm). These calculations were made using the software package East 6.4.

12.8.1 Primary endpoint(s)

The sample size calculation is based on the primary variable rPFS. The hypotheses to be tested and details of the testing strategy are described in Section 12.4.2.

Based on available data, the median rPFS in the control arm is expected to be around 6 months in this population (de Bono et al 2020, de Wit et al 2019, Komura et al 2019). It is expected that treatment with ^{177}Lu-PSMA-617 and BSC will result in a 44% reduction in the hazard rate for rPFS compared to the control arm i.e., an expected hazard ratio of 0.56, which corresponds to an increase in median rPFS by 4.7 months under the exponential model assumption (from 6 to 10.7 months).

In order to ensure at least 95% power to test any null hypothesis: rPFS hazard ratio = 1, versus the alternative hypothesis: rPFS hazard ratio = 0.56, it is calculated that a total of 156 rPFS events need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, participants randomized to the two treatment arms in a 1:1 ratio.

Assuming that enrolment will continue for 10.5 months at a non-uniform rate for a total of approximately 450 patients and losses to follow-up for rPFS of approximately 10% and 20% in the ^{177}Lu-PSMA-617 and BSC and control arm, respectively, the targeted 156 rPFS events are expected to occur at about 3 months after the randomization date of the last participant.

12.8.2 Secondary endpoint(s)

OS, as the key secondary variable, will be formally statistically tested, provided that the primary variable rPFS is statistically significant.

The median OS in the control arm is expected to be around 18 months (de Bono et al 2020, de Wit et al 2019, Komura et al 2019). It is hypothesized that treatment with ^{177}Lu-PSMA-617 will result in a 28% reduction in the hazard rate for OS compared to the control arm i.e., an expected hazard ratio of 0.72, which corresponds to an increase in median OS by 7 months under the exponential model assumption (from 18 months to 25 months).

Then in order to ensure 80% power to test the null hypothesis: OS hazard ratio = 1, versus the alternative hypothesis: OS hazard ratio = 0.72, it is calculated that a total of 297 deaths need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, participants randomized to the two treatment arms in a 1:1 ratio, and a 4-look group sequential design with a Lan-DeMets (O'Brien-Fleming) alpha spending function using information fractions of (approximately 0.135, 0.42, 0.75, 1).

Assuming that enrolment will continue for 10.5 months at a non-uniform rate and losses to follow-up for OS of approximately 5%, a total of approximately 450 participants will need to be randomized to observe the targeted 297 deaths events.Based on the assumptions above and a sample size of approximately 450 participants, the rPFS analysis is estimated to occur at approximately 13.5 months.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (ICH GCP), with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

(2019) A Trial of 177Lu-PSMA617 Theranostic Versus Cabazitaxel in Progressive Metastatic Castration Resistant Prostate Cancer (TheraP) p. //clinicaltrials.gov/ct2/history/NCT03392428. (Accessed 19-SEP-2020)

(2020) ICH-E2D Guidelines p. //database.ich.org/sites/default/files/E2D-R1_ConceptPaper_Final_2020_0115.pdf.

[redacted]

Abida W, Campbell D, Patnaik A, et al (2019) Preliminary Results from the TRITON2 Study of Rucaparib in Patients with DNA Damage Repair (DDR)-Deficient Metastatic Castration-Resistant Prostate Cancer (mCRPC): Updated Analyses //clovisoncology.com/media/1160/esmo2019_wabida_poster.pdf. (Accessed 19-SEP-2020)

Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al (2017) Diagnostic performance of 68 Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patient. 44:1258-1268.

Ahmadzadehfar H, Eppard E, Kilrpig S, et al (2016) Therapeutic response and side effects of repeated radioligand therapy with 177Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer 7(11):12477-88.

Ahmadzadehfar H, Rahbar K, Kürpig S, et al (2015) Early side effects and first results of radioligand therapy with 177Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study 5:36.

Attard G, Reid AHM, A'Hern R, et al (2009) Selective Inhibition of CYP17 With Abiraterone Acetate Is Highly Active in the Treatment of Castration-Resistant Prostate Cancer 27:3742-3748.

[redacted]

Benesova M, Schafer M, Bauder-Wüst U, et al (2015) Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer 56(6):914-20.

[redacted]

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

[redacted]

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

Bräuer A, Grubert LS, Roll W, et al (2017) 177Lu-PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer. Eur. J. Nucl. Med. Mol. Imaging 1663-70.

Cella DF, Tulsky DS, Gray G, et al (1993) The Functional Assessment of Cancer Therapy scale: development and validation of the general measure p. Mar 11(3):570-9.

[redacted]

Cleeland, CS (2009) The Brief Pain Inventory User Guide p. Accessed from: //mdanderson.org/Education and Research/Departments, Programs and Labs/Departments and Divisions/Symptoms Research/Symptoms Assessment Tools. (Accessed 19-SEP-2020)

[redacted]

Delker A, Fendler WP, Kratochwil C, et al (2016) Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer 43(1):42-51.

Dent S, Zee B, Dancey J, et al (2001) Application of a new multinomial phase II stopping rule using response and early progression. J. Clin. Oncol 85-91.

EMA (2017) Guideline on the evaluation of anticancer medicinal products in man p. //ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf. (Accessed 19-SEP-2020)

Eisenhauer EA, Therasse P, Bogaerts J, et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur. J. Cancer 228-47.

Ellis S, Carroll KJ, Pemberton K (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 456-65.

Emmett L, Willowson K, Violet J, et al (2017) Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy p. Mar 64(1):52-60.

Engel-Nitz, Alemayehu, Parry, et al (2011) Differences in treatment patterns among patients with castration-resistant prostate cancer treated by oncologists versus urologists in a US managed care population 2011:3 233–245.

Esper P, Mo F, Chodak G, et al (1997) Measuring quality oflife in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument p. Dec 50(6):920-8.

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

EuroQoL Group (2015) EQ-5D-5L User Guide Basic information on how to use the EQ-5D-5L instrument p. Accessed from: //euroqol.org/wpcontent/uploads/2016/09/EO-5D-5L UserGuide 2015.pdf. (Accessed 19-SEP-2020)

Fendler WP, Biber M, Beheshti M, et al (2017) 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Jun 44(6):1014-1024.

Ferdinandus J, Eppard E, Gaertner FC, et al (2017) Predictors of Response to Radio ligand Therapy of Metastatic Castrate-Resistant Prostate Cancer with 177LuPSMA-617 Feb, 58(2):312-319.

Fizazi K, Herrmann K, Krause BJ, et al (2021) Health-related quality of life (HRQoL), pain and safety outcomes in the phase 3 VISION study of ^{177}Lu-PSMA-617 patients with metastatic castration-resistant prostate cancer [abstract]. Ann Oncol; 32 Suppl 5: S626-S677.

Flaig TW, Potluri RC, Ng Y, et al (2016) Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis ofreal-world data 5(2):182-91.

Ghosh and Heston WD (2004) Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. 91:528-39.

Glimm E, Maurer W, Bretz F (2010) Hierarchical testing of multiple endpoints in group-sequential trials. Stat Med 219-28.

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

Harris V, Lloyd K, Forsey S, et al (2011) A Population-based Study of Prostate Cancer Chemotherapy 23, 706-708.

Haug AR, Shariat S, Eidherr H, et al (2016) Initial experience with aggressive treatment of metastastic prostate cancer using 3 cycles of 7.4 GBq [177Lu]PSMA every 4 weeks. (Suppl 1):S212 EPWl 1.

Hillier SM, Maresca KP, Femia FJ, et al (2009) Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. (17), 6932-40.

Hofman (2020) TheraP: A Randomised Phase II Trial of 177Lu-PSMA-617 Theranostic Versus Cabazitaxel in Metastatic Castration Resistant Prostate Cancer Progressing after Docetaxel: Initial Results (ANZUP protocol 1603) 1-5.

Hofman MS, Violet J, Hicks RJ, et al (2018) 177Lu]-PSMA- 617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (Lu.PSMA trial): a single-centre, single-arm, phase 2 study 19(6):825- 833.

Hofman MS, Violet J, Hicks RJ, et al (2019) Results of a 50 patient single-centre phase II prospective trial of Luteium-177 PSMA-617 theranostics in metastatic castrate-resistant prostate cancer. 37 (suppl 7S): 228.

Hussain M, Mateo J, Fizazi K, et al (2019) PROfound: Phase III study of olaparib versus enzalutamide or abiraterone for metastatic castration-resistant prostate cancer (mCRPC) with homologous recombination repair (HRR) gene alterations v882, Genitourinary tumours, prostate Volume 30, Supplement 5.

Israeli, Powell, Fair, et al (1993) Molecular Cloning of a Complementary DNA Encoding a Prostate-specific Membrane Antigen 53, 227-230, January 15.

Kessel K, Seifert R, Schäfers M, et al. (2019) Second line chemotherapy and visceral metastases are associated with poor survival in patients with mCRPC receiving 177 Lu-PSMA-617 4841–4848.

Kirby M, Hirst C, and Crawford ED (2011) Characterising the castration-resistant prostate cancer population: a systematic review. p. Nov 65(11):1180-92.

[redacted]

Komura et al (2019) Comparison of Radiographic Progression-Free Survival and PSA Response on Sequential Treatment Using Abiraterone and Enzalutamide for Newly Diagnosed Castration-Resistant Prostate Cancer: A Propensity Score Matched Analysis from Multicenter Cohort p. 8, 1251; doi:10.3390/jcm8081251.

Kratochwil C, Giesel FL, Eder M, et al (2015) [^{177}Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. Eur. J. Nucl. Med. Mol. Imaging 987-8.

Kratochwil C, Giesel FL, Stefanova M, et al (2016) PSMA-targeted radionuclide therapy of metastatic castration resistant prostate cancer with 177Lu-labeled PSMA-617 (8): 1170-1176.

Kulkarni H, Schuchardt C, Singh A, et al (2018 b) Early initiation of Lu-177 PSMA radioligand therapy prolongs overall survival in metastatic prostate cancer 529.

Kulkarni H, Singh A, Schuchardt C, et al (2016) PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. Oct 57 (Suppl 3): 97S-104S.

Kulkarni H, Singh A, Schuchardt C, et al (2018 a) Salvage Lu-177 PSMA radioligand therapy in metastatic castration-resistant prostate cancer applying high cumulative radioactivity in repeated cycles p. 1496.

Kulkarni HR, Langbein T, Atay C, et al (2018 c) Safety and long-term efficacy ofradioligand therapy using Lu-177 labeled PSMA ligands in metastatic prostate cancer: A single center experience over 5 years. p. Jul 78 (13): CT015.

Lan KKG, De Mets, DL (1983) Discrete Sequential Boundaries for Clinical Trials. Vol. 70, No. 3 (Dec., 1983), 659-663.

Lissbrant I F, Garmo H, Widmark A, et al (2013) Population-based study on use of chemotherapy in men with castration resistant prostate cancer 52:8, 1593-1601.

Maffey-Steffan J, Scarpa L, Svirydenka A, et al (2020) The 68Ga/177Lu-theragnostic concept in PSMA-targeting of metastatic castration-resistant prostate cancer: impact of post-therapeutic whole-body scintigraphy in the follow-up. Eur. J. Nucl. Med. Mol. Imaging 695-712.

Malvezzi M, Carioli G, Bertuccio P, et al (2019) European cancer mortality predictions for the year 2019 with focus on breast cancer 30(5):781-787. doi: 10.1093/annonc/mdz051.

Mannweiler S, Amersdorfer P, Trajanoski S, et al (2009) Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. 15(2): 167-72.

[redacted]

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Control Clin Trials 11-8.

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

Rahbar K, Ahmadzadehfar H, Kratochwil C, et al (2017) German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. J. Nucl. Med. 85-90.

Rahbar K, Bode A, Weckesser M, et al (2016 a) Radioligand Therapy With 177Lu-PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer. Clin Nucl Med 522-8.

Rahbar K, Boegemann M, Yordanova A, et al (2018) PSMA targeted radioligand therapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. 45(1): 12-19.

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

Rajasekaran SA, Anilkumar G, Oshima E, et al (2003) A Novel Cytoplasmic Tail MXXXL Motif Mediates the Internalization of Prostate-specific Membrane Antigen. (12): 4835-4845.

Rathke H, Giesel FL, Flechsig P, et al (2017) Repeated Lu-177-PSMA-617 radioligand therapy using treatment activities up to 9.3 GBq. p. Aug 10. pii:jnumed.117.194209. doi: 10.2967/jnumed.117.194209. [Epub ahead of print].

Rizzo JD, Brouwers M, Hurley P, et al (2010) American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. J. Clin. Oncol. 317-20.

Robins, Tsiatis (1991) Correcting for non-compliance in randomized trials using rank preserving structural failure time models p. Vol.20(8), 2609-2631.

Ross, Sheehan, Fisher, et al (2003) Correlation of Primary Tumor Prostate-Specific Membrane Antigen Expression with Disease Recurrence in Prostate Cancer p. Vol. 9, 6357–6362.

Saad F, Gleason DM, Murray R, et al (2004) Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone-Refractory Prostate Cancer. (11):879-82.

Sartor O, de Bono J, Chi KN, et al (2021) Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med; 385(12): 1091-1103.

Scher HI, Morris MJ, Stadler WM, et al (2016) Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J. Clin. Oncol. 1402-18.

Siegel RL, Miller KD, and Jemal A (2017) Cancer Statistics, 2017. 67(1): 7-30.

Smith M, De Bono J, Sternberg C, et al (2016) Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. 34: 3005-13.

Smith TJ, Bohlke K, Lyman GH, et al (2015) Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J. Clin. Oncol. 3199-212.

[redacted]

Sweat SD, Pacelli A, Murphy GP, et al (1998) Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Urology 637-40.

Therasse P, Arbuck SG, Eisenhauer EA, et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J. Natl. Cancer Inst. 205-16.

[redacted]

Violet J, Sandhu S, Iravani A, et al (2020) Long-Term Follow-up and Outcomes of Retreatment in an Expanded 50-Patient Single-Center Phase II Prospective Trial of 177Lu-PSMA-617 Theranostics in Metastatic Castration-Resistant Prostate Cancer. J. Nucl. Med. 857-865.

[redacted]

Webster K, Cella D, Yost K (2003) The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. 1:79.

Weinfurt KP, Li Y, Castel LD, et al (2005) The significance of skeletal-related events for the health related quality of life of patients with metastatic prostate cancer. 16(4): 579-84.

Wright G L, Grob, Haley, et al (1996) Upregulation of prostate-specific membrane antigen after androgen-deprivation therapy (2):326-34.

Wright, Haley, Beckett, et al (1995) Expression of prostate-specific membrane antigen in normal, benign, and malignant prostate tissues. Urol. Oncol. 18-28.

Yadav MP, Ballal S, Bal C, et al (2020) Efficacy and Safety of 177Lu-PSMA-617 Radioligand Therapy in Metastatic Castration-Resistant Prostate Cancer Patients. Clin Nucl Med 19-31.

Yadav MP, Ballal S, Tripathi M, et al (2017) 177Lu-DKFZ-PSMA-617 therapy with metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. 44(1): 81-91.

Yordanova A, Becker A, Eppard E, et al (2017) The impact of repeated cycles of radio ligand therapy using [177Lu]Lu-PSMA-617 on renal function in patients with hormone refractory metastatic prostate cancer. p. DOI 10.1007/s00259-017-3681-9.

[redacted]

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

de Bono J, Mateo J, Fizazi K, et al (2020) Olaparib for Metastatic Castration-Resistant Prostate Cancer 382:2091-102.

de Wit R, de Bono J, Sternberg CN, et al (2019) Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer 2506-2518.

van Kalmthout L, Braat A, Lam M, et al (2019) First Experience With 177Lu-PSMA-617 Therapy for Advanced Prostate Cancer in the Netherlands. Clin Nucl Med 446-451.

16 Appendices

16.1 Appendix 1: Common Terminology Criteria for Adverse Events

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

//ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

16.2 Appendix 2: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival, and Overall Survival (based on RECIST 1.1)

Note: This study adheres to PCWG3 modified RECIST 1.1 for all local and central response assessments. Please refer to Section 8.3.1 Radiographic imaging for tumor assessment, for details that are considered in addition to the guidelines described below.

Document type:	TA Specific Guideline
Document status:	Version 3.2: February 11, 2016 Version 3.1: November 29, 2011 Version 3: October 19, 2009 Version 2: January 18, 2007 Version 1: December 13, 2002
Release date:	11-Feb-2016
Authors (Version 3.2):	[redacted]
Authors (Version 3.1):	[redacted]
Authors (Version 3):	[redacted]
Authors (Version 2):	[redacted]
Authors (Version 1):	[redacted]

Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GBM	Glioblastoma multiforme
LPLV	Last patient last visit
MRI	Magnetic resonance imaging
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

16.2.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 16.2.2 and the definition of best response in Section 16.2.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.2.3.2.2 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 16.2.4 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

16.2.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

16.2.2.1 Definitions

16.2.2.1.1 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 16.2.3.2.8

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ³15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ³10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

- Cystic lesions:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with [3] 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

16.2.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 16.2.3.2.8.

16.2.2.2 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v.) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD
  - **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable
  - **Physical exams**: Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10mm size, and can be assessed using calipers.
  - **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
  - **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained

- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

16.2.2.3 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions**: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ)

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 16.2.2.1.1.
- **Nodal target**: See Section 16.2.2.1.1.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

16.2.2.4 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 16-1) and non-target lesions (Table 16-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-3) as well as the presence or absence of new lesions.

16.2.2.4.1 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are participant to substantial “partial volume” effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

16.2.2.4.2 Determination of target lesion response

Table 16-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm [2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1.] SOD for CR may not be zero when nodal lesions are part of target lesions

[2.] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR

[3.] In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 16.2.2.2).

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 16-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to “normal” size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the “merged lesion” should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the “merged lesion” should be recorded for the size of one of the original lesions while a size of “0”mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.

- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.
- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

16.2.2.4.3 Determination of non-target lesion response

Table 16-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline[2.]

[1.] The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer does prevail.
[2.] It is recommended that the investigator and/or central reviewer should use expert judgment to assign a Non-UNK response wherever possible (see notes section for more details)

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.
- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are

any abnormal nodal lesions (i.e. ³ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).

- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 16.2.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

16.2.2.4.4 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 16.2.2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ³ 10 mm for the first time in the study plus 5 mm absolute increase.

FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 16.2.2.2.

16.2.2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 16-3.

Table 16-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1.] This overall lesion response also applies when there are no non-target lesions identified at baseline.

[2.] Once confirmed PR was achieved, all these assessments are considered PR.

[3.] As defined in Section 16.2.2.4.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

16.2.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 16.2.3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

16.2.3.1 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression £ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

The time durations specified in the SD/PD/UNK definitions above are defaults based on a 6 week tumor assessment frequency. However these may be modified for specific indications which are more or less aggressive. In addition, it is envisaged that the time duration may also take into account assessment windows. E.g. if the assessment occurs every 6 weeks with a time window of +/- 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (³30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ³20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered

PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of central blinded review overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD. The objective of this endpoint is to summarize patients with signs of "activity" defined as either shrinkage of tumor (regardless of duration) or slowing down of tumor growth.

Clinical benefit rate (CBR) is the proportion of patients with a best overall response of CR or PR , or an overall lesion response of SD or Non-CR/Non-PD which lasts for a minimum time duration (with a default of at least 24 weeks in breast cancer studies). This endpoint measures signs of activity taking into account duration of disease stabilization.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of (Dent S and Zee B 2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an

unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

16.2.3.2 Time to event variables

16.2.3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

PFS rate at x weeks is an additional measure used to quantify PFS endpoint. It is recommended that a Kaplan Meier estimate is used to assess this endpoint.

16.2.3.2.2 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

16.2.3.2.3 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

16.2.3.2.4 PFS2

A recent EMA guidance (EMA 2017) recommends a substitute end point intermediate to PFS and OS called PFS2, a surrogate for OS when OS cannot be measured reliably, which assesses the impact of the experimental therapy on next-line treatment. The main purpose of this endpoint is to assess long term maintenance strategies, particularly of resensitizing agents and where it is necessary to examine the overall "field of influence".

PFS2, which could be termed PFS deferred, PFS delayed, tandem PFS, or PFS version 2.0, is the time from date of randomization/start of treatment to the date of event defined as the first documented progression on next-line treatment or death from any cause. The censoring rules for this endpoint will incorporate the same principles as those considered for PFS in this document, and in addition may involve other considerations which will need to be detailed in the protocol.

Please note that data collection for the PFS2 is limited to the date of progression and not specific read of the tumor assessments.

It is strongly recommended that the teams consult regulatory agencies for scientific advice given the limited experience with the use of this endpoint in regulatory setting in light of methodological issues w.r.t. censoring foreseen.

16.2.3.2.5 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

16.2.3.2.6 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by (Morgan 1988)

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in (Ellis et al 2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

16.2.3.2.7 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 16.2.3.2.6. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

16.2.3.2.8 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

Start dates

For all “time to event” variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate ‘time to event’ variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.

- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 16.2.3.2.8).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

16.2.3.2.9 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with non-measurable disease is derived slightly differently according to Table 16-1.

Table 16-4 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 16.2.2.4.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

16.2.3.2.10 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 16.2.3.2.7, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 16-5 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)
[1.] =Definitions can be found in Section 16.2.3.2.7. [2.] =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.2.3.2.7. [3.] =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.			

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1) (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary

analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DoR analysis. For example, palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DoR analysis.

The protocol should state that tumor assessments will be performed every x weeks until radiological progression irrespective of initiation of new antineoplastic therapy. It is strongly recommended that a tumor assessment is performed before the patient is switched to a new cancer therapy.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 16-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

16.2.4 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

16.2.4.1 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

16.2.4.2 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

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

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Participant/guardian decision
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment

Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

Death is a reason which "**must**" lead to discontinuation of patient from trial.

16.2.4.3 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Participant/guardian decision
- Death

- Progressive disease
- Study terminated by the sponsor

16.2.4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

16.2.4.5 Programming rules

The following should be used for programming of efficacy results:

16.2.4.5.1 Calculation of time to event variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

16.2.4.5.2 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and

assessment date is calculated as outlined in Section 16.2.3.2.7). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

16.2.4.5.3 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

16.2.4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

16.2.4.5.5 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

16.2.4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 16-5)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

Adequate assessment is defined in Section 16.2.3.2.7. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor

assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent / opposition to use data/biological samples, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

16.2.5 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47

Ellis S, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465

EMA Guidance: 2012 Guideline on the evaluation of anticancer medicinal products in man

FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005

FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18

Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16

16.3 Appendix 3: PCWG3

The sections that apply to this trial are the criteria for radiographic response assessments. It is based on the PCWG3 recommendations (Scher et al 2016).

Table 16-6 PCWG3

Variable	PCWG3 (2016)

Soft-tissue lesions	For control/relieve/eliminate end points:
	General
	• Record changes in nodal, lung, liver adrenal and central nervous system (CNS) sites separately
	• Record up to 5 lesions per site of disease
	• Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats:
	  • Confirm favorable change with second scan
	  • Record complete elimination of disease at any site separately
	Nodal
	• Only report changes in lymph nodes that were ≥1.5 cm in diameter in short axis at baseline
	• Record changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separately
	Visceral
	• Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats:
	  • Record changes in liver, lung, adrenal, and CNS separately
	  • Only report changes in visceral lesions (liver, lung, adrenal, CNS) that were ≥1.0 cm in the longest dimension
	For delay/prevent end points:
	Nodal and visceral
	• Record changes in nodal and visceral disease separately
	• 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.
	• Record up to 5 lesions per site of spread
	• Note that for some treatments, a lesion may increase in size before it decreases.
	Nodal
	• 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, participant to clinical discretion, and nonmeasurable.
	• For existing pathologic adenopathy (≥1.5 cm), progression is defined per RECIST 1.1

Bone	For control/relieve eliminate end points: • Record changes as improved or stable (no new lesions) or worse (new lesions) • Changes in intensity of uptake alone do not constitute progression or regression • No new lesions: continue therapy in absence of other signs of progression • New lesions (See Progression below) For prevent/delay end points (progression): • Exclude pseudoprogression in the absence of symptoms or other signs of progression • At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)

	• If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented • For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan • Date of progression is the date of the scan that first documents the second lesion • Changes in intensity of uptake alone do not constitute either progression or regression

16.4 Appendix 4: Study Specific Adjustments of Response Evaluation Criteria in Solid Tumor

Study-specific Adjustments of Response Evaluation Criteria in Solid Tumors, Guideline based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines RECIST Criteria (Appendix 2)

Definitions.

Measurable lesions

- No trial-specific adjustment for definition of measurable non-nodal extraskeletal lesions (“soft tissue disease”, as per PCWG3). Non-nodal lesions will be considered measurable when their longest diameter is no less than double the slice thickness/reconstruction interval (RI) or 10 mm, whichever is greater, by CT/MRI scan (e.g., the minimum non-nodal lesion size for CT/MRI with 5 mm cuts will be 10 mm).
- Measurement of lesions on chest x-ray will not be performed. Chest CTs will be required for lesion measurement.
- Nodal lesions will be considered measurable at Screening/Baseline, when a lymph node is ≥15 mm in the short axis by CT/MRI. Nodal lesions may be measured by a local reader bidimensionally, however, at Screening/Baseline and on-study, only the short axis should be recorded and will contribute to the objective response. The lymphatic system is considered one (1) site of metastatic spread; however, pelvic and extrapelvic nodal lesions should be recorded separately to represent each group.
- Lesions in a previously irradiated area may be considered measurable if lesions in those areas have documented progression.
- Identifiable soft tissue components of the bone lesion, which can be assessed by CT/MRI, can be considered measurable if the soft tissue component meets the criteria for measurable disease. Note, that the bone lesions without soft tissue component will be assessed at screening/baseline and on-study by whole-body bone scan only

Non-measurable lesions

- All other extraskeletal lesions that do not meet the above criteria for measurable disease, including small lesions (<10 mm in longest diameter), or pathological lymph nodes ≥10mm to <15 mm in the short axis, or other truly non-measurable lesions, will be considered non-measurable

Examples of non-measurable lesions include:

- Identifiable soft tissue components of the bone lesion, which can be assessed by CT/MRI and do not meet above criteria for measurable lesion
- Leptomeningeal disease and brain metastases.
- Lymphangitis of the skin or lung.
- Abdominal/pelvic masses
- Pathological lymph nodes with a short axis measuring ≥10 mm and <15 mm.
- Irradiated lesions that have not shown progression.
- Groups of lesions that are small and numerous (e.g., miliary lung lesions, multiple small nodes).
- Pleural/pericardial effusions and/or ascites

Note: when the patient has

- non-measurable disease only (with radiographic evidence of distant metastases by CT/MRI), OR
- bone disease only by bone scan,

the patient is potentially eligible for the study (when meets other eligibility criteria)

Extent of the disease at Screening/Baseline

The sites of the disease present at screening/baseline will be identified. Sites of soft tissue (extraskeletal) disease will be characterized as either target or non-target lesions. Note, that for the purpose of this study, bone lesions will be identified based on whole-body bone scan and will not be selected as target or non-target (with exception for identifiable soft tissue component of bone lesions as described above; however, bone component will be assessed by bone scan according to PCWG3 recommendations).

Target lesions

- Target lesions must be measurable at Screening/Baseline. These lesions will generally be the largest tumor masses. Target lesions should be selected on the basis of their size (lesions with the longest diameter), and in addition should be assessable by reproducible repeated measurements
- Target lesions should represent all involved organs/sites of metastatic spread (for example, lymph nodes, lung, liver, adrenal glands).
- The number of target lesions representing one (1) site of metastatic spread may be up to five (5)
- The lymphatic system is considered one (1) site of metastatic spread. When pathologic lymph nodes of ≥15 mm in the short axis are located in both pelvic and extra pelvic areas, both locations should be represented by selected target lesions
- The total number of target lesions may be more than five (5) in order to represent all sites of metastatic spread
- The lesion(s) in a prostate gland/prostate bed should not be selected as target even if they meet the criteria for measurable disease
- The lesions in CNS should not be selected as target lesions even if they meet the criteria for measurable disease
- Identifiable and measurable soft tissue components of the bone lesion, which can be assessed by CT/MRI, can be considered target lesion
- Lesions that have been previously irradiated may be selected as target lesions when they have progressed on or after radiotherapy
- Target lesions cannot be measured on plain films, FDG-PET, bone scans or ultrasounds.

Non-target lesions

- Sites of disease present at Screening/Baseline and not selected as target lesions will be classified as non-target lesions.
- Non-target lesions may be reported and assessed collectively by region/organ.
- Non-target lesions will include any measurable lesions beyond the maximum number of five (5) per site of metastatic spread.
- A lymph node may be selected as non-target when considered abnormal and meets the criteria for a pathological lymph node: ≥10mm in a short axis.
- If the abnormal node meets the criteria for pathological lymph nodes, then the entire group may be chosen as a non-target lesion. Subsequent evaluations for response will be based on the abnormal node as well as other nodes in that group.
- The lesion(s) in a prostate gland/prostate bed should not be selected as non-target
- The lesions in CNS will be selected as non-target even if they meet the criteria for measurable disease
- Identifiable soft tissue components of the bone lesion, which can be assessed by CT/MRI, can be considered non-target lesion when does not meet criteria for target lesion
- Lesions that have been previously irradiated may be selected as non-target lesions

Effusions and ascites

- Pleural effusions, pericardial effusions and ascites, present at screening/baseline, will be followed as non-target lesions
- The presence or absence of effusions/ascites will be checked at each timepoint
- To be considered new, a fluid collection must not have been present at Screening/Baseline

- The cytologic confirmation of the neoplastic origin of any effusion which appears or worsens during the study is not required and at the discretion of the investigator

Lesions that divide (split) or merge (coalesce) on treatment

- If a target lesion splits into multiple parts after Screening/Baseline, the longest diameter or short axis of each part, as applicable, will be measured. The sum of the parts of the original tumor will be recorded as the total for the lesion measurement with the original lesion number. The individual split lesions will not be considered as new lesions, and will not qualify for progressive disease
- When lesions merge, maximal diameter measurements of each individual lesion should be obtained, longest diameter or short axis as per RECIST 1.1 guidelines. If the lesions have truly coalesced such that they are no longer separable, the maximal diameter of the merged lesion should be measured, longest diameter or short axis, as per RECIST 1.1 guidelines

New lesions

- The presence of new lesions will be assessed at each time point
- Unequivocal new lesions are those that were not present at Screening/Baseline
- Unequivocal new multi-focal or miliary disease will determine a progressive disease unless there is clear radiographic evidence of a benign etiology.
- Lesions that are seen (subsequent to the Screening/Baseline) in anatomic locations that were not scanned at Screening/Baseline will determine a progressive disease
- The finding of a new soft tissue lesion should be unequivocal
- Lesions in the prostate gland/prostate bed are not qualified as new lesions.
- New nodal lesions must be pathologic in size and represent new metastatic disease
- Note, that the appearance of a new bone lesion will be assessed by bone scan according to PCWG3 Recommendations
- Response at the time point when an equivocal new lesion was first identified may be updated to progressive disease if subsequent images confirm that it truly represents new disease

New lesions, use of FDG-PET

FDG-PET imaging may be used to identify new lesions in the following manner:

- Positive FDG uptake (FDG-positive disease) is defined as a level of activity greater in intensity compared to either the tissue where the lesion is located or the surrounding tissue, which serves as the background activity level.
- FDG-PET will only be used for the assessment of progression
- New FDG-PET positive lesions refer to lesions which were not previously selected on CT as part of the Screening/Baseline extent of disease
- If there is no screening/baseline (or interval) FDG-PET imaging for comparison, or if the on-study FDG-PET imaging shows an FDG-PET positive focus which was not present on the screening/baseline (or interval) FDG-PET imaging, then progression will be determined as follows:
  - If the positive FDG-PET focus on-study corresponds to a new site of disease confirmed by CT, then response will be assessed as PD
  - If the positive FDG-PET focus on-study is not confirmed as a new site of disease on CT, then additional follow-up CT/MRI is needed to determine/confirm progressive disease. When confirmed, response at prior time point may be updated to PD retrospectively

If the positive FDG-PET scan on-study corresponds to a pre-existing site of disease on CT/MRI that is not progressing on the basis of the anatomic changes, then response cannot be assessed as PD

Frequency of tumor re-evaluation while on treatment

- Radiologic assessments (CT/MRI, bone scans) are to be performed every 12 weeks (±7 days) for the first 24 months, then every 16 weeks (±7 days) and at the end of treatment
- Confirmation of Complete response/Partial response by additional CT/MRI of chest/abdomen/pelvis performed not less than 4 weeks after the criteria for response are first met is not mandated in this study

16.5 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

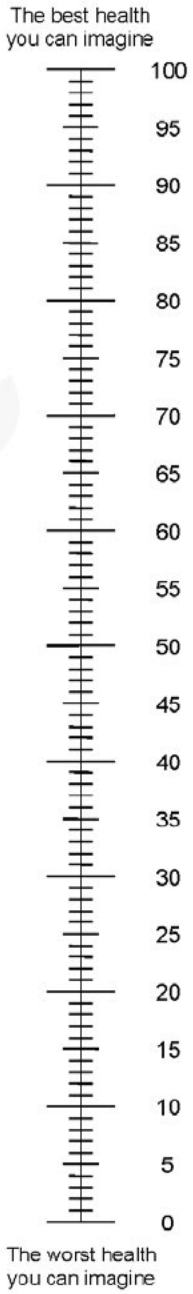
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 = ☐



16.6 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

16.7 BPI-SF, sample only, not for patient use

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

Study Name: _____

Protocol # _____

PI: _____

Revision: 07/01/05

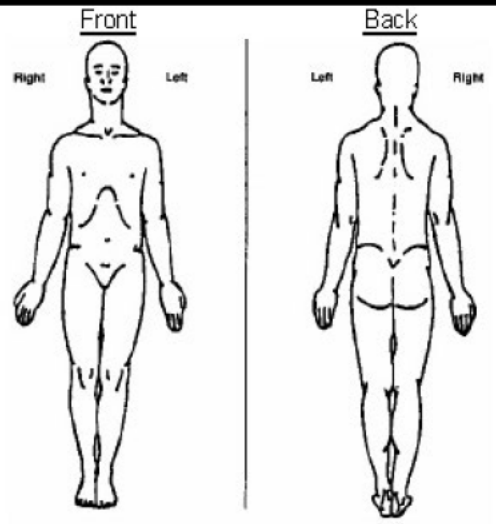
PLEASE USE BLACK INK PEN

Brief Pain Inventory (Short Form)

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 everyday kinds of pain today?

☐ Yes ☐ 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 marking the box beside the 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 marking the box beside the 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 marking the box beside the 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 marking the box beside the number that tells 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

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #: ☐☐☐☐

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

PLEASE USE BLACK INK PEN

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 mark the box below the 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. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

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

B. Mood

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

C. Walking ability

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

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

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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