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Clinical Trial Protocol Title:

PSM Addition: An International Prospective Open-label, Randomized, Phase III Study comparing 177Lu-PSMA-617 in combination with Standard of Care, versus Standard of Care alone, in adult male patients with Metastatic Hormone Sensitive Prostate Cancer (mHSPC)

Clinical Trial Protocol Number:	CAAA617C12301
Version number:	Amended Protocol Version 03 (Clean)
Compound:	AAA617
Brief Title:	A study to investigate the efficacy and safety of 177Lu-PSMA-617 in combination with Standard of Care, versus Standard of Care alone in adult male patients with mHSPC
Clinical Trial Study Phase:	III
Sponsor Name/Address:	Novartis Pharma AG Lichtstrasse 35, 4056 Basel, Switzerland
Regulatory Agency Identifier Number	EUCT number: 2023-507970-42-00
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Clinical Trial Protocol Template Version 3.0 dated 31-Jan-2020

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List of abbreviations

^{68}Ga-PSMA-11	[^{68}Ga]Ga-PSMA-11
^{177}Lu-PSMA-617	[^{177}Lu]Lu-PSMA-617
AA	Antiandrogens
ADT	Androgen Deprivation Therapy
AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ANC	Absolut Neutrophil Count
anti-HAV	Serum Antibody to Hepatitis A
anti-HBc	Antibody to Hepatitis B Core Antigen
anti-HCV	Serum Antibodies to Hepatitis C Virus
anti-HEV	Anti Hepatitis E Virus
APTT	Activated Partial Thromboplastin Time
AR	Androgen Receptor
ARDT	Androgen Receptor Directed Therapy
ASMA	Anti-Smooth Muscle Antibody
AST	Aspartate Aminotransferase
AV	Atrioventricular
AxMP	Auxiliary Medicinal Product
BfS	Bundesamt for Strahlenschutz
BIRC	Blinded Independent Review Committee
BOR	Best Overall Response
BPI-SF	Brief Pain Inventory - Short Form
BUN	Blood Urea Nitrogen
C1D1	Cycle 1 day 1
CABG	Coronary Artery Bypass Graft
CAS	Cross-over Analysis Set
CD -transferrin	Carbohydrate-Deficient-Transferrin
CFR	Code of Federal Regulation
CI	Confidence Interval
CK	Creatine Kinase
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central Nervous System
CO	Country Organization
COA	Clinical Outcome Assessment
CoA	Certificate of Analysis
CoC	Certificate of Compliance
COVID	Coronavirus Disease

CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CRPC	Castrate Resistant Prostate Cancer
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular Disease
[redacted]	[redacted]
DCR	Disease Control Rate
DDE	Direct Data Entry
DILI	Drug-Induced Liver Injury
DKFZ	German Cancer Research Center, Deutsches Krebsforschungszentrum
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECRF	Electronic Case Report Forms
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EOP	End of Production
EOT	End of Treatment
EPO	Epoetin
EQ-5D-5L	European Quality of Life (EuroQol) 5 Domain 5 Level Scale
EQ-5D VAS	EQ-5D Visual Analogue Scale
ERCP	Endoscopic Retrograde Cholangiopancreatography
ESC	Executive Steering Committee
Eu. Ph.	European Pharmacopoeia
FACT-P	Functional Assessment of Cancer Therapy Prostate
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin-Fixed, Paraffin Embedded
GBq	Gigabecquerel
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
GLDH	Glutamate Dehydrogenase
h	Hour
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus

HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HSV	Herpes Simplex Virus
i.v.	Intravenous
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
IMP	Investigational Medicinal Product
IN	Investigator Notification
INN	International Non Proprietary Name
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to treat principle
LDH	Lactate Dehydrogenase
LFT	Liver function test
LHRH	Luteinizing Hormone Releasing Hormone
LLN	Lower Limit of Normal
LPFT	Last Patient First Treatment
MBq	Megabecquerel
mCi	Millicuries
mCRPC	Metastatic Castrate Resistant Prostate Cancer
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
mHSPC	Metastatic Hormone Sensitive Prostate Cancer
MI	Myocardial Infarction
mL	Milliliter(s)
MRI	Magnetic Resonance Imaging
MUGA	Multiple Gated Acquisition
NCI	National Cancer Institute
NED	No Evidence of Disease
NS	Normal Saline
NYHA	New York Heart Association

ORR	Overall Response Rate
OS	Overall Survival
PARP	Poly (Adenosine Diphosphate-Ribose) Polymerase
PC	Prostate Cancer
PCS	Prostate Cancer Subscale
PCWG	Prostate Cancer Working Group
PD	Progressive Disease
PDc	Progressive Disease Confirmed
PDu	Progressive Disease Unconfirmed
PET	Positron Emission Tomography
PFS	Progression Free Survival
PTA	Post-Trial Access
PR	Partial Response
PRO	Patient Reported Outcomes
PSA	Prostate Specific Antigen
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	Fridericia QT Correction Formula
R Value	ALT/ALP x ULN
RAS	RECIST Analysis Set
RBC	Red Blood cell(s)
RECIST	Response Evaluation Criteria In Solid Tumors
RLT	Radioligand Therapy
RMST	Restricted Mean Survival Time
rPFS	Radiographic Progression Free Survival
RPSFT	Rank Preserving Structural Failure Time
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SD	Stable Disease
SMQ	Standardized MedDRA Queries
SoC	Standard of Care
[redacted]	[redacted]
SSE	Symptomatic Skeletal Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
[redacted]	[redacted]
TEAE	Treatment Emergent Adverse Event
TFQ	Trial Feedback Questionnaire
TSH	Thyroid Stimulating Hormone
TTDm	Time to Development of mCRPC
TTPP	Time from Randomization to Pain Progression

TTR	Time to Response
TTSSE	Time to Symptomatic Skeletal Event
TTSTP	Time to Soft Tissue Progression
ULN	Upper Limit of Normal
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
Auxiliary Medicinal Product (AxMP)	Medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., rescue medication, challenge agents, background treatment or medicinal products used to assess endpoints in the clinical trial). Concomitant therapy is not considered as AxMP
Background Therapy	Generally considered to be the current standard of care for a particular condition / disease, in addition to which study treatment is given
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 intervention, 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)
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)
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 intervention 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.
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 Novartis 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	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a

	marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
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, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
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.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the participant about the status of a participant's health condition without amendment or interpretation of the participant's report by a clinician or anyone else.
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.
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.
Rescreening	If a participant fails the initial screening and is considered as a Screen Failure, he can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Rescue Medication	A medication used to control symptoms that are not adequately controlled on investigational and other study treatment
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 consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of its data and/or 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.

Amendment 3 (31-Jan-2024)

The first patient first visit (FPFV) occurred on 09-Jun-2021 and as of 31-Jan-2024, 1144 patients have been enrolled in 20 countries. Recruitment was closed on 25-Jul-2023.

Amendment rationale

Changes that apply to all participants are listed below

The main purpose of this global amendment is to adapt the statistical analysis in group sequential design based on Health Authorities' feedback. The changes to the statistical analysis include:

- rPFS group sequential design: to add clarification that the primary intent of the first interim analysis (IA1) is to determine if the trial should be stopped early for futility. There is no intent to carry out an analysis to declare superior efficacy at the time of IA1. The second IA (IA2) will allow the study to declare statistical superiority in efficacy.
- Overall Survival (OS) group sequential design:
  - To add an additional OS interim analysis at the time of the final rPFS analysis
  - Recalculate the expected number of events and information fraction for OS to align with rPFS analysis time points
  - Remove futility testing for OS at each analysis time (since it is a secondary endpoint likely to be confounded by treatment cross-over)
  - Update the total expected number of OS events at time of the final OS analysis
- Secondary estimands: change the key secondary estimand (OS) regarding the intercurrent event of cross-over to ^{177}Lu-PSMA-617 in combination with Standard of Care arm for patients in the Standard of Care alone arm (consider treatment policy strategy).

Additionally, in this global amendment, [redacted] This additional [redacted] be performed in [redacted]

Changes were made in language throughout the protocol for better clarity and typos were corrected.

Changes that will apply to participants in [redacted] sites only

- Removed the [redacted] extension cohort that was added in protocol amendment 2. The required sample size of [redacted] mainland participants was reached within the enrollment in the main study; hence the extension cohort was not initiated.

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 throughout protocol sections.
- Section 1.1, Background has been updated with:
  - ^{68}Ga-PSMA-11 approval in several countries, including the United States, Great Britain and the European Union under the trademark of LOCAMETZ®
  - Centers from around the world have published their clinical experience with ^{68}Ga-PSMA-11 in patients with prostate cancer, resulting in numerous prospective and retrospective studies including data from over 4500 patients (Crocerossa et al 2021). Despite the multiple and various uses of ^{68}Ga-PSMA-11, and although literature is extensive, safety data reported in the literature is scant, though suggestive that no specific safety issues were encountered during the >10 years of clinical use.
- Section 2, [redacted]
- Section 2.2, Secondary estimands: Changes were made in language for better clarity and typos were corrected.
- Section 3, Study Design updated with:
  - Paragraphs describing the extension cohort for [redacted] deleted.
  - Participants who received ^{177}Lu-PSMA-617 (in ^{177}Lu-PSMA-617+SoC arm and after crossover in the SoC arm) will be asked to join a separate long-term safety follow-up study (CAAA617A12402) while remaining on survival follow-up in this study.
- Section 4.5, Risks and benefits: updated with:
  - One reference added (Prescribing Information for ^{68}Ga-PSMA-11)
  - While the uptake of ^{68}Ga-PSMA-11 reflects the levels of PSMA expression in prostate cancer, ^{68}Ga-PSMA-11 uptake is not specific to prostate cancer and may occur in other types of cancers, non-malignant processes and normal tissues. The risk of PET imaging interpretation errors can be minimized when ^{68}Ga-PSMA-11 is appropriately handled and administered by trained health care professionals and when scans are interpreted by trained experts in the context of histopathology and/or other diagnostic procedures
- Section 6.1 Study treatment: First paragraph updated for better clarity and following paragraphs added:
  - Study drugs 68Ga-PSMA-11 and 177Lu-PSMA-617 both have a marketing authorization, but in this study are considered investigational as 68Ga-PSMA-11 is used for eligibility assessment per protocol-specified criteria, 177Lu-PSMA-617 is used in mHSPC indication.
  - Standard of Care (SoC) refers to Androgen Receptor Directed Therapy (ARDT, also known as second-generation androgen receptor pathway inhibitors) and Androgen Deprivation Therapy (ADT). Examples of ARDT include but are not limited to abiraterone acetate, enzalutamide, apalutamide, darolutamide and rezvilutamide. Standard of Care ADT and ARDT drugs are authorized to treat patients with mHSPC,

in this trial they are considered auxiliary medicinal products and will be administered per local label instructions/local standards

- Section 6.1.1, Investigational and control drugs: Paragraphs updated for more clarity and Table 6-1 updated for better clarity (including a footer)
- Section 6.1.2, Additional study treatments:
  - The following sentence was removed: "No other investigational study treatment beyond investigational drugs 177Lu-PSMA-617 and 68Ga-PSMA-11 are included in this trial"
  - Table 6-2 (Additional study treatment) added
  - Paragraph on "Standard of Care' updated and moved here instead of section 6.2.1 'Concomitant therapy'
- Section 6.1.3, Treatment arms/group: sentence related to extension cohort for [redacted] deleted; and Table 6-3 (Treatment arms) added
- Section 6.1.5, Treatment duration: Text updated and adding following paragraph:
  - [redacted]
- Section 6.1.5.2, Cross-over to ^{177}Lu-PSMA-617: Text clarified and updated with:
  - Reformatted and numbered the eligibility criteria for cross-over
  - PET/CT with ^{68}Ga-PSMA-11 performed following a confirmation of radiographic progression by BIRC should be submitted to a central reader, but should not be used to assess potential eligibility for cross-over. This PET/CT with ^{68}Ga-PSMA-11 assessment is not intended for therapeutic decision making
- Section 6.3.2, Instruction for prescribing and taking study treatment: clarification with regard to Therapy Discharge Instructions
- Section 6.4.2, Treatment assignment, randomization: sentence related to extension cohort for [redacted] deleted.
- Section 6.6.2.1, Follow up on potential drug-induced liver injury (DILI) cases: a sentence was added for potential cases of Hy's law that must be reported as an SAE: "All potential cases of Hy's law must be reported as an SAE. For more details regarding potential Hy`s law case SAE reporting and definition please refer to Section 10.1.2 and Section 10.1.3 of the protocol".
- Table 8-1, Assessment Schedule, ^{177}Lu-PSMA-617 + SoC and SoC arms, Serious Adverse Event: table updated for more clarity and updated with:

- Text on SAE was updated for more clarity
- The sentence "SAE [redacted]" was replaced with "X[10]"
- Footnote "S" added: "Assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database"
- Footnote** added: PET/CT with ^{68}Ga-PSMA-11 scan should be performed in both ^{177}Lu-PSMA-617+SoC and SoC arms participants with radiographic progression confirmed centrally, within 28 days after the site receives a notification about confirmed radiographic progression and submitted to BIRC. Results will not be communicated back to the sites. In SoC arm participants who are the candidates for cross-over, this PET/CT should be preferably performed prior to initiation of ^{177}Lu-PSMA-617, and should not be used to assess potential eligibility for cross-over
- Footnote 9: Word "[redacted]" added, only "Study treatments" kept. Added "Selected AEs [redacted]".
- Footnote 10: "SAEs [redacted], including SAEs of [redacted]" replaced with "SAEs [redacted] will be collected. [redacted]".
- Following sentence added: $Switch from 12 weeks interval to 16 weeks interval in imaging assessments will occur at approximately Post-Cycle 6, Visit 5 (Week 96)
- Footnote*** added: For AE and SAE reporting after 68Ga-PSMA-11 scan (performed during screening and after confirmation of radiographic progression), refer to Section 9.1.1.1.

- Table 8-2, Assessment Schedule, cross-over to 177 Lu-PSMA-617 treatment:
  - Text on SAE was updated for more clarity
  - The sentence "SAE [redacted]" was replaced with "X10"
  - Footnote "S" added: "Assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database"
  - Footnotes 9 and 10: text clarified
- Section 8.5.1, Clinical Outcome Assessments (COAs), minor typos updated
- [redacted]
  - [redacted]
  - [redacted]
- Section 8.5.3, [redacted]:

- [redacted]

- Section 9.1.1, Discontinuation from study treatment: updated with:
  - When a participant in the investigational arm has radiographic progression confirmed by BIRC, PET/CT with ^{68}Ga-PSMA-11 should be performed within 28 days after the site received a notification about confirmed radiographic progression by BIRC (refer to Section 6.1.1 and Table 8-1)
  - When a participant in the control arm has radiographic progression confirmed by BIRC, PET/CT with ^{68}Ga-PSMA-11 should be performed within 28 days after the site received a notification about confirmed radiographic progression from a central reader (regardless of if considered for cross-over or not, refer to Section 6.1.1 and Table 8-1)
- Section 9.1.1.1, Follow up for safety evaluations: updated with
  - Reasons for no administration of subsequent antineoplastic medications since discontinuation of study treatment will be collected in all participants who did not start new antineoplastic medication after study treatment permanent discontinuation.
  - For participants who undergo PET/CT with ^{68}Ga-PSMA-11 at time of radiographic progression confirmed by BIRC, AE monitoring will continue for 14 days after administration of ^{68}Ga-PSMA-11
- Section 9.1.1.2, Follow up for long term safety and efficacy evaluations: text updated for more clarity
- Section 9.1.1.4, Long term follow up study: text updated for more clarity
- Section 9.3, Study completion and post-study treatment: text updated for more clarity
- Section 9.4, Early study termination by the sponsor: updated with:
  - In the situation where the rPFS analysis is statistically not significant (at IA2 and final rPFS analysis), 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 rPFS analysis is statistically significant (at IA2 or final rPFS analysis), the study will continue as initially planned, in order to collect further survival information and perform planned interim and final OS analyses.
- Section 10.1: title updated with adding "other safety"
- Section 10.1.1, Adverse Events: text clarified and updated with:
  - During the long-term safety follow-up at Week 24 and Week 48 safety visits, the following will be captured in the study case report forms, as per Section 10.1.3
    - selected AEs when [redacted] to study treatments: [redacted]:
    - [redacted]
  - Reporting of AEs related to AxMP(s)

    - All AEs related to any authorized auxiliary medicinal product used in this study must be reported to Novartis.
    - In assessing causality, the investigators will use the points as described above in Section 10.1.1.
    - If a suspicion that medical occurrence could be related to study treatment (and/or interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply
- Section 10.1.2, Serious adverse events: text clarified and adding thext with regard to Hy's law cases, with following update
    - During the long-term safety follow-up, the following SAEs will be captured in case report forms, as per Section 10.1.3.
        - [redacted]
        - Any SAEs when [redacted] to study treatments.
    - Reporting of SAEs related to AxMP(s)
        - All SAEs related to any auxiliary medicinal product (whether authorized or not) used in this study must be reported to Novartis within 24 hours of the site becoming aware of it. In assessing causality, the investigators will use the points above. If a suspicion that the medical occurrence could be related to study treatment (or and interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply
- Section 10.1.3, SAE reporting: Text clarified and updated to capture potential Hy's Law cases to comply with [redacted] requirements.
- Section 10.1.5, Title updated with adding "and overdose", text clarified, and Table 10-1 (Guidance for capturing the study treatment errors including misuse/abuse) removed
- Section 10.2.2, Steering committee, text updated for more clarity
- Section 12, Data analysis and statistical methods: text clarified with regards to [redacted] extension cohort
- Section 12.4.2, Statistical model, hypothesis, and method of analysis: clarification that the primary intent of the first interim rPFS analysis is to stop early for futility and no intent for claiming superior efficacy at this first interim analysis. Also, last paragraph updated for better clarity.
- Section 12.5.1.1, Key secondary estimand: section clarified and updated with:
    - The type I error probability will be controlled [redacted] 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).
    - the following ways that OS will be hierarchically tested:

- the time point for the first OS IA will be at the time of second IA for rPFS analysis. At this time point, approximately [redacted] deaths (i.e approximately [redacted] information fraction) are expected to have been recorded in the clinical database. If rPFS is statistically significant at this stage, OS will also be tested. If rPFS is not statistically significant at this stage, then OS will not be tested.
- if OS is not statistically significant at the first OS IA, the second OS analysis will be planned at the time of final rPFS analysis. At this time point, approximately [redacted] deaths (i.e. approximately [redacted] information fraction) are expected to have been recorded in the clinical database. If rPFS is statistically significant at this stage, OS will also be tested. If rPFS is not statistically significant at this stage, then OS will not be tested at this or any later timepoint.
- If OS is not statistically significant at this time of final rPFS analysis, a final OS analysis is planned at the time when approximately [redacted] deaths have been recorded.

- The main OS analysis (based on ITT principle) will be performed without accounting for cross-over, by considering different intercurrent events as explained in the following:
  - 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)
  - Start of a new anti-neoplastic therapy prior to radiographic progression or death: OS data collected irrespective of initiation of new anti-neoplastic therapy will be used for the analysis (treatment policy strategy)
  - cross-over to 177Lu-PSMA-617 in combination with SoC arm for patients in the SoC alone arm: OS data collected irrespective of cross-over (treatment policy strategy).
- The supplementary OS analysis will account for different intercurrent events as explained in the following:
  - 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)
  - Start of a new anti-neoplastic therapy prior to radiographic progression or death: OS data collected irrespective of initiation of new anti-neoplastic therapy will be used for the analysis (treatment policy strategy)
  - Cross-over to 177Lu-PSMA-617 in combination with SoC arm for patients in the SoC alone arm: survival time will be re-calculated based on time spent on 177Lu-PSMA-617 based on appropriate methods as described above (hypothetical strategy)

Further details of sensitivity analyses will be described in the SAP as needed.

- OS monitoring guidelines for assessing potential harm

    - OS monitoring guidelines to consider ruling out any potential OS harm and to help evaluate the benefit/risk profile of 177Lu-PSMA-617 in this study will be considered at each milestone (interim/final OS analyses). Details about such guidelines will be described in the SAP.
- Section 12.5.1.2, Other secondary efficacy endpoints: Text clarified and adding following sentence:
    - Non-CR/Non-PD = at least one non-CR/non-PD assessment (or better) > 11 weeks after treatment start (and not qualifying for CR or PD). PD = progression ≤ 25 weeks after treatment start (and not qualifying for CR, PR or SD).
- Section 12.6, Analysis of exploratory endpoints: updated with:
    - [redacted]
- Section 12.7, Interim analyses: Paragraphs clarified and updated with regards
    - to the primary intent of the first IA
    - the sentence regarding the extension cohort for [redacted] deleted.
    - Table 12-1 updated
    - Key secondary endpoint (overall survival): text updated and Table 12-2 added
- Section 12.8.2, Secondary endpoints: Section updated for more clarity
- Section 13.1, Regulatory and ethical compliance: section updated with Clinical Trial Regulation number
- Section 15, References: list of references updated
- Section 16.2.2.5, Evaluation of overall lesion response: text updated
- Section 16.9, Appendix 9: text clarified

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 2 (12-Dec-2022)

The study started on 09-Jun-2021 (FPFV) and as of 12-Dec-2022, 493 patients have been enrolled in 18 countries.

Amendment rationale

Changes that will apply to participants in [redacted] sites only

- The main purpose of this amendment is to add the option to continue recruitment in [redacted] via an extension cohort following completion of enrollment in the main study. The aim is to [redacted] on ^{177}Lu-PSMA-617 treatment of eligible participants with mHSPC [redacted]. The inclusion of the [redacted] extension cohort has no impact on the planned primary analysis, in particular the total sample size and number of rPFS events required for the primary analysis remain unchanged.
- Once recruitment in the main study is completed (at the time of last patient first treatment), recruitment in the [redacted] extension cohort may begin in order to reach a total sample size of approximately [redacted] participants in the study. The sample size is driven by feasibility. The recruitment of [redacted] extension cohort will continue following the same study design as the main study until DMC declares statistically significant rPFS results at planned second interim analysis or at the final primary analysis for rPFS of the main study.

Changes that will apply to all participants are listed below

- 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 CAAA617C12301 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 to the investigators on 25-May-2022. Language has been added to clarify how sites should proceed in case of potential supply disruption and/or a quality incident.
- Updated higher dose limit of ^{68}Ga-PSMA-11 to 259 MBq as per latest AAA517 IB.
- Added the option for patient to enroll into a separate long term safety follow-up clinical study CAAA617A12402, as requested by US Food and Drug Administration (FDA).
- The scope of reporting for AEs and SAEs in the long-term follow-up period is updated to capture specific toxicities per FDA request.
- Update of the schedule of assessments to ensure proper patient safety follow up per FDA request:
  - Physical exam is added to be performed at long term follow-up visits (30-day safety follow-up and weeks 24 and 48).
  - For Cross-over new safety follow-up visits have been added at weeks 24 and 48 with assessments in order to collect more safety information.

- Collection of additional pre-treatment data for screen failure patients who underwent ^{68}Ga-PSMA-11 PET/CT scan and did not meet Inclusion Criterion #6 as assessed by BIRC (minimal treatment in metastatic HSPC given prior to ^{68}Ga-PSMA-11 PET/CT scan), for better understanding how early SoC initiation impacts PSMA expression status.
- Permitted concomitant therapy requiring caution and/or action and prohibited medication have been revised to provide more clarity.
- Changes were made in language throughout the protocol for better clarity and typos were 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 throughout protocol sections.
- List of abbreviations table: T3 and T4 abbreviations removed as it reflects primary prostate tumor stage T3 or T4 and not Triiodothyronine or Thyroxin. New abbreviations added to the table as well as removal of abbreviations not in the protocol.
- Section 1.1, Background:
- INN included for both IMPs
  - ^{177}Lu-PSMA-617 INN lutetium (^{177}Lu) vipivotide tetraxetan
  - ^{68}Ga–PSMA-11 INN gallium (^{68}Ga) gozetotide
  - Information on approval of Pluvicto added
  - Information on approval of Locametz added
- Section 2.1, Primary estimands: sentence added in line with the current Novartis protocol template to provide definition of estimands.
- Section 2.1, Primary estimands and Section 2.2, Secondary estimands: Study drug changed to “Study treatment”.
- Section 3, Study Design:
  - Updated to add the [redacted] extension cohort to allow recruitment of these participants from [redacted] following achievement of last patient first treatment in the main study recruitment. The extension cohort will follow the same study design. Rationale for the [redacted] extension included.
  - Clarification that PSMA positivity and eligibility with relation to ^{68}Ga-PSMA-11 PET/CT scan is confirmed by BIRC. Clarification on tumor spread and correction of abbreviations for T3 T4.
- Section 4.1, Rationale for study design: Stratification factors clarified with more details.
- Section 4.5, Risks and benefits:
  - Information on dosimetry estimates for ^{177}Lu-PSMA-617 from VISION sub-study added.

  - Risk from radiation exposure added.
- Section 5, Study population: Sentence has been added to refer to the addition of the [redacted] extension cohort.
- Section 5.2, Exclusion Criteria: Exclusion Criterion 15 is clarified. Inability to complete the study imaging procedures due to any reason (e.g., severe claustrophobia, inability to lie still for the entire imaging time, any condition that precludes raised arms position).
- Section 6.1.1, Investigational and control drugs:
  - Higher dose limit of ^{68}Ga-PSMA-11 updated to 259 MBq as per latest AAA517 IB.
  - Reference made to Pharmacy Manual for details on dose preparation and administration.
- Section 6.1.3, Treatment arms/group: Participants in the [redacted] extension cohort will be randomly assigned to the same treatment arms as in the main study.
- Section 6.1.4, Guidelines for continuation of treatment:
  - Clarification added on how to manage discontinuation from study treatment.
- Section 6.1.5, Treatment duration:
  - Clarification that Management of drug interruption due to drug related toxicities are described in Section 6.6.1 and Table 6-2.
  - For participants who have delay of treatment due to any other reasons than drug related toxicities, every effort should be made to reschedule treatment as early as possible to minimize deviations from the treatment schedule.
  - Term experimental drug is replaced by investigational drug.
- Section 6.1.5.2, Cross-over to ^{177}Lu-PSMA-617:
  - Clarification that cross over to receive ^{177}Lu-PSMA-617 is allowed for the control arm participants who have radiographic progression confirmed by BIRC upon discontinuation of Standard of Care in the control arm due to it. Participants with progression events other than radiographic progression confirmed by BIRC such as radiographic progression per investigator's assessment not confirmed by BIRC, clinical progression, and/or PSA progression, will not be allowed to cross-over.
  - Clarification that Assessments required for the cross over baseline as per Table 8-2 must be repeated if they are older than 28 days prior to registration of cross-over in IRT. CT/MRI with contrast of chest/abdomen/pelvis and whole-body bone scan are mandatory images for Cross-over baseline. Images used for a confirmation of radiographic progression by BIRC should not be repeated and are allowed to be used as cross-over baseline images. Missing images must be performed within 28 days prior registration for cross-over.
  - New language adding post treatment follow-up visits 30 days follow-up visit, 24 and 48 weeks visits and then survival follow-up.
- Section 6.2.1, Concomitant therapy:
  - The term experimental drug is replaced with investigational drug.

  - Clarification on allowed change (switch) in ARDT.
  - Additional language added to clarify that hydration and diuretics are allowed and that EANM Procedure Guidelines and institutional standards should be followed.
- Section 6.2.1.1, Permitted concomitant therapy requiring caution and/or action: Clarified (e.g., supplements, traditional medicines etc.) added where product information and data on clinically relevant drug-product interactions are limited or not well established.
  - Term overdose in this section updated with safety or efficacy concern
- Section 6.2.1.2, Use of bone modifying agents: Bisphosphonates replaced with bone modifying agents, this update is made to the section heading.
- Section 6.2.2, Prohibited medications are clarified:
  - Biological therapies are prohibited (except pre-exposure COVID-19 prophylaxis with registered biologic agent), this aligns with Exclusion Criterion#2.
  - Those prohibited medications must not be administered on study (including the cross-over period) for treatment of malignancies (prostate cancer, other malignant neoplasms, non-malignant disease or conditions), other concomitant disease or conditions (e.g., hydroxyurea in benign hematologic disorders, methotrexate in inflammatory types of arthritis, immunosuppressants after transplant, TNF-alpha inhibitors in autoimmune conditions).
- Section 6.3.1.1, Handling of study treatment:
  - Clarification that technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.
  - ^{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.
  - The Investigator must provide accountability also for locally sourced materials used for administration (e.g., i.v. bags).
- Section 6.3.2, Instruction for prescribing and taking study treatment:
  - Clarification that since ^{177}Lu-PSMA-617 is a ready-to-use single-dose vial, no manipulation of the investigational product is intended at the clinical site.
  - When a participant with manageable bladder outflow obstruction/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). Clarification that radiation isolation following administration needs to be handled as per local recommendations.
  - Updated recommendation to cross-refer to General rules for bathroom use and hygiene (i.e. flush tissue paper and anything from your body) in the Therapy Discharge Instructions that should be followed for at least 2 days after treatment.
  - Updated higher dose limit of ^{68}Ga-PSMA-11 to 259 MBq as per latest AAA517 IB.

  - A saline flush ≥10 mL normal saline (NS) should be administered after administration of ^{68}Ga-PSMA-11 to assure that there isn't any residual drug in the intravenous line.
- Section 6.4.2, Treatment assignment, randomization: A sentence was added to clarify that [redacted] extension cohort will be stratified by the same stratification factors.
- Section 6.6.1, Dose modifications: Dose adjustments are not permitted for the investigational imaging agent during the study. Clarification added to any AE that requires drug discontinuation or treatment delay for >4 weeks (dose interval between the cycles more than 10 weeks).
- Section 6.7.2, Treatment of overdose: new section added to provide further guidance in event of overdose.
- Section 7, Informed consent procedures:
  - Participants who are rescreened are required to sign a new ICF.
  - Clarification added on optional sub studies.
- Section 8, Visit schedule and assessments:
  - Language has been added to clarify how sites should proceed in case of potential supply disruption and/or a quality incident.
  - Public Health emergency - Clarification about off-site healthcare professional(s) staff visits to the participant´s home, can replace certain protocol assessments. Those visits remain under Investigator oversight with documented delegation of duties.
  - Clarification on when C1D1 should be scheduled for each arm.
  - Guidance added in case of visit delayed for each arm and for withdrawal of consent.
- Table 8-1, Assessment Schedule, ^{177}Lu-PSMA-617 + SoC and SoC arms: updates are as follows:
  - Physical exam is added to be performed at long term follow-up visits (30 day safety follow-up and weeks 24 and 48).
  - Footnote 9 added regarding [redacted] AEs [redacted] will be collected during long term follow-up (safety weeks 24 and 48 and efficacy follow-up).
  - Footnote 10 added regarding SAEs [redacted] will be collected during long term follow-up (safety weeks 24 and 48, efficacy and survival follow-up periods).
  - Footnote 11 added, radiographic imaging assessments must be scheduled based on [redacted]. Each [redacted] is clarified:
    - For patients enrolled in investigational arm, [redacted]
    - For patients enrolled in SoC arm, the [redacted] is defined by:

  - If ARDT is initiated prior ICF signature, [redacted]
  - If ARDT is initiated after randomization, [redacted]
- Table 8-2, Assessment Schedule, cross-over to ^{177}Lu-PSMA-617 treatment updated as follows:
  - New safety follow-up visits at weeks 24 and 48.
  - Performance of Physical exam is added to be performed at post treatment follow-up visits (30-day safety follow-up and weeks 24 and 48). Hematology and clinical chemistry is added to be performed at safety follow-up week 24 and 48.
  - Footnote 9 added regarding [redacted] AEs [redacted] will be collected during long term follow-up (weeks 24 and 48).
  - Footnote 10 added regarding SAEs [redacted], including SAEs [redacted] will be collected during long term follow-up (safety weeks 24 and 48 and survival follow-up).
  - Footnote 11 added Radiographic imaging assessments for patients in cross-over will be assessed locally.
- Section 8.1.2, Information to be collected on screening failures:
  - New sentence added in line with the current Novartis protocol template to provide rational for data collection for screening failures.
  - Collection of additional pre- treatment data for screen failure patients who underwent ^{68}Ga-PSMA-11 PET/CT scan and did not meet Inclusion Criterion #6 as assessed by BIRC (minimal treatment in metastatic HSPC given prior to ^{68}Ga-PSMA-11 PET/CT scan).
- Section 8.3.1, Radiographic imaging for tumor assessment:
  - Additional language clarifying bone response assessment was included to ensure consistent use of the 2+2 PCWG3 criteria:
    - For scan at Week 12: at least 2 new bone lesions at the first on-treatment scan (i.e., the week 12 scan), that persist on the next scan, with at least two additional lesions on the next (confirmatory) scan.
    - For scans after the [redacted] flare window: the first observation of at least two new lesions relative to the baseline scan confirmed on a subsequent scan.
  - The tables clarifying PCWG3 bone response assessment were added to provide additional guidance regarding the response criteria for bone disease and ensure their consistent use: Table 8-3 Bone disease response and Table 8-4 Bone Disease Progression on Bone Scan".
  - As result of added Table 8-3 Bone Disease response and Table 8-4 insertion subsequent tables numbers have been updated.

  - Clarification on the [redacted] to be used to schedule radiographic imaging assessments in each arm and for patients who cross-over.
  - Clarification added on Radiographic imaging assessments schedule.
  - Table 8-5 updated to clarify that Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement) and Whole body bone scan with technetium-99m labeled diphosphonate are mandated, every 12 weeks [redacted] for the first 24 months and then every 16 weeks until confirmation of radiographic progression by BIRC.
  - Definition of a superscan and bone response assessment management in the participants with superscan seen at different timepoints was added to clarify how to apply the 2+2 PCWG3 criteria in case of superscan.
- Section 8.4, Safety: Table 8-6, new wording has been included for a complete physical exam. Addition of eyes, ears, nose, and throat examination.
- Section 8.4.1, Laboratory evaluations:
  - Table 8-8, the word “fasting” was removed for “glucose”
- Clarification has been included for eGFR calculation when local laboratory is used for eligibility evaluation, the local laboratory/investigator may use MDRD calculators. The link is provided in this section of the protocol.
- Section 9.1.1, Discontinuation from study treatment:
  - Discontinuation of ^{68}Ga-PSMA-11 PET investigational imaging agent is administered as a single intravenous injection; discontinuation of the investigational imaging agent is not applicable.
  - Clarification added on switch of ARDT for participants in both investigational and in control arms.
- Section 9.1.1.4, Long term Follow-up study:
  - Added the option for patient to enroll into a separate long term safety follow-up clinical study CAAA617A12402, as requested by US Food and Drug Administration (FDA).
  - Clarification that while the patient enters the long-term safety follow-up study, the participant's status will continue to be collected every 90 days in this study CAAA617C12301.Section 9.1.3, Lost to follow up: wording clarified with the addition of “or fail to respond to any site attempts to contact them”.
- Section 9.3, Study completion and post-study treatment: new language added for clarification of post-trial access mechanisms.
- Section 10.1.1, Adverse events: updated to capture [redacted] safety data collection to comply with [redacted] requirements.
  - Participants receiving ^{177}Lu-PSMA-617 in investigational and cross over arm will continue to be followed for safety every 24 weeks for a period of 48 weeks from the EOT/EOT2 (long-term safety follow-up). During this long-term follow-up, sufficient information will be obtained to permit an adequate determination of the outcome of

the event and an assessment of the casual relationship between the AE and study treatment.

- At Week 24 and Week 48 safety visits of long-term safety follow-up [redacted] AEs [redacted] are to be reported.

- Section 10.1.2, Serious Adverse Events: [redacted]
- Section 10.1.3, SAE reporting: updated to capture [redacted] safety data collection to comply with [redacted] requirements.
  - Any SAEs (including but not limited to SAEs [redacted], experienced after the 30 day period after the EOT or EOT2 if cross-over occur should only be reported to Novartis Safety, if the investigator [redacted] to study treatment (^{177}Lu-PSMA-617), unless otherwise specified by local law/regulations.
- 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, Data analysis and statistical methods and Section 12.4.2, Statistical model, hypothesis, and method of analysis: updated to include discussion regarding the [redacted] extension cohort with respect to the primary analysis of rPFS.
- Section 12.5.1.2, Other secondary efficacy endpoints: PSA progression definition included.
- Section 12.5.2, Safety endpoints: alignment with previous changes for [redacted] safety data collection to comply with [redacted] requirements.
  - During long-term follow-up, serious adverse events and selected AEs related to [redacted] will be collected.
- Section 12.6, Analysis of exploratory endpoints: [redacted]
- Section 12.7, Language added providing information on the analysis for [redacted] extension patients.
- Section 13.3, Publication of study protocol and results: sentence added in line with the current Novartis protocol template.
- Section 15, Reference:
  - Kratochwil C, Wolfgang PF, Eiber M, et al (2019) EANM procedure guidelines for radionuclide therapy with ^{177}Lu-labelled PSMA-ligands (^{177}Lu-PSMA-RLT). Eur J Nucl Mol Imaging; 46:2536-44.

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 (07-Feb-2022)

The study started on 09-Jun-2021 (FPFV) and as of 22-Dec-2021, 92 patients have been enrolled in 7 countries.

Amendment rationale

[redacted]

- [redacted]
- [redacted]

Changes that will apply to all participants are listed below.

Updates related to background and rationale, eligibility criteria and stratification, cover:

- preclinical study results on PSMA expression, VISION (NCT03511664) study results (included to address the requests on recently published data from sites/ethic committees/regulators)
- safety findings from the first prospective clinical trials with ^{177}Lu-PSMA-617 (summaries added to risk/benefit assessment), and risks minimization strategy (updated)
- criteria for high/low tumor volume (clarified)
- criteria for PSMA positivity/eligibility criteria (added)
- disease extent eligibility criteria (clarified)
- minimal treatment in mHSPC including ADT in adjuvant setting (clarified)
- prior and on-study systemic treatment for prostate cancer (clarified)
- eligibility criteria related to bladder outflow obstruction/urinary incontinence (in response to DMC's request), to prior malignancies, recovery from COVID-19 infection (clarified to prevent unnecessary exclusion of the patients)

Updates related to study conduct were done with the purpose to provide the sites with more detailed and specific guidance, they include:

- An extension of screening period to give enough time to site to complete all screening assessments
- Better specified ^{68}Ga-PSMA-11 imaging guidance
- Guidance on various aspects of study treatment: time to initiate ^{177}Lu-PSMA-617/SoC, allowable windows, SoC duration, treatment beyond PD, cross-over
- Guidance on assessment of disease extent at study entry with corresponding appendices (Prostate Cancer Grading System, AJCC Prognostic Stage Grouping)
- Guidance on various aspects of radiographic imaging for disease extent and response assessment: mandated/optional imaging methods, definitions for soft tissue/bone disease as per PCWG3, considerations on the caveats for RECIST 1.1 as outlined in PCWG3 and

explanations how this will apply, clarification on target/non-target lesions selection, response assessment for soft tissue disease, evaluation/response assessment for bone disease according to the RECIST 1.1 with the caveats as outlined in PCWG3

- [redacted]

Updates related to safety management, monitoring and reporting include:

- Clarifications on safety FU, SAE reporting, contraception, criteria for mandatory discontinuation from study treatment, criteria for ^{177}Lu-PSMA-617 dose reduction/interruption/re-initiation, follow up for toxicity, potential DILI cases, guidance on hospital admission for the purpose of ^{177}Lu-PSMA-617 administration, management of the patients with urinary outflow obstruction/incontinence, and extravasation preventive and management measures
- Clarifications on concomitant therapies, concomitant and prohibited medications
- A new requirement to collect safety information and record ConMed during 42 days after last administration of ^{177}Lu-PSMA-617; in order to match with 6 weeks of cycle duration

Clarifications and updates in the data analysis Section included definition of safety set and on-treatment period for safety summaries, update of the timeframe for evaluation of PSA response (from 3, 6 and 12 months to 12, 24, 48 weeks to align with the schedule of assessments).

Changes to the protocol

Changes to specifics Sections of the protocol are shown in the track changes version of the protocol using strike though red font for deletions and red underline for insertions.

- Change of RLT nomenclature, correct name of both IMPs: [^{177}Lu]Lu-PSMA-617 and [^{68}Ga]Ga-PSMA-11 has been added the first time it is used in the text (i.e. in the Protocol summary and in the introduction Section) and abbreviated forms will be used throughout the document. Abbreviations are captured in the list of abbreviations.
- Throughout the protocol, "Subjects" has been replaced with the term "participants" when referencing study participants per new protocol template version 4.0.
- Typographical and grammatical errors addressed throughout the protocol.
- List of Abbreviation update.
- 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 "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 enrollment 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 performs certain protocol procedures for the participant in an off-site location such as a participant's home."
- Under the definition of "participant", clarification is provided that ""Participant" terminology is used in the protocol whereas term "Subject" is used in data collection."
- 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" has been updated as per CTP version 5.0 to "Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of its data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. 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.

- 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 preclinical studies describing PSMA expression after exposure to pharmacological inhibitors of androgen receptors (such as abiraterone, enzalutamide).
  - a summary of results from VISION (NCT03511664) study, a phase III trial evaluating best standard of care with or without [^{177}Lu]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 (^{68}Ga)–labeled PSMA-11 positron emission tomographic–computed scans.
- Section 2: Section title changed from "Objectives and endpoints" to "Objectives, endpoints and estimands" per new protocol template version 4.0.
- Table 2-1, Secondary objectives:
  - The timeframe for evaluation of PSA response is updated from 3, 6 and 12 months to 12, 24, 48 weeks to align with the schedule of assessments.
- Table 2-1, Exploratory objective:
  - [redacted]
- Section 3, Study design: Timing of screening period has been revised from "28 days prior Cycle 1 Day1" to "within 28 days prior to the randomization".
  - Clarification has been added to collect blood sample for hematology, chemistry and coagulation at screening before the ^{68}Ga-PSMA-11 administration.
  - Clarification has been added that the PSMA positivity result for eligibility is determined by central readers and criteria for positivity/eligibility detailed.
  - Study design, On study treatment: Clarification added regarding 1st generation antiandrogens.
  - Additional guidance provided that, C1D1 can be delayed by up to an additional 3 days for unexpected scheduling delays, and clarification added regarding the initiation of SoC treatment.
- Figure 3.1, the figure has been updated to add PSMA positive on Ga-PSMA-11 PET/CT in the Patient Population.
- Section 4.1 Rational for study design: References have been added and Clarification on the Tumor Volume definition has been made.
- Section 4.1.1 A statement "Androgen deprivation therapy is a standard of care in patients with hormone-sensitive metastatic prostate cancer" was changed to "Androgen deprivation therapy combined with novel agents such as abiraterone, enzalutamide, or apalutamide is a standard of care in patients with hormone-sensitive metastatic prostate cancer rather than ADT alone", and complimented with new references, to present recent standard of care. A part of the statement "in order to maintain castrate serum testosterone levels (i.e., 50 ng/dL) and" was removed, as monitoring of testosterone level is not mandated for the patients with mHSPC receiving SoC.

- Section 4.5 Risks and benefits:
  - Update of this Section made based on new available data.
- Section 4.6, Rationale for Public Health Emergency mitigation procedures: Section 4.6 was introduced based on new Novartis template.
- Section 5.1, Inclusion criteria:
  - Inclusion criterion #7 was reworded for clarity from "Patients must have documented metastatic disease to bone and/or soft tissue/visceral sites documented in one of the following manners within 28 days prior randomization" to "Patients must have at least one metastatic bone and/or soft tissue/visceral lesion documented in the following manners within 28 days prior randomization".
  - Inclusion criterion #11 was reworded to reflect that 1st generation AA must not exceed 45 days and must stop before initiation of study therapy and separate the last sentence in a new bullet point.
- Section 5.2, Exclusion criteria:
  - Exclusion criterion 2: Any previous systemic anti-prostate cancer therapy has been changed by any prior systemic anti-prostate cancer therapy.
  - Exclusion criterion # 3 Concurrent treatment that would exclude candidates from participation in the study was updated to include PARP inhibitors and biological therapy.
  - Exclusion criterion # 9 Clarification added regarding patient with parenchymal CNS metastasis "that have received prior therapy and are neurologically stable, asymptomatic and not receiving steroids for CNS metastases, are allowed" (this clarification was previously in criterion 10).
  - Exclusion criterion # 10 was reworded to clarify from "Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. However, patient with a prior history of malignancy that has been adequately treated and who have been disease free for more than three years as are patients with adequately treated non-melanoma skin cancer, superficial bladder cancer, are eligible. Note: Patients with a history of CNS metastases that have received prior therapy and are neurologically stable, asymptomatic and not receiving corticosteroids are allowed" to "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, treatment free for more than 3 years prior to randomization, or participants with adequately treated non-melanoma skin cancer, superficial bladder cancer, are eligible". A note about the participants with a history of CNS metastases was removed, in respect to the clarification to Exclusion criterion 9.
  - Exclusion criterion # 11 was revised to remove the requirement to have no symptoms for at least 28 days.

  - Exclusion # 12 Correction done to reflect the exclusion criterion- was revised to remove “No”.
  - Exclusion criterion # 16 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.
  - Exclusion Criteria # 17 was updated “Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 14 weeks after stopping study treatment instead of 6 months
- Section 6, Treatment: This Section has been updated based on the new Novartis Template version 4.0 and then the links have been updated accordingly.
- Section 6.1.1 Table 6-1:
  - Dosage form for ^{177}Lu-PSMA-617 was updated from “Radiopharmaceutical solution” to “Radiopharmaceutical solution for infusion/injection”.
  - Column header “Supply type” has been changed to “Presentation” per new protocol template version 4.0.
- Section 6.1.1 Investigational and control drug
  - Clarification has been added regarding ^{68}Ga-PSMA-11 imaging assessment: “During screening, all participants will undergo PET/CT scan imaging for determination of the purpose of PSMA positivity and eligibility determination. Participants must have metastatic disease that expresses PSMA as seen by BIRC on a ^{68}Ga-PSMA-11 PET/CT scan. This assessment will be performed only once at screening, any following assessment of PSMA expression with ^{68}Ga-PSMA-11 radiopharmaceutical are not considered.
  - 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 [redacted] prior to repeating ^{68}Ga-PSMA-11 PET imaging as screening for this study. Imaging assessment must be performed only with use of Sponsor ^{68}Ga-PSMA-11”.
  - Clarification has been added regarding other Ga-containing PSMA-targeting, “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 this medication 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”.
- Section 6.1.3 Supply of study treatment has been removed from protocol. The details of study treatments supply are included in the pharmacy manuals.
- Section 6.1.5 Treatment duration
  - Clarification has been made in this Section.

- Section 6.1.5.1 Treatment beyond disease progression
  - Rewording of some sentences to make it clearer.
- Section 6.1.5.2 Cross-over to ^{177}Lu-PSMA-617
  - Clarification of the windows period allowing patient to cross-over:
  - When radiographic progression is confirmed by BIRC, the participants initially randomized to the SoC alone arm will be allowed to cross-over within 28 days after confirmation of rPFS by BIRC, and start receiving ^{177}Lu-PSMA-617 within [redacted] after registration of cross-over in IRT system. Progression events other than radiographic progression confirmed by BIRC will not qualify for cross-over.
- Section 6.2.1 Concomitant therapy
  - Clarification on the period to report concomitant medication in the CRF. Clarification added regarding the start of SoC treatment and that participant should be instructed to take a daily dose of ARDT on the Day 1 of a treatment cycle (CxD1) at the site, after completion of pre-dose evaluations
  - In Other Therapy part, addition of detail regarding Participants with manageable and controlled urinary outflow obstruction or urinary incontinence should continue receiving best available standard of care (incl. pads, drainage) at the discretion of the investigator/attending physician. Clarification regarding need for palliative radiation has been added "If the need for palliative radiation to symptomatic bone disease is considered after the 1st post-baseline scan, bone metastases should be assessed to rule out radiographic progression. When the need for palliative radiation to the lesions other than bone is considered after the baseline scan, the lesion should be assessed per RECIST 1.1 criteria and palliative radiation to the target lesion should be possibly avoided. Initiation of a palliative radiation may result in study discontinuation when radiographic progression is confirmed."
  - Clarification that the use of growth factors could also follow other international/national guidelines at the discretion of the investigator/attending physician.
  - Addition of "Therapy with hormones including steroids (systemic, localized, topical) may be given for diseases/conditions other than prostate cancer (e.g., insulin for diabetes). Steroids are also allowed for adrenal failure, in combination with ARDT as per label/local standards (prednisone given in combination with abiraterone)".
- Section 6.2.1.2 Use of bisphosphonates
  - Clarification added in this Section "Bone modulating agents (bisphosphonates, RANKL inhibitors) and/or therapy with bone health agents can be started, changed or stopped at the discretion of the investigator throughout the study".
- Section 6.2.2 Prohibited medication
  - Correction has been made regarding treatment to primary tumor should be done within 6 months after randomization and not after ICF signature as already detailed in Section 6.2.1

  - Addition of "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 "
- Section 6.3 Preparation and dispensation previously in Section 6.7 has been moved in Section 6.3 as per new protocol template version 4.0
  - The sentence "A unique medication number is printed on the study medication label has been removed" to be aligned with what is done, as both IMP label content is different it is described further in Section 6.3.1.1 for each.
- Section 6.3.1 Handling of study treatment and additional treatment and Section 6.3.1.1 have been added per new protocol template version 4.0
  - A sentence has been updated to refer to the pharmacy manuals for products ordering/supply, receipt, storage, handling, administration and for technical complaints reporting.
  - Destruction procedure has been added for ^{68}Ga-PSMA-11
- Section 6.3.2 Instruction for prescribing and taking study treatment- sub Section title has been added per new protocol template version 4.0
  - Clarification has been added about documents sent for each dose release and calibration steps with cross-reference to Pharmacy Manual.
  - Clarification has been added for use of pads, catheters and other drainage "Use of pads, catheters, other drainage is allowed to control bladder outflow/urinary incontinence. Management of these conditions is at the discretion of the investigators, they should also consider appropriate radioprotection measures according to local regulations/standards" and update for requirement linked to local regulation "A participant may be admitted to a hospital to get a cycle of investigational therapy with ^{177}Lu-PSMA-617 and/or after administration of ^{177}Lu-PSMA-617 dose if it is required as per local regulation related to provision of radioligand therapy".
  - Clarification added regarding extravasation "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".
  - ^{68}Ga-PSMA-11 part:
  - Update on additional record to be done on eCRF regarding dose preparation information.

  - ^{68}Ga-PSMA-11 dose requirements detailed in this section.
  - Standard of Care part:
  - Clarification that contraceptive measures from package insert and guidelines should also be followed for Standard of Care.
  - 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 6.5 Treatment blinding
  - Clarification done regarding the confidentiality of the randomization list per new protocol template version 4.0.
- Section 6.6 Dose escalation and dose modification
  - Clarification added to specify that dose adjustment per local package insert and/or guidelines applies to both ARDT and ADT part of Standard of Care, as needed.
- Section 6.6.1 Dose modifications
  - Further clarification have been added regarding management of ^{177}Lu-PSMA617 treatment and dose reduction guidance.
  - In case of adverse events not related, in opinion of the investigator, 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.
  - Discontinuation of ^{177}Lu-PSMA-617 treatment is mandated regardless relationship between ^{177}Lu-PSMA-617 and toxicity coming from adverse event in case of:
  - Any AE that requires drug discontinuation or treatment delay for >4 weeks.
  - Any unacceptable toxicity when it may not be corrected with appropriate concomitant treatment.
- Section 6.6.1 Table 6-2 has been updated to provide clearer guidance.
- Section 6.6.1,
  - Additional text has been added to describe the process to follow in case of dose reduction “In case a dose reduction is needed, full dose will be provided by the manufacturing site to the clinical site and it will be Investigator or delegates’ responsibility for measuring the activity in vial and pulling out and administering the current dose activity based on the planned dose for the participant, i.e. 5.9 GBq (160 mCi) in this case.
  - Other option is also for site to let activity decay and dose patient later but not after the expiry date and time of the dose which is stated on the label and on the product batch release certificate”.
- Section 6.6.2 Follow up for toxicities
  - Clarification added regarding the duration of safety follow up after ^{177}Lu-PSMA-617 “All participants must be followed up for adverse events and serious adverse events for 30 days following the last dose of ARDT and 42 days after the last dose of ^{177}Lu-PSMA-617 whichever is longer”.

- Section 6.6.2.1 Follow up on potential drug induced liver injury (DILI) cases per new protocol template version 4.0
  - A recommendation added that Glutamate Dehydrogenase testing is additionally recommended if available for the assessment of DILI. Updated for better monitoring of DILI.
  - "livertox.nih.gov/rucam.html" removed as per protocol template v4.0.
- Section 6.7.1 Treatment compliance
  - Addition of the ^{68}Ga-PSMA-11 in this Section.
  - Previous Section 6.7 moved to Section 6.3.
- Section 7 Informed Consent Procedure
  - [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" per new protocol template version 4.0.
  - 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 per new protocol template version 4.0.
- Section 8, Visit schedule and assessments
  - 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.
  - Sentence "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 CRF" has been updated as per new protocol template version 4.0
  - 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" per new protocol template version 4.0.
  - Cycle 1 Day 1 has been granted additional 3 days to allow for unexpected schedule delays.
  - 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.
- The sentence "At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously recorded must be recorded on the eCRF" has been updated as per protocol template version 4.0.
- Correction has been made "Cycle 2 D1 start 43 days after C1D1 and not 42 days"

- Section 8, Table 8-1
  - Correction of the Title, removal of duplicate wording "Assessment Schedule" and clarification regarding the investigational arm
  - Correction of Cycle ID in Period 2, 3 and 4.
  - Start of screening was changed from day -28 to day -42 to allow for enough operational time to complete screening assessments.
  - Update in the sentence "Participants who discontinue from study are to return for the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule"
  - Note 5 has been annotated for inclusion/exclusion criteria at screening and PSMA eligibility by ^{68}Ga-PSMA-11" and note 4 has been annotated for vital sings assessment and footnote#1 updated and annotated for vital signs at C1W1, C2W1,C3W1, and C6W1, note moved to good column for Vital Sign.
  - Clarification for ECG schedule added.
  - Clarification added regarding the optional TFQ per new protocol template version 5.0.
  - Addition of a raw for the Radiolabeling –Dose preparation ^{68}Ga-PSMA-11 at Screening and PSMA eligibility by ^{68}Ga-PSMA-11".
  - [redacted]
  - In Raw Standard of Care, addition of the reference to the related Section
  - Clarification of the note 1 regarding Vital sign.
  - Clarification of note 2 regarding the sample collection to be done before the ^{68} Ga-PSMA-11 administration at screening
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - Testosterone collection was removed, as monitoring of testosterone level is not mandated for the patients with mHSPC receiving SoC

- Section 8, Table 8-2
  - Correction of the title, removal of duplicate wording "Assessment Schedule"
  - Correction of the Days in Cross Over Baseline
  - In Inclusion/exclusion criteria raw, correction was made "X" was replaced by "S"
  - Correction of Cycle ID in Cross-over baseline, Cross-over C2-C5 and Cross-over Cycle 6.
  - Clarification for ECG schedule added.
  - Clarification added regarding the optional TFQ.
  - Added ""X in Radiographic imaging for rebaseline at cross-over baseline.
  - [redacted]
  - Clarification of the note 1 regarding Vital sign.
  - The annotation of this note 5 has been added next to their corresponding assessments.
  - [redacted]
  - In Standard of Care raw addition the reference to appropriate section
  - Testosterone collection was removed, as monitoring of testosterone level is not mandated for the patients with mHSPC receiving SoC
- Section 8.1 Clarification made regarding screening assessment and timelines. Description of the imaging assessment added.
  - Screening period clarified that it occurs after ICF signature and within 28 days of randomization in IRT.
  - Clarification has been added to collect blood sample for hematology, chemistry and coagulation at screening before the ^{68}Ga-PSMA-11 administration
  - Testosterone collection was removed, as monitoring of testosterone level is not mandated for the patients with mHSPC receiving SoC
  - Clarification regarding rescreening procedure has been added "If a participant undergoes re-screening following screen failure, the results of assessments (including, but not limited to images) performed prior to a decision to rescreen the participant, may be used for rescreening as long as they were performed within protocol-predefined timelines"

- 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 and clarification added regarding the randomization in IRT. References to section have been updated.
- Section 8.2 Participants 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.
  - Clarification regarding stratification factor has been added.
  - Clarified that prostate cancer history should include also Gleason score at diagnosis, AJCC stage at diagnosis and extent of disease.
  - Clarification added for date and type of progression: "radiographic, metastasis to bone, Soft tissue"
  - Clarification added to "all other clinically important medical/ surgical interventions and medical conditions
- Section 8.3.1, Radiographic imaging for tumor assessment
  - Clarification made regarding the caveat outlined in the PCWG3 recommendations
  - "optimally identify at least 1 target lesion from each major site of metastatic spread, and up to 5 target lesions per site of metastatic spread in total, distinguishing pelvic from extrapelvic nodes, etc. as well as 2+2 rules for progression and assessment of bone disease"
  - Sites of "soft-tissue" disease will be characterized as either target or non-target lesions based on CT/MR images. The distribution of the target and non-target lesions should be representative of the participant's overall disease. Note, that for the purpose of the study a maximum of five (5) target lesions per site of metastatic spread (per PCWG3, disease site; 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 extraosseus 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 soft tissue component of bone metastasis 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 and should not be selected as target or non-target (except soft tissue component as described above) even when detectable on CT/MRI images.
- 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 8.3.1, Table 8-3
  - Alignment with the PCWG3 guidance, bone lesion reviewed based on Whole body bone scan technetium-99m labeled diphosphonates only, then removal of the Localized bone CT, MRI or X-ray in the table and the text, the note contraindication to CT intravenous contrast moved just below the table.
- Section 8.3.1, Baseline Imaging assessments,
  - Alignment with the PCWG3 guidance, bone lesion reviewed based on Whole body bone scan technetium-99m labeled diphosphonates only, then removal of the Localized bone CT, MRI or X-ray in the table and the text, the note contraindication to CT intravenous contrast moved just below the table. Removal of text already provided in other section of the protocol. Clarification regarding other methods that will not be used to evaluate disease burden at screening/baseline and will not be used to assess response.
- Section 8.3.1, Post-baseline imaging assessments
  - Addition of sentence “For “soft-tissue” disease, an additional confirmatory CT or MRI scan of chest, abdomen and pelvis is not mandated to confirm complete or partial response.
  - Clarification made regarding FDG-PET scan use “FDG-PET scans may be performed to compliment the documentation of radiographic progression but will not be used to determine radiographic progression.
  - Clarification added that the expedited review by BIRC is requested by investigator and the result provided to the site.

- Section 8.3.2 Symptomatic skeletal events
  - 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 8.3.3 Clinical Progression
  - Clarification that the clinical progression will be declared. Rewording of the last condition to be clearer: “For participant requiring palliative therapy within 12 weeks after randomization and beyond” replace “For participant requiring palliative therapy up to 12 weeks after 1st study treatment dose.
- Section 8.3.4 PSA levels
  - 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” per new protocol template version 4.0.
- Section 8.3.5 Appropriateness of efficacy assessments
  - Clarification to the PCWG3 and Addition of the references to the PCWG3 (Scher at al 2016).
- Section 8.4 Safety
  - 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 that limits or prevents on-site study visits, if participants cannot visit the site for protocol specified safety lab assessments, a, alternative lab (local) collection site may be used.
- Section 8.4 Table 8-4
  - Clarification added that Temperature needs to be recorded once during the visit prior treatment and addition of inches for the height and pounds for the weight.
- Section 8.4.1 Laboratory evaluation
  - Addition of reference to Table 8-2 and Table 8-6 for Hematology.
  - 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”.
  - Testosterone collection was removed, as monitoring of testosterone level is not mandated for the patients with mHSPC receiving SoC. Removal of reference to Table 8-4 .
- Section 8.4.1 Table 8-6
  - Additional of the title of the Table with Laboratory description.
  - Changes of the nomenclature of the laboratory based on new CDISC format (per new CTP template).
  - Testosterone collection was removed, as monitoring of testosterone level is not mandated for the patients with mHSPC receiving SoC
- Section 8.4.2 Electrocardiogram (ECG)

  - Clarification regarding the ECG to be done week 3 after last dose of ^{177}Lu-PSMA-617, that can be done as soon as feasible after last dose of ^{177}Lu-PSMA-617.
- Section 8.4.3 Pregnancy
  - Clarification added that recommendation is given for the male participant who are sexually active with women of child-bearing potential. 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. Addition that "Participant receiving standard of care treatment (ADT and ARDT) must follow contraceptive requirements as detailed in the local SmPC for the respective drug".
- Section 8.5.1 Additional Assessments
  - 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, that limits or prevents on-site study visits, COA data may be collected remotely (e.g. web portal, telephone interviews) depending on local regulations, technical capabilities, and following any applicable training in the required process".
- Section 8.5.1.4 Trial Feedback questionnaire
  - Clarification added that this is optional.
- [redacted]
- [redacted]
- [redacted]
- Section 8.5.3 [redacted]
- Section 9: Title modified to Discontinuation and completion per new protocol template version 4.0.
- Section 9.1: Title modified to Discontinuation from study treatment and from study per new protocol template version 4.0.
- Section 9.1.1: Title modified to Discontinuation from study treatment per new protocol template version 4.0.
- Situation when discontinuation of study treatment for a participant is considered to occur was updated for better clarity.
- Section 9.1.1.1 Follow up for safety evaluation

  - Clarification added “If on site safety visit is not possible, the site must put all effort to collect safety information remotely”.
- Section 9.1.2 Participant discontinuation from study: A new Section “Discontinuation from study” was introduced to define a situation when a participant is considered discontinued from study per new protocol template version 5.0.
- Section 9.1.2 Previous Section “Withdrawal of informed consent” was moved on Section 9.2 per new protocol template version 4.0. The deleted previous section “Withdrawal of consent was numbered as ‘Section 9.1.2’
- Section 9.1.4 Early study termination by sponsor: Previous Section 9.1.4 was moved to Section 9.4 per new protocol template version 4.0.
- Section 9.2 Title updated from “Withdrawal of informed consent” to “Withdrawal of informed consent and exercise of participants’ data privacy rights” per new protocol template version 5.0.
  - Guidance updated
- Section 10 Title updated from Safety monitoring and reporting to Safety monitoring, reporting and committees.
- Section 10.1.1 Adverse Events
- Drug interrupted/Withdrawn has been updated to Drug interrupted/permanently discontinued as per new protocol template version 4.0
- 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 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 change of the title of the Section from Additional Safety Monitoring to Committees
- Section 10.2.2 is updated from “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" to "The Executive Steering Committee (ESC) 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, and will integrate the responsibilities of the Steering Committee (SC). The ESC will provide scientific leadership for the study including but not limited to research activities, analysis of clinical trial data and its sharing through medical publications, ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The ESC will review protocol amendments as appropriate. Together with the clinical trial team, the ESC will also develop recommendations for publications of study results including authorship rules. The details of the role of the executive steering committee will be defined in the executive steering committee charter".

- Section 11.2 Database management and quality control
  - This section has been updated as pet protocol template version 4.0
- Section 12.1 Analysis set
  - [redacted]
- Section 12.4 Title change from "Analysis of the primary endpoint(s)/estimands(s)" to "Analysis supporting primary objectives" per new protocol template version 4.0.
- Section 12.4.1 Title change from "Definition of primary endpoint(s)/estimand(s)" to "Definition of primary endpoints" per new protocol template version 4.0.
- Section 12.4.2 Statistical model, hypothesis, and method of analysis
- High Volume disease definition has been clarified.
- Section 12.4.3 Title change from "Handling of remaining intercurrent events of primary estimand" to "Handling of intercurrent events of primary estimand" per new protocol template version 4.0.
- Section 12.4.5 Title change from "Sensitive analyses for primary endpoint/estimand" to "Sensitive analyses" per new protocol template version 4.0.
- Section 12.5 Title change from "Analysis of secondary endpoints/estimands" to "Analysis supporting secondary objectives" per new protocol template version 4.0.
- Section 12.5.1.2 Other secondary efficacy endpoints
  - Clarification on the definition of ORR, DCR, DOR and update on the timeframe for evaluation of PSA.
- Section 12.5.2 Safety endpoints
  - Update on the pretreatment period, on treatment period and post treatment period definition.
  - Clarification done on the Ga-PSMA-11 TEAE definition.

  - Updated of Vital Signs, 12-lead ECG and Clinical Laboratory evaluation subpart as per new protocol template version 4.0
- Section 12.6 Analysis exploratory endpoints
  - [redacted]
- Section 13.5 Participant Engagement added per new protocol template version 4.0
- Section 15 References

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- Section 16
  - Update of Appendix 3, PCWG3, The recommendations on baseline assessment. The criteria for radiographic response assessment. Deletion of PSA variable from Table 16-6.
  - Addition of Appendix 7, American Joint Committee on Cancer Prognostic Stage Grouping
  - Addition of Appendix 8, Prostate Cancer Grading System
  - Addition of Appendix 9, Study Specific Adjustments of Response Evaluation Criteria in Solid Tumor

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	CAAA617C12301
Full Title	PSMAddition: An International Prospective Open-label, Randomized, Phase III Study comparing ^{177}Lu-PSMA-617 in combination with Standard of Care, versus Standard of Care alone, in adult male patients with Metastatic Hormone Sensitive Prostate Cancer (mHSPC)
Brief title	An Open-label study comparing ^{177}Lu-PSMA-617 plus Standard of Care vs. Standard of Care in the Treatment of mHSPC
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the efficacy and safety of ^{177}Lu-PSMA-617 in combination with Standard of Care (SoC), versus Standard of Care alone, in adult male patients with mHSPC. Available data demonstrate that PSMA expression is nearly universal in unselected patients/tumors without prior exposure to hormonal therapy, as evidenced by multiple pathology studies accounting for thousands of patient samples plus the emerging wealth of PSMA imaging studies in the recurrent disease setting. Moreover targeting the Androgen Receptor (AR) pathway leads to radiosensitization. In multiple phase III trials in intermediate to high risk prostate cancer (PC), the combination of androgen deprivation with radiation therapy improved local control, distant metastases free survival, disease progression and overall survival (OS) when compared to radiation therapy alone. It is expected that there will be fewer genomic alterations that may lead to radiation-resistance (such as TP53) in the setting of mHSPC as opposed to Castrate Resistant Prostate Cancer (CRPC). Therefore PSMA-radioligand therapy (RLT) is hypothesized to be more effective in this setting. Androgen deprivation therapy (ADT) together with Androgen Receptor Directed Therapy (ARDT) may enhance the Deoxyribonucleic acid (DNA) damage induced by ^{177}Lu-PSMA-617 and improve the outcomes in patients with metastatic hormone-sensitive prostate cancer. To assess the treatment effect of ^{177}Lu-PSMA-617 in combination with SoC in patients with mHSPC approximately 1126 patients will be randomized into the study. Randomization will be stratified according to the following three factors: 1. Tumor Volume (as per CHAARTED study): high vs low, 2. Age ≥ 70 years (yes/no) • Patients less than 70 years of age are expected to derive incremental benefit (in terms of the time to event endpoints) over patients ≥ 70 years. 3. Previous or planned treatment (prostatectomy or radiation) to primary (prostate) tumor (Yes vs No) • The effect on time-to-event endpoints for patients having received prior definitive surgical or radiologic treatment to the prostate is expected to provide benefit that requires stratification. Note: If randomized to the investigational arm, intended treatment to the primary tumor should be delayed until the completion of ^{177}Lu-PSMA-617. If randomized to the control arm, intended treatment to the primary tumor should be performed within 6 months of randomization. Stratification by presence of high-volume disease, age and previously or planned treatment to primary tumor will support the analytic framework for pre-specified subgroup analyses in order to avoid arm-to-arm imbalances of factors known to effect primary and key secondary

	study outcomes. Assignment to treatment arm will be performed centrally following determination of eligibility.
Primary Objective(s)	The primary objective of this study is to evaluate radiographic progression free survival (rPFS) as assessed by Blinded Independent Review Committee (BIRC) in patients with mHSPC receiving Standard of Care and ^{177}Lu-PSMA-617 versus patients receiving Standard of Care without ^{177}Lu-PSMA-617.The primary clinical question of interest: what is the treatment effect based on rPFS for ^{177}Lu-PSMA-617 in combination with Standard of Care versus Standard of Care alone in the treatment of adult male patients with mHSPC as defined through inclusion/exclusion criteria, regardless of study treatment discontinuation (STD) or start of new antineoplastic therapy prior to rPFS event.
Secondary Objectives	Key Secondary objective: • To evaluate the contribution of ^{177}Lu-PSMA-617 to Standard of Care in terms of overall survival (OS) in patients with mHSPC. Other Secondary Objectives: • To evaluate PSA90 response at 12, 24 and 48 weeks • To evaluate the time to development of metastatic castration resistant prostate cancer (TTDm) as determined by investigators. • To evaluate Progression Free Survival (PFS) by investigator • To evaluate the second progression Free Survival (PFS2) by investigator • To evaluate the change in the nadir levels of PSA < 0.2 ng/mL at months 12, 24 and 48 weeks • To evaluate the overall response rate (ORR), disease control rate (DCR), time to response (TTR), duration of response (DOR) and Time to soft tissue progression (TTSTP) based on Prostate Cancer Working Group 3 (PCWG3)-modified Response evaluation criteria in solid tumor (RECIST) 1.1 by Blinded Independent Review Committee (BIRC) assessment • To evaluate safety and tolerability of ^{177}Lu-PSMA-617 • To assess the effect of ^{177}Lu-PSMA-617 on the health-related quality of life (HRQoL) • To evaluate the time to first symptomatic skeletal event (SSE).
Study design	In this international, open-label, prospective, phase III study, where approximately 1126 patients with treatment naïve or minimally treated PSMA-positive mHSPC will be randomized in a 1:1 ratio to receive Standard of Care (SoC) with or without the radioligand ^{177}Lu-PSMA-617. In this study, the combination for Androgen Receptor Directed Therapy + Androgen Deprivation Therapy are allowed as SoC. After patients randomized to the SoC alone (i.e., control) arm experience radiographic progression (the rPFS event) as confirmed by BIRC, they will be allowed to cross-over to receive ^{177}Lu-PSMA-617 +/- SoC per the discretion of the treating physician. If cross-over to ^{177}Lu-PSMA-617 is selected, then ^{177}Lu-PSMA-617 will be administered with the same dose/schedule as participants who were initially randomized to receive ^{177}Lu-PSMA-617.
Study population	The study population consists of adult male patients with mHSPC that are treatment naïve, or minimally treated with: • up to 45 days of luteinizing hormone-releasing hormone (LHRH) agonist/antagonists (ADT) or bilateral orchiectomy with or without first generation antiandrogen (e.g. bicalutamide, flutamide) for metastatic prostate cancer. If given, first generation antiandrogen must be discontinued prior to start of therapy. Time on first generation antiandrogen will not count towards the 45 day limit of LHRH analog exposure. • If received, prior LHRH agonist/antagonist use in the adjuvant/neoadjuvant setting must have been discontinued > 12 months prior to Informed Consent Form (ICF) signature AND must not have exceeded 24 months of therapy AND must not have shown disease progression within 12 months of completing adjuvant/neoadjuvant therapy.

	• Up to 45 days of CYP17 inhibitor or potent androgen receptor signaling inhibitor (ARDT) exposure for metastatic prostate cancer is allowed prior ICF signature. • No exposure to ARDT for earlier stages of prostate cancer is allowed. Approximately 1126 mHSPC patients will be randomized and stratified according to the following three factors: disease volume (high vs low), age ≥70 years (yes/no), and previous or planned treatment (prostatectomy or radiation) to primary (prostate) tumor (yes/no)
Key Inclusion criteria	1. Patients must have metastatic prostate cancer with histologically or cytologically confirmed adenocarcinoma (current or prior biopsy of the prostate and/or metastatic site) 2. Patients must be: • Treatment naïve -OR- • minimally treated with: • Up to 45 days of LHRH agonist /antagonists (ADT) or bilateral orchiectomy with or without first generation antiandrogen (e.g. bicalutamide, flutamide) for metastatic prostate cancer is allowed prior to ICF signature. If given, first generation antiandrogen must be discontinued prior to start of study therapy or after 45 days whatever happens first. • If received, prior LHRH agonist/antagonist with or without first generation antiandrogen use in the adjuvant/neo-adjuvant setting must have been discontinued > 12 months prior to ICF signature AND must not have exceeded 24 months of therapy AND must not have shown disease progression within 12 months of completing adjuvant/neo-adjuvant therapy. • Up to 45 days of CYP17 inhibitor or ARDT exposure for metastatic prostate cancer is allowed prior to ICF signature. • No CYP17 inhibitor or ARDT exposure for earlier stages of prostate cancer is allowed. 3. Patients must have an ECOG performance status of 0 to 2 4. Patients must be adults ≥18 years of age 5. Patients must have at least one metastatic bone and/or soft tissue/visceral lesion documented in the following manners within 28 days prior randomization: • Metastatic disease to the bone (in any distribution) visible on ^{99}Tc-MDP bone scintigraphy on either pre-ADT scans or baseline scans –AND/OR- • Lymph node metastases of any size or distribution. If lymph nodes are the only site of metastasis, then one node must be at least 1.5 cm in short axis AND outside of the pelvis –AND/OR- • Visceral metastases of any size or distribution. If a participant has a history of visceral metastases at any time prior to randomization, he should be coded as having visceral metastases at baseline (i.e., patients with visceral metastases prior to ADT that disappear at baseline will be counted as having visceral metastases and would therefore have high volume disease for stratification purposes). 6. Patients must have evidence of PSMA-positive disease as seen on a [^{68}Ga]Ga-PSMA-11 PET/CT scan, and eligible as determined by the sponsor's central reader 7. Patients must have adequate major organ function defined as : **Bone marrow reserve:** • Absolute Neutrophil Count (ANC) ≥1.5 x 10^9/L • Platelets ≥100 x 10^9/L • Hemoglobin ≥9 g/dL **Hepatic function:**

	• Total bilirubin ≤2 x the institutional upper limit of normal (ULN). • For patients 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 • Albumin ≥ 2.5 g/dL **Renal function:** • eGFR ≥ 50 mL/min/1.73m^2 using the Modification of Diet in Renal Disease (MDRD) equation
Key Exclusion criteria	1. Patients with rapidly progressing tumor that requires urgent exposure to taxane-based chemotherapy 2. Participant with CNS metastases that are neurologically unstable, symptomatic, or receiving corticosteroids for the purpose of maintaining neurologic integrity. Participants with epidural disease, canal disease and prior cord involvement are allowed if those areas have been treated, are stable, and not neurologically impaired. Patients with parenchymal CNS metastasis (or a history of CNS metastasis), that have received prior therapy and are neurologically stable, asymptomatic and not receiving steroids for CNS metastases, are allowed, baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast). 3. History of somatic or psychiatric disease/condition that may interfere with the objectives and assessments of the study 4. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression 5. Active clinically significant cardiac disease defined as any of the following: • New York Heart Association (NYHA) class 3/4 congestive heart failure within 6 months prior to ICF signature unless treated with improvement and echocardiogram or MUGA demonstrates EF > 45% with improvement in symptoms to class < 3. • History or current diagnosis of Electrocardiogram (ECG) abnormalities indicating significant risk of safety for participants in the study such as: 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), unstable angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to ICF signature. • History of familial long QT syndrome or known family history of Torsades de Pointe 6. Transfusion for the sole purpose of making a participant eligible for study inclusion
Study treatment	In this study, the term "Study Drug" indicates compound AAA617 (also known as lutetium (^{177}Lu) vipivotide tetraxetan and [^{177}Lu]Lu-PSMA-617, abbreviated to ^{177}Lu-PSMA-617), the radioligand imaging compound AAA517 (also known as gallium (^{68}Ga) gozetotide and [^{68}Ga]Ga-PSMA-11, abbreviated to ^{68}Ga-PSMA-11) used for imaging purposes during screening. In this protocol, the terms ^{177}Lu-PSMA-617 and the radioligand imaging compound ^{68}Ga-PSMA-11 will be used throughout the document. Background therapy: All participants randomized to the study (i.e., investigational and control arms) will receive Standard of Care based on Androgen Deprivation therapy (ADT) and Androgen Receptor Directed Therapies (ARDT). Androgen deprivation therapy (ADT) will be administered to all patients randomized to the study (both arms) on a continuous basis. Bilateral surgical orchiectomy, LHRH agonist, or LHRH antagonist are acceptable. ADT are approved drugs and will be provided locally by the study site, subsidiary or designee as commercially available, and as per local regulations. Please refer to the Local Package Insert for complete guidelines for administration and for safety monitoring guidelines.

	Change of ADT during the course of the study is allowed for the purpose of symptom management or optimal suppression of testosterone. The choice of ADT is at the discretion of the investigator. The Androgen-Receptor–Directed Therapies (ARDT) are approved drugs and will be provided locally by the study site, subsidiary or designee as commercially available, and as per local regulations. Please refer to the Package Insert for complete guidelines for dosage and administration, for contraception and for safety monitoring guidelines. Examples of ARDT include but are not limited to abiraterone acetate with prednisone, apalutamide, and enzalutamide. The choice of ARDT is at the discretion of the investigating physician. In the case of ARDT - related adverse events (AE) or intolerability, investigators should refer to the respective package insert for guidance on dose reductions. A single change in ARDT (e.g., abiraterone to enzalutamide) is allowed.
Treatment of interest	AAA617, also known as lutetium (^{177}Lu) vipivotide tetraxetan and [^{177}Lu]Lu-PSMA-617 or ^{177}Lu-PSMA-617
Efficacy assessments	• **Radiographic imaging for tumor assessment** Tumor response of soft tissue, lymph node, and visceral lesions to treatment will be assessed locally and centrally according to Novartis guideline version 3.2 (Appendix 2 Section 16.2) based on RECIST 1.1 (Eisenhauer et al 2009) with caveats outlined in the PCWG3 recommendations Scher et al. 2016 The modification used for this trial is limited to the periodicity of the scan schedule (i.e., q 12 weeks x 2 years, and q 16 weeks thereafter). Periodic radiographic imaging will include both: • CT with contrast/MRI imaging • Bone scans with technetium-99m labeled diphosphonates CT with contrast/ Magnetic resonance imaging (MRI) tumor assessments should include evaluations of the chest, abdomen, and pelvis. Disease progression by bone scan will be defined as at least 2 new bone lesions at the first on-treatment scan (i.e., the week 12 scan), with at least two additional lesions on the next (confirmatory) scan (2+2 PCWG3 criteria). For scans after the week 12 scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan (2+2 PCWG3 criteria). If the second scan confirms the metastases, then the date of progression is the date of the scan when the first 2 new metastases were documented. Radiologic assessments are to be performed every 12 weeks [redacted] from [redacted] (as defined in Section 8.3.1) for the first 24 months (independent of dose delays, and premature discontinuation for any other reasons than Disease progression, lost of follow-up or withdraw consent), then every 16 weeks [redacted] and at End of Treatment (EOT/EOT2) Visit if the last scan was done more than 12 weeks (for patients in the study for less than 24 months), or more than 16 weeks (for patient in the study for more than 24 months). The disease progression will be assessed via blinded centralized review of radiographic images provided by the treating physician for participants randomized in either arm. • **Symptomatic skeletal event** 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. • **Clinical Progression** Clinical progression will be assessed by the investigator and will be declared when a participant has met at least one of the following criteria used to determine unequivocal evidence of clinical progression: - Marked escalation in cancer-related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy

	- Immediate need for initiation of new anticancer treatment, surgical, or radiological intervention for complications due to tumor progression even in the absence of radiological progression - Marked deterioration in ECOG performance status to ~ Grade 3 and a finding of the investigator that the deterioration indicates clinical progression - Other clinically meaningful deterioration in a patient condition, even in the absence of radiological progression, when in the opinion of the investigator, it is in the best interest of the participant to discontinue treatment due to clinical progression • **PSA level** Central lab will measure PSA levels. Increases and decreases will be tracked to assess PSA responses as per PCWG3
Other assessments	[redacted]
Data analysis	**Analysis of the primary endpoint(s) / estimand(s)** The primary endpoint is radiographic progression-free survival (rPFS). **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 + SoC arm versus SoC 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. tumor volume (high vs low volume), age≥70 years (yes/no), Previous or planned treatment (prostatectomy or radiation) to primary (prostate) tumor (yes/no). High-volume disease defined as presence of visceral metastases and/or at least four bone lesions with at least one lesion outside of the vertebral bodies and pelvis (CHAARTED). The primary efficacy variable, rPFS, will be analyzed at the interim analyses (IA) and final analysis of a group sequential design, using a [redacted] function. Analyses will be based on the Full Analysis Set (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 (CI) 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 first interim rPFS analysis is performed to determine non-binding futility at approximately [redacted] rPFS events ([redacted] information fraction). If the study continues to the 2nd IA for rPFS, it will be performed when approximately [redacted] rPFS events ([redacted] information fraction) have been documented. If the study continues to the final rPFS analysis, the final rPFS analysis will be performed when approximately [redacted] rPFS events have been documented. **Analysis of secondary endpoints / estimands** **Key secondary estimand** OS is defined as the time from date of randomization to date of death due to any cause.

	If a participant is not known to have died, then OS will be censored at the latest date the participant was known to be alive (on or before the cut-off date). 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 + SoC arm versus SoC 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. A three-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 to determine efficacy will be at the time of second interim for rPFS analysis. At this time, approximately [redacted] deaths (i.e. approximately [redacted] information fraction) are expected to have been recorded in the clinical database. If rPFS is statistically significant at this stage, OS will also be tested. If rPFS is not statistically significant at this stage, then OS will not be tested. If OS is not statistically significant at the first OS interim analysis, the second OS analysis will be planned at the time of final analysis for rPFS. At this point, approximately [redacted] deaths (i.e. approximately [redacted] information fraction) have been recorded in the clinical database. If rPFS is statistically significant at this stage, OS will also be tested. If rPFS is not statistically significant at the time of final rPFS analysis, then OS will not be tested. If OS is not statistically significant at this stage, a final analysis is planned at the time when approximately [redacted] deaths have been recorded. 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.
Key words	^{177}Lu-PSMA-617, ARDT, ADT, mHSPC, rPFS, PSMA

1 Introduction

1.1 Background

An estimated 1.3 million new cases of prostate cancer (PC) and 359,000 cancer deaths were attributed to PC in 2018 worldwide (International Agency for Research on Cancer 2018) and a majority of patients who die of prostate cancer will pass through the metastatic hormone sensitive prostate cancer (mHSPC) phase of the disease. Historically mHSPC has been treated, since the discovery of its hormone dependence in the 1940s, with surgical or medical castration resulting in frequent and rapid palliative benefits and a presumptive improvement in cancer-specific and overall survival. Attempts to improve survival and quality of life have included, but have not been limited to, earlier use of androgen deprivation therapy (ADT) for asymptomatic advanced disease, use of traditional antiandrogens to achieve combined androgen blockade (Prostate Cancer Trialists' Collaborative 2000), intermittent androgen therapy (Hussain et al 2013), early bisphosphonate use (Dearnaley et al 2009, James et al 2016b, James et al 2016a, Smith et al 2014), gonadotropin releasing hormone antagonists, targeted biologic agents (Yu et al 2015) and radiopharmaceuticals (Bilen et al 2014, James et al 2016a) with either absent, limited or controversial success.

Combination of Androgen Deprivation Therapy (ADT) and Androgen Receptor Directed Therapy (ARDT) in mHSPC

CYP17 (17 alpha-hydroxylase/C17,20-lyase) is an enzyme that is involved in the synthesis of testosterone, and found in the testes, adrenal glands, and in prostate tumors. Abiraterone is a selective, irreversible, inhibitor of the CYP17 enzyme. The addition of abiraterone and low dose prednisone to ADT represents the most commonly prescribed initial treatment of mHSPC currently in the U.S (Prostate Cancer Trialists' Collaborative 2000). The addition of abiraterone to androgen deprivation therapy in patients with metastatic castration resistant prostate cancer (mCRPC) pre- and post-docetaxel improved survival (de Bono et al 2011, Ryan et al 2013). More recently, the results of LATITUDE were presented and published and showed a major benefit to overall survival for the concurrent administration of abiraterone and prednisone with ADT. In the LATITUDE trial, the overall survival rate at 3 years was 66% in the abiraterone group and 49% in the placebo group. The relative risk of death was 38% lower (HR=0.62; $p<0.001$) in the abiraterone group than in the placebo group, which was similar in efficacy to that observed with the CHAARTED trial evaluating the addition of docetaxel chemotherapy to ADT (HR 0.61) (Fizazi et al 2017). The toxicity of concurrent abiraterone and androgen deprivation therapy was acceptable with the number of serious adverse events (SAE) similar in the two groups. Grade 3 or greater mineralocorticoid-related toxic effects such as hypertension and hypokalemia occurred at a rate of 20% and 10.8% respectively. The STAMPEDE abiraterone trial demonstrated a similar benefit in overall survival with the addition of abiraterone and prednisone to androgen deprivation therapy in patients with castration-sensitive disease (HR=0.61, $p<0.001$). The addition of abiraterone and prednisone also decreased treatment failure by 71% ($p<0.001$) (James et al 2017). Treatment was well tolerated with the

main adverse events over and above standard of care androgen deprivation therapy consisting of hypertension, mild increases in aminotransferase levels, and respiratory disorders.

Enzalutamide, apalutamide, and darolutamide are potent androgen-receptor signaling inhibitors with proven efficacy for castration-resistant prostate cancer. (Beer TM et al, Fizazi et al 2019a, Hussain et al 2018, Scher et al 2012,Smith et al 2018). In the ARCHES trial, the addition of enzalutamide to ADT (with or without prior docetaxel) has demonstrated efficacy as measured by radiographic progression-free survival in men with mHSPC (Armstrong et al 2019). Enzalutamide added to ADT (17.9% also received docetaxel) led to a 61% reduction in risk of radiographic progression (HR, 0.39; 95% CI, 0.30 to 0.50) and demonstrated prolonged time to prostate specific antigen (PSA) progression, improved undetectable PSA, and improved objective response. In the ANZUP cooperative group ENZAMET study, the addition of enzalutamide to ADT with or without docetaxel led to improved progression-free and overall survival versus the same therapy with older antiandrogens (Davis et al 2019). Enzalutamide improved the risk of all-cause mortality by 33% [HR 0.67, 95% CI 0.52-0.86, p=0.002]. Similarly, in the TITAN study, apalutamide added to ADT (with or without docetaxel) led to an improvement of both radiographic progression-free survival and overall survival in men with mHSPC (Chi et al 2019). Apalutamide also led to a 33% improvement in overall survival in this population [HR 0.67, 95% CI 0.51-0.89, p=0.005].

Prostate specific membrane antigen (PSMA) and PSMA-targeted radionuclide therapy

Prostate cancer is a radiosensitive disease. Radiation is a validated treatment with potential curative benefit for men with clinically localized PC and is also beneficial in the palliation of metastases. Sm-153 and Sr-89 are β-emitting radiopharmaceuticals approved for palliation of painful bony metastases (Porter et al 1993, Sartor et al 2004) and more recently, radium-223 dichloride was approved based upon a survival benefit. (Parker et al 2013, Sartor et al 2014). Because these “unsealed” radiation sources (153Sm, 89Sr, 223Ra) target sites of increased bone metabolism and turnover (i.e. they do not directly target tumor), the utilization of a more targeted radionuclide therapy (TRT) directly to tumor cells is preferred.

One molecular target for TRT is the PSMA. PSMA is an ideal PC target because:

- it has limited expression in "normal" tissue,
- it is expressed by 90 +/-5% of all PCs,
- it is expressed at high levels on the tumor cell plasma membrane, and
- PSMA functions as an internalizing cell surface receptor. (Liu et al 1998, Silver et al 1997)

According to in vivo animal studies (human prostate cancer xenograft models), pharmacological inhibitors of androgen receptors might antagonize androgen-dependent PSMA suppression. It was demonstrated that PSMA is repressed by androgen treatment in multiple models of AR-positive prostate cancer in an AR-dependent manner. Conversely, antiandrogens (AA) increase PSMA expression, and it results in larger overall upregulation Evans et al 2011. In the human castration resistant prostate cancer cell line, exposure to abiraterone acetate

resulted in eightfold higher uptake of ^{68}Ga-labelled PSMA-HBEDCC indicative to PSMA expression, additional withdrawal of external testosterone increased the uptake up to tenfold. The increase of PSMA expression upon ADT and AA treatments was confirmed by qPCR and Western blot data Meller et al 2015. It was also described that treatment with enzalutamide and abiraterone amplified PSMA expression gradually and the PSMA level returned to its baseline expression after halt Murga et al 2015.

Therefore, viable (resistant) cells following anti-AR therapy commonly have upregulated PSMA expression, increasing its relevance and utility as a target in the current study. While there are reports of PSMA negative tumors in the setting of heavily pre-treated mCRPC, expression is universal in castration-naïve disease.

Stimulated by results with radioligand targeting of the somatostatin receptor in neuroendocrine cancers, physicians predominantly in Germany began using small molecule ligands (PSMA enzymatic inhibitors) that bind PSMA to deliver ^{177}Lu J591 and other radionuclides to tumors (radioligand therapy, RLT) (Haberkorn et al 2016). While various different peptide-linker chelates have been used, the most commonly used agent has been PSMA-617 (a.k.a. Deutsches Krebsforschungszentrum DKFZ-PSMA-617). A number of patients with mCRPC have been treated and demonstrated PSA declines, diminished uptake on post-treatment PSMA imaging, and some reports of pain reduction. These initial reports indicated relatively minimal toxicity. However, the initial reports were retrospective or anecdotal experiences, no standardized dosing or scheduling was developed, and patient follow up was of a short duration.

The results of the first prospective studies using [^{177}Lu]Lu-PSMA-617 in progressive mCRPC were published (Hofman et al 2018). Australian investigators enrolled 43 men with mCRPC and treated 30 (7 excluded due to imaging results, 6 others for eligibility issues). Following PSMA and FDG Positron emission tomography (PET)/CT, participants received 4-8 Gigabecquerel (GBq) of ^{177}Lu-PSMA-617 and were planned to receive 4 doses every 6 weeks. Seventeen (57%) had at >50% PSA decline with median PFS 6.3 and OS 12.7 months and acceptable toxicity. In a trial expansion with longer follow up, 50 patients were treated with median follow up of 31.4 months (Violet et al 2020). Thirty two (64%) had at least 50% PSA decline and 15 of 27 (56%) with measurable disease had objective response by RECIST. Median overall survival 13.3 months (95% CI, 10.5-18.7 mo). Low grade xerostomia was reported in 55% and nausea in 26.7% with grade 3-4 thrombocytopenia in 26.7%. An additional study tested dose-escalation of ^{177}Lu-PSMA-617 in a fractionated dose schedule (Tagawa et al 2018). No dose-limiting toxicity was observed despite escalating to a cumulative dose of 22.2 GBq per cycle (delivered day 1 and day 15). Without selection for PSMA expression, 70% had any PSA decline (44.5% with >50% PSA decline), median PFS was 5.5 month and median OS was16 months. Updated data including additional patients in the phase II cohort confirm the safety of the dose-intense regimen with 61% of patients unselected for PSMA expression with >50% PSA decline (71.4% at recommended phase II dose) (Tagawa et al 2019). An additional prospective dataset is now available from a pilot study of 14 men in Australia (Emmett et al 2019).

The results of two randomized trials with PSMA-617 in men with late stage mCRPC were published:

VISION (NCT03511664), a phase III trial evaluating best standard of care with or without ^{177}Lu-PSMA-617 (INN (International Non-Proprietary Name) lutetium (^{177}Lu) vipivotide tetraxetan) 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 (^{68}Ga)–labeled PSMA-11 (INN gallium (^{68}Ga) gozetotide) 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 end points were objective response, disease control, and time to symptomatic skeletal events. ^{177}Lu-PSMA-617 plus standard care significantly prolonged, 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 patients (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. In both arms, grade 3 or higher AEs were relatively infrequent (< 5.0% in any arms) except for anemia (12.9% vs. 4.9%), thrombocytopenia (7.9% vs.1.0%), lymphopenia (7.8% vs. 0.5%) and fatigue (5.9% vs. 1.5%) in the ^{177}Lu-PSMA-617 group and the control group, respectively (Sartor et al 2021)

Additionally, ^{177}Lu-PSMA-617 plus standard care 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 (Fizazi et al 2021). TheraP (NCT03392428), a randomized phase II trial of ^{177}Lu-PSMA-617 versus cabazitaxel with a PSA50 response primary endpoint conducted in Australia. In this prospective phase II study, 200 patients with PSMA-expressing mCRPC who had prior docetaxel chemotherapy and were permitted to have abiraterone or enzalutamide were enrolled to one of two arms, stratified by disease burden (>20 sites vs ≤20 sites as measured on ^{68}Ga -PSMA-11 PET/CT), prior

enzalutamide or abiraterone treatment, and study site. Patients were randomized in a 1:1 ratio to receive either ^{177}Lu-PSMA-617 or cabazitaxel. The standard treatment group (Arm A) received cabazitaxel, given i.v. every 21 days at a dose of 20 mg/m^2, for up to a maximum of 10 cycles. Prednisolone 10 mg orally daily was administered throughout treatment with cabazitaxel. The experimental treatment group (Arm B) received ^{177}Lu-PSMA-617, administered by slow i.v. injection every 6 weeks. Treatment was administered for up to a maximum of six cycles. For each patient, the administered activity started at 8.5 GBq in Cycle 1, and was to be reduced by 0.5 GBq per cycle if there were no dose-limiting toxicities requiring additional dose reduction. All patients underwent screening imaging with ^{18}F-fludeoxyglucose (FDG) and ^{68}Ga-PSMA-11 PET/CT scans, in addition to staging bone scan and CT of chest, abdomen, and pelvis.

Two-hundred of 291 screened men were randomized to ^{177}Lu-PSMA-617 (N=99) or cabazitaxel (N=101). Seventeen men withdrew or died before receiving study treatment (^{177}Lu-PSMA-617 1 patient and cabazitaxel 16 patients). All patients were treated with docetaxel prior to randomized treatment. In both arms, 91 patients (92% ^{177}Lu-PSMA-617 and 90% cabazitaxel) had also received either abiraterone or enzalutamide.

The PSA50 response rate (decline ≥ 50%) was higher in those assigned ^{177}Lu-PSMA-617 than cabazitaxel (65/99 [66%; 95%CI 56-75] vs 37/101 [37%; 95%CI 27-46]; P<0.001). At a median follow-up of 13.3 months, preliminary results showed ^{177}Lu-PSMA-617 significantly improved PSA-PFS (HR 0.69, 95%CI 0.50-0.95, P=0.02; 157 events of the required 170 pre-specified events). Efficacy results were similar when analyses were restricted to the per-protocol treated men. OS data remains immature (71 deaths).

Grade 1-2 adverse events occurred in 53% of ^{177}Lu-PSMA-617 treated men vs 40% of cabazitaxel treated men. Grade 3-4 adverse events occurred in 35% of ^{177}Lu-PSMA-617 treated men vs 54% of cabazitaxel treated men. Grade 3-4 neutropenia was higher in the cabazitaxel arm (13%) as compared to the ^{177}Lu-PSMA-617 arm (4%). However, Grade 3-4 thrombocytopenia was higher in the ^{177}Lu-PSMA-617 (11%) as compared to the cabazitaxel arm (0%). There were 5 Grade 5 AEs for cabazitaxel and 11 Grade 5 AEs for ^{177}Lu-PSMA-617 (none were treatment related). Discontinuations for toxicity occurred in 1/98 (1%) ^{177}Lu-PSMA-617-treated vs 3/85 (4%) cabazitaxel-treated.

Given these findings, significant rationale exists to study the use of PSMA RLT in the setting of hormone-sensitive disease. Firstly, available data demonstrate that PSMA expression is nearly universal in unselected tumors prior to patient treatment with hormonal therapy, as evidenced by multiple pathology studies accounting for thousands of patient samples plus the emerging wealth of PSMA imaging studies in the recurrent disease setting (Bostwick et al 1998, Hope et al 2017, Schmittgen et al 2003, Sweat et al 1998). Secondly, targeting the AR pathway leads to radiosensitization. In multiple phase III trials involving patients with intermediate to high-risk prostate cancer, the combination of androgen deprivation with radiation therapy improved local control, distant metastases free survival, disease progression and overall survival when compared to radiation therapy alone (Bolla et al 2010, Warde et al 2011). Androgen deprivation therapy forms the therapeutic anchor for care in patients with hormone-sensitive metastatic prostate cancer. Activation of the androgen receptor signaling pathway

promotes resolution of DNA breaks induced by radiation therapy and leads to radioresistance. Blockade of this androgen receptor signaling pathway with androgen deprivation therapy inhibits DNA strand break repair sensitizing prostate cancer cells and tumors to radiation therapy (Goodwin et al 2013, Polkinghorn et al 2013). In the current study, the combination of ADT, ARDT and ^{177}Lu-PSMA-617 will be studied. ADT together with ARDTs may enhance the DNA damage induced by ^{177}Lu-PSMA-617 and improve the outcomes in patients with metastatic hormone-sensitive prostate cancer (mHSPC). Thirdly, it is expected that there will be fewer genomic alterations that may lead to radiation-resistance (such as TP53) in the setting of mHSPC as opposed to CRPC. Therefore PSMA-RLT is hypothesized to be more effective in this setting.

An increasing number of both academic and community centers are able to administer radionuclide therapy. While Sm-153 and Sr-89 were used occasionally for palliation, the introduction of Ra-223 led to widespread use of therapeutic radionuclides in the clinical prostate cancer setting. The approval of ^{177}Lu-dotatate (LUTATHERA®), brought radio ligand therapy (also known as targeted radionuclide therapy or peptide receptor radionuclide therapy) to many academic and community centers.

^{177}Lu-PSMA-617 is approved in the US, Canada and United Kingdom names 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.

^{68}Ga-PSMA-11 is approved in several countries, including the United States, Great Britain and the European Union 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. Centers from around the world have published their clinical experience with ^{68}Ga-PSMA-11 in patients with prostate cancer, resulting in numerous prospective and retrospective studies including data from over 4500 patients (Crocerossa et al 2021). Despite the multiple and various uses of ^{68}Ga-PSMA-11, and although literature is extensive, safety data reported in the literature is scant, though suggestive that no specific safety issues were encountered during the >10 years of clinical use.

The combination of ADT and abiraterone/prednisone or enzalutamide with the beta particle emitter ^{177}Lu-PSMA-617 has been utilized anecdotally in Europe without reported safety concerns. In addition, in the phase III VISION study, participants were randomized to best standard therapy (which most often includes potent ARDTs) with or without ^{177}Lu-PSMA-617 and the Data Safety Monitoring Board (DSMB) has not identified any significant safety concerns, allowing the study to continue to date. External beam radiation has been utilized in many studies with concurrent ADT/ARDT. The most common toxicities of the main agents are largely non-overlapping. While a study with concurrent initiation of abiraterone with prednisone plus the alpha particle emitter Ra-223 had both safety and efficacy problems and

recent safety data from the PEACE3 study of concurrent enzalutamide plus Ra-223 also demonstrated a higher fracture rate with the addition of Ra-223 (though current studies with radium and docetaxel continue). Targeting of PSMA with PSMA-617, rather than hydroxyappetite, as was the case in the radium studies, is not expected to lead to any additional fractures.

The study population, has been selected to mimic and build upon the CHAARTED (Sweeney et al 2015) and LATITUDE (Fizazi et al 2017) trial populations, which together with STAMPEDE (James et al 2016b) established escalated up-front increased-potency therapy as the standard of care for men with mHSPC. Data from ARCHES (Armstrong et al 2019), ENZAMET (Boegemann 2020), and TITAN (Agarwal et al 2019) have further demonstrated the efficacy of the approach adding ARDT to initial ADT.

An early and pronounced beneficial effect on prostate cancer related morbidity and death is expected with associated salutary impacts on symptomatic skeletal events, quality of life and survival outcomes. Stratification by presence of high volume disease (CHAARTED), age, and presence or absence of an untreated primary tumor will support the analytical framework for pre-specified subgroup analyses. Since all patients will receive ADT as best supportive care, the potential synergies between ARDT and radiation from ^{177}Lu-PSMA-617, due to the increased expression of the PSMA target after treatment with ARDT, can be maximally exploited.

1.2 Purpose

The purpose of this study is to evaluate the efficacy and safety of ^{177}Lu-PSMA-617 in combination with Standard of Care, versus Standard of Care alone, in adult male patients with mHSPC.

In this study, the SoC is defined as a combination of Androgen Receptor Directed Therapy + Androgen Deprivation Therapy.

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 radiographic progression free survival (rPFS) as assessed by Blinded Independent Review Committee (BIRC) in patients with mHSPC receiving Standard of Care and ^{177}Lu-PSMA-617 versus patients receiving Standard of Care without ^{177}Lu-PSMA-617.	• 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 (BIRC) and as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death due to any cause
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Key Secondary objective:	• Overall survival is defined as the time from the date of randomization to the date of death due to any cause

Objective(s)	Endpoint(s)
To evaluate the contribution of ^{177}Lu-PSMA-617 to Standard of Care in terms of overall survival (OS) in patients with mHSPC.	
• To evaluate PSA90 response at 12, 24 and 48 weeks	• PSA90 response is defined as the proportion of patients who have a ≥90% decrease in PSA from baseline that is confirmed by a second (the next) PSA measurement ≥4 weeks later. • PSA90 at 12, 24 and 48 weeks will be evaluated.
• ·To evaluate the time to development of metastatic castration resistant prostate cancer (mCRPC) as determined by investigators.	• Time to development of mCRPC is defined as the time from date of randomization to disease progression despite androgen deprivation therapy (ADT) presenting as either a continuous rise in serum prostate specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases.
• To evaluate Progression Free Survival (PFS)	• PFS is defined as the time from date of randomization to the date of first documented progression by investigator assessment (radiographic progression, clinical progression, PSA progression) or death from any cause, whichever occurs first
• To evaluate the second progression Free Survival (PFS2)	• PFS2 is defined as time from date of randomization to the first documented progression by investigator assessment (radiographic progression, clinical progression, PSA progression) on next-line therapy or death from any cause, whichever occurs first.
• To evaluate the change in the nadir levels of PSA < 0.2 ng/mL at 12, 24 and 48 weeks	• Proportion of patients with PSA < 0.2 ng/mL at 12, 24 and 48 weeks
• To evaluate the overall response rate (ORR), disease control rate (DCR), time to response (TTR), duration of response (DOR) and Time to soft tissue progression (TTSTP) based on PCWG3-modified RECIST 1.1 by Blinded Independent Review Committee (BIRC) assessment.	• ORR, DCR, TTR, DOR, TTSTP based on PCWG3-modified RECIST 1.1 by BIRC. Details of the definitions of endpoints is provided in Section 12.5.1.2.
• To evaluate safety and tolerability of ^{177}Lu-PSMA-617	• Safety: incidence and severity of AEs and serious adverse event (SAE)s, changes in laboratory values, vital signs and ECGs. Any clinically significant lab, vital signs, ECG abnormalities will be captured as an AE. • Tolerability: dose interruptions, reductions and dose intensity
• To assess the effect of ^{177}Lu-PSMA-617 on the health-related quality of life (HRQoL) • TTPP • Time to definitive deterioration • Time to pain improvement response after initial pain worsening	• HRQoL as assessed by Functional Assessment of Cancer Therapy Prostate (FACT-P), Brief Pain Inventory (Short Form (BPI-SF) and European Quality of Life (EuroQol) 5 Domain 5 Level scale (EQ-5D-5L)
• To evaluate the time from the date of randomization to the date to first symptomatic skeletal event (SSE).	• 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,

Objective(s)	Endpoint(s)
	requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first
[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.

The primary clinical question of interest: what is the treatment effect based on rPFS for ^{177}Lu-PSMA-617 in combination with Standard of Care versus Standard of Care alone in the treatment of adult male patients with mHSPC as defined through inclusion/exclusion criteria, regardless of study treatment discontinuation or start of new antineoplastic therapy prior to rPFS event.

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 adult male patients with mHSPC defined through inclusion/exclusion criteria. Further details about the population are provided in Section 5.
2. Variable/endpoint: rPFS defined as the time from the date of randomization to the date of first documented radiographic disease progression as assessed by BIRC and as defined by modified PCWG3 criteria or death from 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 in combination with Standard of Care regardless of subsequent anti-neoplastic treatment. The control treatment is Standard of Care alone regardless of being followed by any anti-neoplastic therapy as needed. Further details about the investigational treatment and control treatment is provided in Section 6.
4. Intercurrent events:
   - discontinuation of study treatment for any reason

- start of new anti-neoplastic therapy prior to radiographic disease progression or death

Details on handling of intercurrent events are provided in Section 12.4.3.

The summary measure is rPFS hazard ratio (^{177}Lu-PSMA-617 in combination with Standard of Care versus Standard of Care alone) along with 95% confidence interval (CI) in the targeted population, estimated using 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

The key secondary clinical question of interest: what is the treatment effect based on OS for ^{177}Lu-PSMA-617 in combination with Standard of Care versus Standard of Care alone in adult male patients with mHSPC as defined through inclusion/exclusion criteria regardless of study treatment discontinuation or start of new antineoplastic therapy?

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 not accounting for the impact of cross-over. Further details can be found in Section 12.

The key secondary estimand is described by the following attributes:

1. Population: the same population as that of the primary estimand.
2. Variable/endpoint: OS defined as the time from the date of randomization to the date of death due to any cause. Further details on OS are provided in Section 12.5.1.1.
3. Treatment of interest: same as that of the primary estimand.
4. Intercurrent events:
   - discontinuation of study treatment for any reason
   - start of new anti-neoplastic therapy prior to radiographic progression or death
   - cross-over to ^{177}Lu-PSMA-617 in combination with Standard of Care arm for patients in the Standard of Care alone arm

Details on handling of intercurrent events are provided in Section 12.5.1.1.

The summary measure is OS hazard ratio (^{177}Lu-PSMA-617 in combination with Standard of Care versus Standard of Care alone) along with 95% CI in the targeted population, estimated using 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

In this international, open-label, prospective, phase III study, where approximately 1126 patients with treatment naïve or minimally treated PSMA-positive mHSPC will be randomized in a 1:1 ratio to receive Standard of Care (SoC) with or without the radioligand ^{177}Lu-PSMA-617.

The primary objective of the study is to determine whether the combination of ^{177}Lu-PSMA-617 + SoC improves rPFS over that obtained by administration of SoC alone in mHSPC patients. The randomization will be stratified according to the following three factors:

Randomization will be stratified on disease volume (high v low), age ≥70 years (yes/no), and on Previous or planned treatment (prostatectomy or radiation) to primary (prostate) tumor (yes/no).

Screening

Participants must sign an informed consent form (ICF) prior to any study specific screening evaluations. All screening procedures must be completed within 28 days prior to the randomization.

During screening, patients will be scanned with ^{68}Ga-PSMA-11 to identify PSMA expression status. Screening blood samples (including chemistry, hematology and coagulation) must be collected before the ^{68}Ga-PSMA-11 administration. It is recommended that the ^{68}Ga-PSMA-11 scan is performed once all other eligibility requirements are confirmed.

Screening assessment is defined as the last available assessment on or before the date of ^{68}Ga-PSMA-11 dosing.

Baseline assessment is defined as the last available assessment on or before the date of start of randomized treatment.

Participants with evidence of PSMA-"positive" (i.e., expressing) tumors will be allowed to enter the study when they meet criteria for PSMA positivity and eligibility with relation to ^{68}Ga-PSMA-11 PET/CT scan as confirmed by BIRC. PSMA expression qualification will be determined by the BIRC central readers.

Criteria for ^{68}Ga-PSMA-11 Positivity are based on the visual assessment, as follows:

- A participant will be judged positive if at least one distant metastatic lesion in any region is visually positive (presuming that if liver lesions are present, they are not all ^{68}Ga -PSMA-11 PET negative)
- A visually PET positive lesion is a lesion that shows a greater uptake intensity compared to background liver uptake for that participant

Eligibility Criteria with Relation to ^{68}Ga-PSMA-11 PET/CT:

- There must be at least one (1) ^{68}Ga-PSMA-11 PET positive distant metastatic lesion in order for a participant to be deemed eligible. Note: distant metastatic lesions include soft tissue lesions (including, but not limited to, extra-pelvic lymph nodes and visceral disease) and bone lesions. Primary tumor spread (e.g., Stages T3a and T3b when the tumor extends outside of the prostate, spreads to the seminal vesicles, respectively, stage T4 when the tumor spreads to the nearby tissues/organs such as bladder, rectum, the pelvic wall) and/or local relapse within pelvis, regional metastases in pelvic lymph nodes are not considered distant metastatic disease.

- If all present liver metastases are ^{68}Ga-PSMA-11 PET negative, the participant will be deemed ineligible.

Following completion of all required screening procedures and verifying participant eligibility, the participant will be randomized via the interactive response technology (IRT) system.

For patients randomized to the ^{177}Lu-PSMA-617 arm, at least 6 days must have transpired from the date of the ^{68}Ga-PSMA-11 scan to the start of treatment with ^{177}Lu-PSMA-617.

Prior Treatment

Prior treatment allowed are described in Section 5.

On-Study Treatment

For all patients:

- Up to 45 days of LHRH agonist/antagonists is allowed prior to ICF signature. If patient did not start the ADT prior randomization, ADT should start as soon as possible and ideally no later than 2 weeks after randomization.
- Up to 45 days of ARDT is allowed prior ICF signature. If patient did not start the ARDT prior randomization, ARDT should start as soon as possible and ideally no later than 2 weeks after randomization. Patients will receive ARDT as per label instructions/ local standards.

The participants are allowed to receive up to 45 days of 1st generation antiandrogens before randomization; 1st generation antiandrogens must be stopped after maximum of 45 days, or before randomization, or 1st dose of ARDT whichever comes first.

Participants randomized to the investigational arm (i.e. SoC+^{177}Lu-PSMA-617): Patients will receive SoC as per label instructions/local standards, after randomization, if not started earlier and in the time frame allowed by the protocol. Patients must begin ^{177}Lu-PSMA-617 dosing within [redacted] after randomization or as soon as possible after the product is received. ^{177}Lu-PSMA-617 is administered at the dose of 7.4 GBq (±10%), once every 6 weeks (±1 week) for a planned 6 cycles. For further information about study treatment, refer to Section 6.1.

Patients randomized to the control arm will begin receiving SoC as per label instructions/local standards after randomization, within [redacted], if not started earlier and in the time frame allowed by the protocol. The same will apply to initiation of SoC treatment in the patients randomized to the investigational arm.

The primary endpoint of rPFS will be assessed by a centralized blinded image review committee (i.e., BIRC) using radiographic images provided by the treating physician.

An end of treatment (EOT) visit will be performed when participants permanently discontinue study treatment as described in Section 9.1.1.

A participant may choose to discontinue the treatment and follow-up components of the study at any time. If a patient withdraws consent for the treatment component of the study, all efforts

should be made to ensure the participant will continue to be followed in the post-treatment follow-up period, or in the survival follow-up period, unless they specifically withdraw consent.

Cross-over period

After patients randomized to the SoC alone (i.e., control) arm experience radiographic progression (the rPFS event) as confirmed by BIRC, they will be allowed to cross-over to receive ^{177}Lu-PSMA-617 +/- SoC per the discretion of the treating physician. If cross-over to ^{177}Lu-PSMA-617 is selected, then ^{177}Lu-PSMA-617 will be administered with the same dose/schedule as participants who were initially randomized to receive ^{177}Lu-PSMA-617 as described above. For more details see Section 6.1.5.2.

Study cross-over participants for whom ^{177}Lu-PSMA-617 is discontinued must have a second End of Treatment (EOT2) visit performed ≤ 7 days and enter the Post-treatment Follow-up as per the assessment indicated in Table 8-2.

Post-Treatment Follow-Up (Safety, Efficacy)

After discontinuation of study treatment, all participants will be followed for safety with a 30-day safety follow-up visit (FUP) as well as longer term safety follow-up assessments for a period of approximately 12 months.

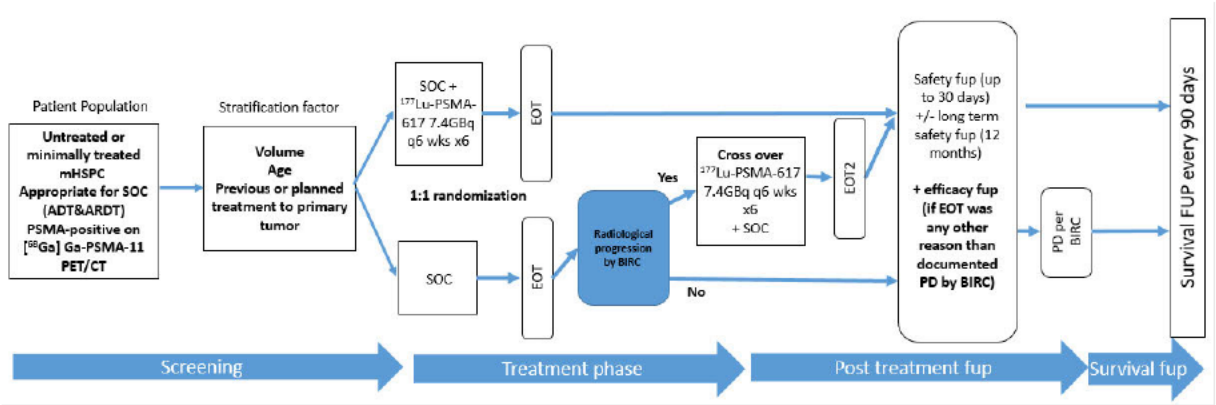
Participants who discontinue study treatment without having progressive disease confirmed by BIRC, will continue to be assessed for efficacy (efficacy follow-up) during the post-treatment follow-up period until the occurrence of their BIRC-confirmed radiographic disease progression (rPFS) event, or if the total number of protocol-defined rPFS events has occurred triggering the primary analysis, whichever occurs first. For more details see Section 9.1.1.1 and Section 9.1.1.2.

Survival Follow-Up:

After study treatment discontinuation, or post-treatment follow-up period discontinuation, the participant's status will be collected every 90 days (via phone calls) as part of the survival follow-up. Every effort should be made to comply with the survival follow-up schedule and ensure collection of participant survival. The survival follow-up and the study will end when the number of OS events required for final OS analysis will be reached. Participants who received ^{177}Lu-PSMA-617 (in ^{177}Lu-PSMA-617+SoC arm and after crossover in the SoC arm) will be asked to join a separate long-term safety follow-up study (CAAA617A12402) while remaining on survival follow-up in this study.

For more details see Section 9.1.1.3 and Section 9.1.1.4.

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

^{177}Lu-PSMA-617 in the setting of hormone-sensitive prostate cancer

As detailed in Section 1.1, several studies confirmed PSMA expression in the recurrent disease setting and that targeting the AR pathway leads to radiosensitization improving patient condition compared to radiation therapy alone Che et al 2007, Sekhar et al 2019. Furthermore, it is expected that there will be fewer genomic alterations that may lead to radiation-resistance (such as TP53) in the setting of mHSPC as opposed to CRPC Boyd et al 2012, Stopsack et al 2020. Therefore PSMA-RLT is hypothesized to be more effective in this setting.

Androgen deprivation therapy together with ARDT may enhance the DNA damage induced by ^{177}Lu-PSMA-617 and improve the outcomes in patients with metastatic hormone-sensitive prostate cancer.

To assess the treatment effect of ^{177}Lu-PSMA-617 in combination with SoC in patients with mHSPC approximately 1126 patients will be randomized into the study.

Randomization will be stratified according to the following three factors:

1. Tumor Volume (as per CHAARTED study, Sweeney et al 2015): high vs low,
   - Where "high volume" is defined as the presence of visceral metastases and/or ≥ 4 bone lesions with ≥1 beyond the vertebral bodies and pelvis. Patients with low volume disease are expected to derive incrementally greater benefit (in terms of time-to-event endpoints) over patients with higher tumor burden.
2. Age ≥ 70 years (yes/no)
   - Patients less than 70 years of age are expected to derive incremental benefit (in terms of the time to event endpoints) over patients ≥ 70 years.
3. Previous or planned treatment (prostatectomy or radiation) to primary (prostate) tumor (Yes vs No)

- The effect on time-to-event endpoints for patients having received prior definitive surgical or radiologic treatment to the prostate is expected to provide benefit that requires stratification.

  Note: If randomized to the investigational arm, intended treatment to the primary tumor should be delayed until the completion of ^{177}Lu-PSMA-617. If randomized to the control arm, intended treatment to the primary tumor should be performed within 6 months of randomization.

High versus low tumor volume will be assessed by the investigator based on screening/baseline CT/MRI of chest/abdomen/pelvis and whole body bone scan with technetium-99m labeled diphosphonate. Distant metastases visible on CT/MRI and located outside of pelvis such as liver, lung, adrenal, and/or CNS lesions will qualify as evidence of visceral disease (±other lesions qualifying for visceral metastases such as pleura or peritoneum). If a participant had a history of visceral metastases at any time prior to randomization, but these visceral metastases disappeared with systemic treatment initiated prior to screening/baseline imaging assessments, he should be coded as having visceral metastases at baseline. Metastases to non-regional lymph nodes (M1a), bones (M1b), local spread of primary tumor within pelvis (stages T3a, T3b, T4), local relapse in pelvis will not qualify as visceral disease. The number and location of bone lesions used for stratification purposes should be assessed based on whole body bone scan.

Prostatectomy (or radical prostatectomy), definitive dose radiation given to the primary prostate tumor in the past qualifies for previous treatment to primary prostate tumor. When a participant had other types of surgery (e.g., biopsy, transurethral resection, cryoablation) or radiotherapy (e.g., on prostate bed after prostatectomy, on distant metastases) in the past, he should be coded as not having previous treatment to primary prostate tumor. Planned treatment to a primary prostate tumor for stratification includes prostatectomy or definitive dose radiation on primary prostate tumor planned prior to randomization; when other types of surgery/radiotherapy are planned, the participant should be coded as "no planned treatment (prostatectomy or radiation) to primary (prostate) tumor".

Stratification by presence of high-volume disease, age and previous or planned treatment to primary tumor will support the analytic framework for pre-specified subgroup analyses in order to avoid arm-to-arm imbalances of factors known to affect primary and key secondary study outcomes. Assignment to treatment arm will be performed centrally following determination of eligibility.

4.1.1 Rationale for choice of background therapy

In this study, the background therapy is the SoC and is a combination of Androgen Receptor Directed Therapy + Androgen Deprivation Therapy.

Androgen Deprivation Therapy (ADT):

Androgen deprivation therapy combined with novel agents such as abiraterone, enzalutamide, or apalutamide is a standard of care in patients with hormone-sensitive metastatic prostate cancer rather than ADT alone (James et al 2017, Armstrong et al 2019, Davis et al 2019,

Fizazi et al 2019, Ozguroglu et al 2020) (Androgen suppression or deprivation occurs either through surgical castration (orchiectomy) or through the use of LHRH agonists/antagonists as part of management of overall disease symptomatology per discretion of the treating physician.

Participants of the study will undergo androgen deprivation.

Androgen Receptor Directed Therapies (ARDT)

Androgen deprivation therapy along with Androgen Receptor Directed Therapies (ARDT) with agents such as abiraterone, enzalutamide, apalutamide, etc. constitute a standard of care for treatment of men with mHSPC that will be administered to all participants of this study.

The addition of abiraterone and low dose prednisone to ADT represents the most commonly prescribed initial treatment of mHSPC.

The STAMPEDE abiraterone trial demonstrated a benefit in overall survival with the addition of abiraterone and prednisone to androgen deprivation therapy in patients with castration-sensitive disease (HR=0.61, p<0.001). The addition of abiraterone and prednisone also decreased treatment failure by 71% (p<0.001)

In the ARCHES trial, the addition of enzalutamide to ADT (with or without prior docetaxel) has demonstrated efficacy as measured by radiographic progression-free survival in men with mHSPC (Armstrong et al 2019).

Enzalutamide added to ADT (17.9% also received docetaxel) led to a 61% reduction in risk of radiographic progression [95% CI 0.30 – 0.50] and also demonstrated prolonged time to PSA progression, improved undetectable PSA, and improved objective response. In the ANZUP cooperative group ENZAMET study, the addition of enzalutamide to ADT with or without docetaxel led to improved progression-free and overall survival versus the same therapy with older antiandrogens (Davis et al 2019).

Enzalutamide improved the risk of all-cause mortality by 33% [HR 0.67, 95% CI 0.52-0.86, p=0.002]. Similarly, in the TITAN study, apalutamide added to ADT (with or without docetaxel) led to an improvement of both radiographic progression-free survival and overall survival in men with mHSPC (Chi et al 2019).

Apalutamide also led to a 33% improvement in overall survival in this population [HR 0.67, 95% CI 0.51-0.89, p=0.005].

Activation of the androgen receptor signaling pathway promotes resolution of DNA breaks induced by radiation therapy and leads to radio-resistance. Blockade of this androgen receptor signaling pathway with androgen deprivation therapy inhibits DNA strand break repair sensitizing prostate cancer cells and tumors to radiation therapy (Goodwin et al 2013, Polkinghorn et al 2013).

In the current study, the combination of Standard of Care (ADT plus ARDT), and ^{177}Lu-PSMA-617 will be studied. Androgen deprivation therapy together with ARDT may enhance the DNA damage induced by ^{177}Lu-PSMA-617 and improve the outcomes in patients with metastatic hormone-sensitive prostate cancer.

4.2 Rationale for dose/regimen and duration of treatment

The basic principle of targeted ^{177}Lu-PSMA-617 radioligand therapy is to systemically deliver low dose rate radiation specifically to PSMA positive prostate cancer lesions, while sparing normal tissues. To date, 12 dosimetry studies have been conducted in 158 patients. The results are consistent across the studies and demonstrate exposure that correlates well with the expected rapid clearance of a small molecule, and the limited distribution pattern of a PSMA-targeted radionuclide. The primary sites of non-tumor uptake were the salivary glands 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, such as 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 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 the 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 patient (Rahbar et al 2018, Kulkarni et al 2018 a, Kulkarni et al 2018 b, Kulkarni HR et al 2018, Bräuer et al 2017, Yordanova et al 2017, van Kalmthout et al 2019, Kessel K et al 2019, Maffey-Steffan et al 2020, Yadav et al 2020).

In the phase II TheraP study (Hofman et al 2020)(ANZUP protocol) 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.

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

The rationale for choice of Standard of Care is described in Section 4.1.1.

4.4 Purpose and timing of interim analyses/design adaptations

A maximum of three (two interim and one final) analyses will be performed for rPFS and OS to determine efficacy (or non-binding futility at first interim). If the interim or final rPFS is

statistically significant, interim or final analysis for OS will also be conducted as detailed in Section 12.7.

The timing of the interim and final rPFS and OS analyses are detailed in Section 12.4.2 and Section 12.7.

4.5 Risks and benefits

Patients will be screened for study eligibility using criteria that are appropriate for adult male with treatment naive mHSPC. Only patients whose tumors express the PSMA target will be enrolled in the study, minimizing exposure to patients not expected to benefit from treatment with ^{177}Lu PSMA-617. Eligibility "waivers" will not be allowed. Specific dose modification and adverse event-based stopping rules are included in this protocol and recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Table 6-2 and Table 6-4.

The risk to participants in this trial will be further minimized by compliance with the eligibility criteria and study procedures as written in the protocol, as well as close clinical monitoring. The safety profile of the SoC such as the combination ADT + ARDT is well characterized. The addition of ^{177}Lu PSMA-617 to this combination is not expected to cause significant toxicity.

Dosimetry studies have confirmed sssssssthat ^{177}Lu PSMA-617 is targeted to PSMA-expressing prostate cancer cells and some normal tissues that express PSMA (Delker et al 2016). These tissues are salivary glands, renal, and small and large bowel. The renal absorbed dose is cleared rapidly, and exposure appears similar to that seen with ^{177}Lu-DOTATATE.

Nephrotoxicity has not been notable in clinical studies conducted to date. There has been evidence of reversible hematological toxicity. No significant diarrhea or renal impairment were reported from a retrospective review of doctors' reports (Rahbar et al 2017).

In the prospective studies VISION study and RESIST-PC, the commonly reported adverse events (>10% of patients) to date include: anemia, dry mouth, constipation, diarrhea, nausea, vomiting, fatigue, decreased appetite, arthralgia and back pain(Refer to Sartor et al 2021, 'Section 1.1' and [^{177}Lu-PSMA-617 Investigator's Brochure (IB)]). A small number of hematological events (leukopenia, pancytopenia) have been reported and few of them (thrombocytopenia, anemia and pancytopenia) have been reported as fatal. Five adverse events that led to death in the ^{177}Lu-PSMA-617 group were considered by the investigators to be related to the drug: pancytopenia (in 2 patients), bone marrow failure (in 1), subdural hematoma (in 1), and intracranial hemorrhage (in 1). (Refer to Sartor et al. 2021 and ^{177}Lu-PSMA-617 IB). This data is consistent with safety observations from the study in 50 mCRPC participants dosed with up to 4 cycles of 4-8 GBq, the regimen was characterized as well-tolerated (Hofman et al 2019, Hofman et al 2020).

Potential risks of ^{177}Lu-PSMA-617 include the effects of radiological toxicity, late renal toxicity and bleeding events.

Dosimetry estimates for ^{177}Lu-PSMA-617 from the VISION sub-study showed that the organs with the highest radiation absorbed doses were the lacrimal glands, salivary glands, large

intestine (left and right colon), kidneys, and urinary bladder wall. Such dosimetry estimates were consistent with the ranges published in literature.

The risk to participants in this trial may be minimized by compliance with the eligibility criteria Section 5 and study procedures Section 8, 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.

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

The exposure to bone marrow should be low and correspond with normal plasma clearance.

The best supportive/best standard of care for the patient in either arm will be administered as per physician's orders and supportive care should be optimized throughout study participation.

Other treatments for prostate cancer patients management, not specifically excluded as part of the study, should be used in accordance with the routine clinical practice and at the discretion of the investigator. These may include, but are not limited, to optimal pain control, hydration, transfusions, etc.

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this study if there is significant interaction with chosen ARDT. If relevant, patients on strong CYP3A4 inhibitors must discontinue the drug for 14 days prior to initiation of ARDT treatment.

Sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur 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. Additional details of the nonclinical and clinical experience with ^{177}Lu-PSMA-617 are provided in the Investigator's Brochure.

The use of ^{68}Ga-PSMA-11 for PET scanning of prostate cancer patients has been ongoing since 2011 to assess disease burden in various settings including advanced/metastatic disease (See Prescribing Information). There are now numerous centers around the world that have clinical experience with ^{68}Ga-PSMA-11, with over 600 publications reporting results from both retrospective and prospective experiences.

The published data consistently demonstrate that imaging with ^{68}Ga-PSMA-11 is well tolerated. Four publications report on a total of 7047 prostate cancer patients that have received ^{68}Ga-PSMA-11, N=4149 (Hope et al 2019), N=1007 (Afshar-Oromieh et al 2017), N=1256 (von Eyben et al 2018), N=635 (Fendler et al 2019). These four studies have further reinforced the ability of ^{68}Ga-PSMA-11 to identify PSMA-expressing PC and demonstrate it is well tolerated. While the uptake of ^{68}Ga-PSMA-11 reflects the levels of PSMA expression in prostate cancer, ^{68}Ga-PSMA-11 uptake is not specific to prostate cancer and may occur in other types of cancers, non-malignant processes and normal tissues. The risk of PET imaging interpretation errors can be minimized when ^{68}Ga-PSMA-11 is appropriately handled and administered by trained health

care professionals and when scans are interpreted by trained experts in the context of histopathology and/or other diagnostic procedures.

The risk-benefit ratio is expected to be favorable to the ^{68}Ga-PSMA-11 imaging agent. Further details can be found in the ^{68}Ga-PSMA-11 IB.

Risk from radiation exposure:

^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617 contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer.

Radiation exposure to patients, medical personnel, and household contacts should be minimized during and after treatment with ^{177}Lu-PSMA-617 consistent with institutional good radiation safety practices, patient management procedures, and instructions to the patient for follow-up radiation protection at home. For additional information, please refer to the Pharmacy Manual.

Patients should be encouraged to increase oral fluids and urged to void as often as possible to reduce bladder radiation, especially after high activities, e.g., radionuclide therapy.

The available evidence suggests that the symptoms of Coronavirus disease 19 (COVID-19) are probably more severe in patients with cancer and that this patient population are at a higher risk of COVID-19 infection-related complications. Treatment decisions during the pandemic should rely on diligent preventive care measures and aggressive surveillance for earlier detection of COVID-19 infection.

There are limited data on the concomitant administration of ADT, ARDT or ^{177}Lu-PSMA-617 in individuals infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) the strain of coronavirus that causes the respiratory illness responsible for the COVID-19 pandemic. Although ADT, ARDT or ^{177}Lu-PSMA-617 appear to have a non-overlapping adverse event profile with that of SARS-CoV-2 related (i.e., respiratory) symptoms, given the variable, and at times difficult, clinical course of infected patients, clinical management is at the discretion of the investigating physician, taking precedent over study-related procedures as needed.

4.6 Rationale for Public Health Emergency mitigation procedure

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

The study population consists of adult male patients with treatment-naive or minimally treated mHSPC as defined through inclusion/exclusion criteria and candidate to Hormonal therapy. Approximately 1126 patients will be randomized into the study.

Additional patients may be enrolled in the [redacted] extension upon completion of enrollment (LPFT) of the main study in order to support registration in [redacted] The total sample size of [redacted] participants is estimated to be approximately 40 to 60.

Eligible participants should not have received prior systemic radioisotope therapy.

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. Patients must be adults ≥18 years of age
3. Patients must have an ECOG performance status of 0 to 2
4. Patients must have a life expectancy >9 months as determined by the study investigator
5. Patients must have metastatic prostate cancer with histologically or cytologically confirmed adenocarcinoma (current or prior biopsy of the prostate and/or metastatic site)
6. Patients must have evidence of PSMA-positive disease as seen on a ^{68}Ga-PSMA-11 PET/CT scan, and eligible as determined by the sponsor's central reader
7. Patients must have at least one metastatic bone and/or soft tissue/visceral lesion documented in the following manners within 28 days prior randomization:
   a. Metastatic disease to the bone (in any distribution) visible on ^{99}Tc-MDP bone scintigraphy on either pre-ADT scans or baseline scans AND/ OR
   b. Lymph node metastases of any size or distribution. If lymph nodes are the only site of metastasis, then at least one must be at least 1.5 cm in short axis AND outside of the pelvis AND/ OR
   c. Visceral metastases of any size or distribution. If a participant has a history of visceral metastases at any time prior to randomization, he should be coded as having visceral metastases at baseline (i.e., patients with visceral metastases prior to ADT that disappear at baseline will be counted as having visceral metastases and would therefore have high volume disease for stratification purposes).
8. Patients 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 patients 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

9. Albumin ≥2.5 g/dL
10. Human immunodeficiency virus (HIV)-infected patients who are healthy and have a low risk of acquired immune deficiency syndrome (AIDS)-related outcomes can participate in this trial
11. Patients must be:

Treatment naïve OR minimally treated with:

- Up to 45 days of luteinizing hormone-releasing hormone (LHRH) agonist /antagonists or bilateral orchiectomy with or without first generation antiandrogen (e.g. bicalutamide, flutamide) for metastatic prostate cancer is allowed prior to ICF signature. If given, first generation antiandrogen must be discontinued prior to start of study therapy or after 45 days whatever happens first.
- If received, prior LHRH agonist/antagonist with or without first generation antiandrogen use in the adjuvant/neo-adjuvant setting must have been discontinued > 12 months prior to ICF signature AND must not have exceeded 24 months of therapy AND must not have shown disease progression within 12 months of completing adjuvant/neo-adjuvant therapy.
- Up to 45 days of CYP17 inhibitor or ARDT exposure for metastatic prostate cancer is allowed prior to ICF signature.
- No CYP17 inhibitor or ARDT exposure for earlier stages of prostate cancer is allowed.

5.2 Exclusion criteria

Participants meeting **any** of the following criteria are **not** eligible for inclusion in this study.

1. Patients with rapidly progressing tumor that requires urgent exposure to taxane-based chemotherapy
2. Any prior systemic anti-prostate cancer therapy (with the exception of the drugs listed on inclusion criteria 11), including chemotherapy, Poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors, immunotherapy or biological therapy (including monoclonal antibodies).
3. Concurrent cytotoxicity chemotherapy, immunotherapy, radioligand therapy, PARP inhibitor, biological therapy or investigational therapy
4. Previous treatment with any of the following within 6 months of randomization: Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation. Previous PSMA-targeted radioligand therapy is not allowed
5. Ongoing participation in any other clinical trial

6. Use of other investigational drugs within 30 days prior to day of randomization
7. Known hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes
8. Transfusion for the sole purpose of making a participant eligible for study inclusion
9. Participant with CNS metastases that are neurologically unstable, symptomatic, or receiving corticosteroids for the purpose of maintaining neurologic integrity. Participant with epidural disease, canal disease and prior cord involvement are allowed if those areas have been treated, are stable, and not neurologically impaired. Patients with parenchymal CNS metastasis (or a history of CNS metastasis), that have received prior therapy and are neurologically stable, asymptomatic and not receiving steroids for CNS metastases, are allowed; baseline and subsequent radiological imaging for them must include evaluation of the brain (magnetic resonance imaging (MRI) preferred or CT with contrast).
10. 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, treatment free for more than 3 years prior to randomization, or participants with adequately treated non-melanoma skin cancer, superficial bladder cancer are eligible.
11. Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, 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. 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)
12. Active clinically significant cardiac disease defined as any of the following:
    - NYHA class 3/4 congestive heart failure within 6 months prior to ICF signature unless treated with improvement and echocardiogram or MUGA demonstrates EF > 45% with improvement in symptoms to class < 3.
    - History or current diagnosis of ECG abnormalities indicating significant risk of safety for participants in the study such as: Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, complete left bundle branch block, high-grade atrioventicular (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 Pointes
    - Cardiac or cardiac repolarization abnormality, including any of the following: History of myocardial infarction (MI), angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to ICF signature
13. History of somatic or psychiatric disease/condition that may interfere with the objectives and assessments of the study
14. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression

15. Inability to complete the study imaging procedures due to any reason (e.g., severe claustrophobia, inability to lie still for the entire imaging time, any condition that precludes raised arms position)
16. Unmanageable concurrent bladder outflow obstruction or urinary incontinence. Note: patients with bladder outflow obstruction or urinary incontinence, which is manageable and controlled with best available standard of care (incl. pads, drainage) are allowed.
17. 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

6 Treatment

6.1 Study treatment

In this study, the term "Study Drug" refers to the radioligand therapeutic compound ^{177}Lu-PSMA-617 (also known as lutetium [^{177}Lu] vipivotide tetraxetan and AAA617), the radioligand imaging compound ^{68}Ga-PSMA-11 (also known as gallium (^{68}Ga) gozetotide and radiolabeled AAA517) used for imaging purposes during screening, Androgen Deprivation Therapy (ADT) and Androgen Receptor Directed Therapy (ARDT). In this protocol, the terms ^{177}Lu-PSMA-617 and the radioligand imaging compound ^{68}Ga-PSMA-11 will be used throughout the document.

Study drugs ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617 both have a marketing authorization, but in this study are considered investigational as ^{68}Ga-PSMA-11 is used for eligibility assessment per protocol-specified criteria, ^{177}Lu-PSMA-617 is used in mHSPC indication.

Standard of Care (SoC) refers to Androgen Receptor Directed Therapy (ARDT, also known as second-generation androgen receptor pathway inhibitors) and Androgen Deprivation Therapy (ADT). Examples of ARDT include but are not limited to abiraterone acetate, enzalutamide, apalutamide, darolutamide and rezvilutamide. Standard of Care ADT and ARDT drugs are authorized to treat patients with mHSPC, in this trial they are considered auxiliary medicinal products and will be administered per local label instructions/local standards.

Patients will be administered ^{177}Lu-PSMA-617 intravenously as per best practice and Investigator's decision (Refer to Section 6.3 for study drug preparation and dispensation).

The general doses of the investigational drugs are listed in Table 6-1.

6.1.1 Investigational and control drugs

Table 6-1 Investigational drugs

Investigational Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
^{177}Lu-PSMA-617 (AAA617; lutetium [^{177}Lu] vipivotide tetraxetan) (1 GBq/mL at End of Production)	Radiopharmaceutical solution for infusion/injection	Intravenous use	Open label, vial	Sponsor (global)
AAA517 cold kit (also known as gozetotide or PSMA-11) (25µg)	Either provided as PSMA-11 Kit for the radiopharmaceutical preparation of gallium (^{68}Ga) gozetotide or as ready to use radiopharmaceutical solution for injection	Intravenous use	Open label, vial or syringe	Sponsor (global/local)*

*Locametz kits could be used in those countries where commercially available, and local sourcing is approved by the sponsor.

^{68}Ga-PSMA-11 Imaging

During screening, all participants will undergo PET/CT scan with ^{68}Ga-PSMA-11 for determination of PSMA positivity and eligibility. Participants must have metastatic disease that expresses PSMA as seen by BIRC on a ^{68}Ga-PSMA-11 PET/CT scan. Participants from ^{177}Lu-PSMA-617+SoC and SoC arms will also undergo PET/CT scan with ^{68}Ga-PSMA-11 following central confirmation of radiographic progression by BIRC. Assessments of PSMA expression with ^{68}Ga-PSMA-11 radiopharmaceutical other than mentioned above will not be performed for study purpose (for more details, please refer to Table 8-1).

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 [redacted] prior to repeating ^{68}Ga-PSMA-11 PET imaging as screening for this study, the same wash out period will apply to PET/CT with ^{68}Ga-PSMA-11 at time of radiographic progression if an exam with Ga-PSMA imaging agent was earlier performed outside of study.

Imaging assessment must be performed locally only with use of Sponsor kits for the radiopharmaceutical preparation of ^{68}Ga-PSMA-11 or with ^{68}Ga-PSMA-11 radiopharmaceutical solution for injection supplied by the Central Radiopharmacies. Other Ga-containing PSMA-targeting radiopharmaceuticals must not be used for imaging at screening to evaluate PSMA-positivity or at time of centrally confirmed radiographic progression. 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 this medication 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.

For background and additional details on ^{68}Ga-PSMA-11, refer to Section 6.3 for study drug preparation and dispensation and to the ^{68}Ga-PSMA-11 Investigator's Brochure (IB). The ^{68}Ga-PSMA-11 radiopharmaceutical will be administered as a single intravenous (i.v.) dose of approximately 150 Megabecquerel (MBq). Administered doses must not be lower than 111 MBq or higher than 259 MBq in any case.

Refer to Pharmacy Manual for details on dose preparation and administration.

Treatment with ^{177}Lu-PSMA-617

Study participants randomized to the investigational arm will receive a dose of 7.4 GBq (200 Millicuries (mCi)) +/-10% of ^{177}Lu-PSMA-617 which will be administered once every 6 weeks (1 cycle) for a planned 6 cycles. (Refer to Section 6.3 for study drug preparation and dispensation).

6.1.2 Additional study treatments

Table 6-2 Additional study treatment

Treatment Title	Anatomical Therapeutic Chemical [ATC] code category L02AE	Anatomical Therapeutic Chemical [ATC] code category L02BB	Anatomical Therapeutic Chemical [ATC] code category L02BX
Treatment Description	Gonadotropin releasing hormone analogues	Anti-androgens	Other hormone antagonists and related agents
Type	drug	drug	drug
Dose Formulation	various	various	various
Unit Dose Strength(s)	various	various	various
Dosage Level(s)	various	various	various
Route of Administration	various	various	various
Use	Background intervention	Background intervention	Background intervention
Authorization status of the AxMP in EEA	Yes	Yes	Yes
Sourcing	Locally by each investigator/site from each MSC market	Locally by each investigator/site from each MSC market	Locally by each investigator/site from each MSC market
Packaging and Labeling	Each AxMP will be labeled as required per country requirement when applicable.	Each AxMPwill be labeled as required per country requirement when applicable.	Each AxMP will be labeled as required per country requirement when applicable.

Standard of Care

All participants randomized to the study (i.e., investigational and control arms) will receive Standard of Care.

SoC in all patients of both arms must be initiated within [redacted] after randomization if not started earlier and given as per label instructions/local standards.

ADT will be administered to all patients randomized to the study (both arms) on a continuous basis. Bilateral surgical orchiectomy, LHRH agonist, or LHRH antagonist are acceptable. Drugs approved for ADT will be provided locally by the study site, subsidiary or designee as commercially available, and as per local regulations. Please refer to the Local Package Insert for complete guidelines for dosage and administration, for contraception and for safety monitoring guidelines.

The choice of ARDT is at the discretion of the investigating physician. In the case of ARDT - related adverse events or intolerability, investigators should refer to the respective package insert for guidance on dose reductions. A single change (switch) in ARDT (e.g., abiraterone to enzalutamide) prior to rPFS event confirmed by BIRC is allowed in both investigational and control arm in case of ARDT intolerability or any reason other than rPFS (e.g., related to access to ARDT). A change from one trade name to another trade name is allowed and not considered ARDT switch when the patient continues receiving the same active ingredient. ARDT treatment in the cross over arm is at the discretion of the investigator (refer to Section 6.1.5.1).

Drugs approved for ARDT will be provided locally by the study site, subsidiary or designee as commercially available, and as per local regulations. Please refer to the Package Insert for complete guidelines for dosage and administration, for contraception and for safety monitoring guidelines. Examples of ARDT include but are not limited to abiraterone acetate , enzalutamide, apalutamide, darolutamide and rezvilutamide. The participant should be instructed to take a daily dose of ARDT on the Day 1 of a treatment cycle (CxD1) at the site, after completion of pre-dose evaluations.

6.1.3 Treatment arms/group

This is a randomized, open-label trial. Participants will be assigned at randomization to one of the following 2 treatment arms/groups in a ratio of 1:1.

Participants randomized to investigational arm will receive treatment with ^{177}Lu-PSMA-617 + SoC

Participants randomized to control arm will receive treatment with SoC alone.

Table 6-3 Treatment arm(s)

Arm title	Investigational arm	Control arm
Arm type	^{177}Lu-PSMA-617+SoC	SoC
Arm description	^{177}Lu-PSMA-617 at a dose of 7.4 GBq (±10%) once every 6 weeks (± 7 days) for up to planned 6 cycles; SoC (ADT+ARDT) as per local label instructions/local standards.	SoC (ADT+ARDT) as per local label instructions/local standards.

6.1.4 Guidelines for continuation of treatment

Participants who permanently discontinue SoC for any reason other than disease progression (e.g., intolerance) will be allowed to continue receiving ^{177}Lu-PSMA-617 as scheduled. One

ARDT switch is allowed in the investigational and control arm prior to rPFS by BIRC in the study. Discontinuation from first ARDT due to switch to another should not be considered SoC discontinuation. SoC discontinuation will apply to permanent discontinuation of second ARDT given after the switch. For more details on ARDT switch refer to Section 6.2.1. Participants who permanently discontinue ^{177}Lu-PSMA-617 for any reason other than disease progression (e.g., intolerance) may continue to receive SoC at the investigator's discretion until disease progression, unacceptable toxicity, death or discontinuation from study treatment due to any other reason and should follow the protocol safety and efficacy assessments as scheduled. Treatment beyond disease progression is allowed as described in Section 6.1.5.1.

After discontinuing all study treatment due to progression or study withdrawal (Section 9.1.1), subsequent treatment is left to the investigator's discretion.

Guidelines for dose modification of treatment can be found in Section 6.6

6.1.5 Treatment duration

Participants randomized to the investigational arm must begin ^{177}Lu-PSMA-617 dosing within [redacted] after randomization. Participants will receive a dose of 7.4 GBq (±10%) of ^{177}Lu-PSMA-617 once every 6 weeks (± 7 days) for up to planned 6 cycles.

Please refer to Section 9.2 and Table 8-1 for further details. Management of drug interruption due to drug related toxicities are described in Section 6.6.1 and Table 6-2.

For participants who have delay of treatment due to any other reasons than drug related toxicities, every effort should be made to reschedule treatment as early as possible to minimize deviations from the treatment schedule.

Patients will continue SoC with or without ^{177}Lu-PSMA-617 (depending on treatment arm) until radiographic progression assessed by BIRC or until no longer clinically benefitting or meeting other criteria for discontinuation as detailed in Section 9.1.1 After the initial treatment (SoC with or without ^{177}Lu-PSMA-617) is discontinued, patients will enter long-term follow-up period unless control arm patients decide to cross-over to receive ^{177}Lu-PSMA-617. Cross-over patients will adhere to the schedule used for the investigational arm until investigator assesses radiographic progression or until no longer clinically benefitting.



Please note that the care of study participants must include specialists accomplished in the care of patients with metastatic prostate cancer, (e.g., oncologist, urologists, radiation oncologists,

nuclear medicine physicians) with a clear understanding of the PCWG3 criteria, including the caveats that distinguish it from RECIST 1.1.

6.1.5.1 Treatment beyond disease progression

Upon the occurrence of radiographic progression, as assessed by BIRC, participants randomized to SoC + ^{177}Lu-PSMA-617 should stop study treatment or may continue receiving SoC and/or ^{177}Lu-PSMA-617 (for up to planned 6 cycles) as long as considered benefiting from continuation of treatment, by the investigator.

Upon the occurrence of radiographic progression, as assessed by BIRC, participants randomized to SoC only will be allowed to cross-over to receive ^{177}Lu-PSMA-617 or may receive any subsequent therapy per the discretion of the treating physician. For patients that cross-over to ^{177}Lu-PSMA-617 after progression, ^{177}Lu-PSMA-617 will be administered under the same dose and schedule as participants who were initially randomized to receive SoC and ^{177}Lu-PSMA-617 as described above.

ARDT and androgen deprivation therapy, as part of SoC may be administered beyond radiographic progression, per the discretion of the treating physician. For more details, please refer to Section 6.2.1 and Section 9.1.1.

After discontinuing all study treatments due to progression or study withdrawal, subsequent treatment is left to the investigator's discretion.

6.1.5.2 Cross-over to ^{177}Lu-PSMA-617

Upon confirmation of radiographic progression by BIRC, cross-over to receive ^{177}Lu-PSMA-617 is allowed for the control arm participants upon discontinuation of the Standard of Care.

Participants with progression events other than radiographic progression confirmed by BIRC such as radiographic progression per investigator's assessment not confirmed by BIRC, clinical progression, and/or PSA progression, will not be allowed to cross-over.

When the End of Treatment visit is performed, following confirmation of radiographic progression by BIRC, the participants initially randomized to the SoC alone arm will be allowed to cross-over within 28 days after confirmation of rPFS by BIRC, and start receiving ^{177}Lu-PSMA-617 within [redacted] after registration of cross-over in the IRT system.

If in the investigator judgement, the patient has any serious or unstable medical condition during the study that would prevent the patient from participating in the cross-over phase, then the patient should be excluded.

SoC alone arm patients who start new anti-neoplastic treatment during the treatment period or post-treatment follow-up period will not be eligible to cross-over.

After the rPFS event confirmed by BIRC, switching to another ARDT is allowed at Investigator's discretion. It is also possible that the investigator decides not to give another ARDT, in this case the patient will receive ^{177}Lu-PSMA-617 alone in addition to ADT (if applicable).

The following eligibility criteria must be confirmed prior to registration for cross-over to ^{177}Lu-PSMA-617:

1. Radiographic progression confirmed by BIRC
2. Patients with CNS metastases must be neurologically stable
3. Patients must have an ECOG PS of 0-2
4. Patients must be compliant with the contraception guidelines outlined in Section 8.4.3
5. Patients must have adequate organ function including the following laboratory values prior to commencing cycles with ^{177}Lu-PSMA-617 in the Cross-over:
   - eGFR ≥ 50 mL/min/1.73m^2 using the Modification of Diet in Renal Disease (MDRD) equation
   - 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
   - (ANC) ≥1.5 x 10^9/L
   - Platelets ≥100 x 10^9/L
   - Hemoglobin ≥9 g/dL

Assessments required for the cross-over baseline as per Table 8-2 must be repeated if they are older than 28 days prior to registration of cross-over in IRT.

CT/MRI with contrast of chest/abdomen/pelvis and whole body bone scan are mandatory images for cross-over baseline.

Images used for a confirmation of radiographic progression by BIRC should not be repeated and are allowed to be used as cross-over baseline images.

Missing images must be performed within 28 days prior registration for cross-over.

PET/CT with ^{68}Ga-PSMA-11 performed following a confirmation of radiographic progression by BIRC should be submitted to a central reader, but should not be used to assess potential eligibility for cross-over. This PET/CT with ^{68}Ga-PSMA-11 assessment is not intended for therapeutic decision making.

After cross-over, all images will be reviewed and assessed only locally.

Following investigator's confirmation of patient eligibility for the cross-over, the participant will be assigned to the cross-over via the IRT system.

Patients in the SoC alone arm who elect to cross-over to ^{177}Lu-PSMA-617 therapy must follow the study assessments as per visit schedule in Table 8-2.

When ^{177}Lu-PSMA-617 is discontinued, patients must have a second End of Treatment (EOT2) visit performed ≤ 7 days and enter the Post-treatment Follow-up (30 days follow-up visit, 24 and 48 weeks visits and then survival follow-up) as per the assessment indicated in Table 8-2.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study and until 30 days after the last ARDT dose and until 42 days after the last ^{177}Lu-PSMA-617 dose whichever is longer, must be recorded on the appropriate Case Report Forms (CRF).

Prostatectomy or treatment dose radiation

Unless specified below, patients should not receive any other treatment which would be considered treatment for the prostate cancer or impact the primary endpoint with the following exception: Patients with low volume metastatic disease and/or pre-existing symptomatic disease due to primary tumor will be allowed to undergo treatment to the primary tumor, including prostatectomy or treatment dose radiation. If randomized to the investigational arm, treatment to the primary tumor should be delayed until the completion of ^{177}Lu-PSMA-617. If randomized to the control arm, treatment to the primary tumor should be performed within 6 months of randomization.

Other therapies

Participants should receive full supportive care while on this 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 occurs 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 investigator/ 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.

Participants with manageable and controlled urinary outflow obstruction or urinary incontinence should continue receiving best available standard of care (incl. pads, drainage) at the discretion of the investigator/attending physician.

Palliative radiation therapy may be administered to symptomatic bone disease at any time from randomization until the 1st post-baseline scan occurring at 12 weeks and it is not considered as prohibited therapy, 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. After the 1st post-baseline scan (i.e., at

12 weeks), the need for palliative radiation may indicate radiographic disease progression. If the need for palliative radiation to symptomatic bone disease is considered after the 1st post-baseline scan, bone metastases should be assessed to rule out radiographic progression. When the need for palliative radiation to the lesions other than bone is considered after the baseline scan, the lesion should be assessed per RECIST 1.1 criteria and palliative radiation to the target lesion should be possibly avoided. Initiation of a palliative radiation may result in study discontinuation when radiographic progression is confirmed.

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 (EPO) 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.

Hydration and diuretics as per individual cardiovascular and voiding conditions are allowed and are at the discretion of the investigator, following EANM Procedure Guidelines (Kratochwil C et al 2019); institutional standards should be followed.

Hypersensitivity/infusion reactions: Treat hypersensitivity and infusion reactions to per institutional standards.

Therapy with hormones including steroids (systemic, localized, topical) may be given for diseases/conditions other than prostate cancer (e.g., insulin for diabetes). Steroids are also allowed for adrenal failure, in combination with ARDT as per label/ local standards (prednisone given in combination with abiraterone)

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.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

The ARDT chosen for treatment may interact via CYP3A4 induction or inhibition with concomitant medications. If such concomitant medications cannot be avoided, caution should be used during treatment with ARDT. The participant and the investigator should be aware of potential signs of safety or efficacy concern with the concomitant medication and in the event of suspected toxicity; administration of either drug should be discontinued according to investigator judgment. This also applies to concomitant use of supplements (e.g., nutrition and/or herbal), traditional medicines, natural products where product information and data on clinically relevant drug-product interactions are limited or not well established.

Anticoagulants and platelet aggregation inhibitors when patients experience thrombocytopenia is to be used with caution.

6.2.1.2 Use of bone modifying agents

Investigators are encouraged to consider the concomitant use of bone health agents such as bisphosphonates (for example zoledronic acid), RANKL inhibitors (for example denosumab), or other medicines/supplements (for example, miacalcin, vitamins) or similar therapy for patients on either arm of the study. Patients receiving bone health agents prior to randomization may be maintained on this therapy during the study. Bone modulating agents (bisphosphonates, RANKL inhibitors) and/or therapy with bone health agents can be started, changed or stopped at the discretion of the investigator throughout the study.

6.2.2 Prohibited medication

Other investigational agents, cytotoxic chemotherapy, immunotherapy, biological therapy (except pre-exposure COVID-19 prophylaxis with registered biologic agent), 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 (including the cross-over period) regardless indication (prostate cancer, other malignant neoplasms, non-malignant disease or conditions). For example, hydroxyurea in benign hematologic disorders, methotrexate in inflammatory types of arthritis, immunosuppressants after transplant, TNF-alpha inhibitors in autoimmune conditions are prohibited.

Patients should not receive any other anti-cancer treatment (including taxane based therapies) or treatment which would impact the primary endpoint of rPFS with the following exception: Patients enrolled with the intent of receiving definitive treatment to the primary tumor, including prostatectomy or radiation will be allowed to do so. If randomized to the investigational arm, treatment to the primary tumor should be delayed until the completion of all cycles of ^{177}Lu-PSMA-617. If randomized to the control arm, treatment to the primary tumor should be performed within 6 months after randomization.

ARDT drugs have potential drug interactions with medications that include but are 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.

Treatment with hormones other than LHRH agonist/antagonist and ARDT may not be administered except therapies described in Section 6.2.1 Concomitant Therapy / Other Therapies

CYP3A4 Inhibitors

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this study if there is significant interaction with chosen ARDT. If relevant, patients on strong CYP3A4 inhibitors must discontinue the drug for 14 days prior to initiation of study treatment.

The following drugs are EXAMPLES of strong CYP3A4 inhibitors and are not allowed during treatment:

- Indinavir
- Clarithromycin
- Ketoconazole

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the Food and Drug Administration (FDA) website, or your local institution's pharmacist.

CYP3A4 Inducers

Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed during on this trial if there is significant interaction with the chosen ARDT. If relevant, patients must discontinue the drug 14 days prior to the start of study treatment.

The following drugs are EXAMPLES of strong CYP3A4 inducers and are not allowed during treatment:

- Rifampin
- Carbamazepine

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

A list of strong CYP3A4 inhibitors and inducers may be found at medicine.iupui.edu/CLINPHARM/ddis/clinical-table.

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

6.3 Preparation and dispensation

Each study site will be supplied with study drugs as described under Section 6.1.1 investigational and control drugs.

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

As per the treatment assigned to the participant by the IRT at the time of randomization, investigator staff will identify the study treatment to dispense to the participant.

Immediately after administration of ^{177}Lu-PSMA-617 and ^{68}Ga-PSMA-11 to the participant, site personnel will complete the study treatments accountability logs for traceability purpose. For more detailed instructions please refer to the Pharmacy Manual.

6.3.1 Handling of study treatment and additional treatment

6.3.1.1 Handling of study treatment

^{177}Lu-PSMA-617

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 in the Investigator's Brochure.

Clinical supplies are to be dispensed only in accordance with the protocol. Please refer to the Pharmacy Manual for detailed instructions on product ordering, receipt, storage, handling, administration and for technical complaints reporting. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

^{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.

^{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 patient ID.

^{68}Ga-PSMA-11

^{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:

a. the clinical site, in case of the kit's reconstitution and radiolabeling will be performed at hospital's radiopharmacy,
b. 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 (b.), 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.

Clinical supplies are to be dispensed only in accordance with the protocol. Please refer to the Pharmacy Manual for detailed instructions on product supply/ordering, receipt, storage, preparation (when applicable), handling, administration and for technical complaints reporting.

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 patient ID.

The investigator must maintain an accurate record of the shipment and dispensing of study treatments in drug accountability logs. Monitoring of drug accountability will be performed by

monitors during site visits or remotely and at the completion of the trial. The Investigator must provide accountability also for locally sourced materials used for administration (e.g., i.v. bags).

At the conclusion of the study, and as appropriate during the course of the study, 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. The investigator will return 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.

6.3.2 Instruction for prescribing and taking study treatment

^{177}Lu-PSMA-617

Preparation

Since ^{177}Lu-PSMA-617 is a ready-to-use single-dose vial, no manipulation of the investigational product is intended at the clinical site. The solution should be inspected visually prior to use, and only clear colorless to slightly yellow solution, 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 review of the batch release certificate with Certificate of Compliance (CoC) and Certificate of Analysis (CoA). 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.

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

A saline flush with ≥10 mL of normal saline (NS) 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. Please refer to Pharmacy manual for details about possible methods of administration.

The time of administration must be recorded.

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 patients. Such calibration should be performed before the administration of the first patient first cycle, using either a dose supplied

for the patient (before the administration) or the dose sent to validate the shipment route and then annually. Please refer to Pharmacy manual for further details.

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 15(+/- 5) minutes before and at 30(+/- 15) and 60(+/- 15) minutes following administration.

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

When a participant with manageable bladder outflow obstruction/urinary incontinence is randomized to receive treatment with ^{177}Lu-PSMA-617, the investigator should consult a 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). To minimize irradiation of the urinary bladder, patients will be encouraged to increase fluid intake and to void frequently through the first days after administration. Patients should be advised to observe rigorous hygiene to avoid contamination risk of others using the same toilet facility. Use of pads, catheters, other drainage is allowed to control bladder outflow/urinary incontinence. Management of these conditions is at the discretion of the investigators, they should also consider appropriate radioprotection measures according to local regulations/standards.

As a precaution patients may be kept in radiation isolation following administration as per local recommendations and should be allowed to urinate during this time, and before release. Therapy Discharge Instructions provided by the sponsor must be followed. General rules for bathroom use and hygiene (i.e. flush tissue paper and anything from your body) in the Therapy Discharge Instructions must be followed for at least 2 days after treatment.

A participant may be admitted to a hospital to get a cycle of investigational therapy with ^{177}Lu-PSMA-617 and/or after administration of^{177}Lu-PSMA-617 dose if it is required as per local regulation related to provision of radioligand therapy.

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

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 is 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 (IMP) including the pharmacological class and action, the dosage form including excipients, and any available packaging and labelling.

All vials of study treatment will be recorded in the IRT system.

^{68}Ga-PSMA-11

Preparation

In case of the kit's reconstitution and radiolabeling 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.

Dose Preparation information including Date & time and Radioactivity measurement after radiolabeling must be recorded in the corresponding eCRF pages.

Administration

^{68}Ga-PSMA-11 dose will be of approximately 150 Megabecquerel (MBq). Administered doses must not be lower than 111 MBq or higher than 259 MBq in any case.

^{68}Ga-PSMA-11 must be administered as a single intravenous injection at the investigational site by appropriately trained personnel. A saline flush ≥10 mL NS (normal saline) should be administered after administration of ^{68}Ga-PSMA-11 to assure that there isn't any residual drug in the intravenous line.

The instructions for 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 (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). The radioactivity measured (non decay corrected) pre and post administration and time of measurements together with the date and time of administration must be recorded in patient accountability log and in the corresponding eCRF pages.

All kits of study treatment will be recorded in the IRT system.

Standard of Care

Standard of Care should be administered as per local 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 ARDT & ADT 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 SoC 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.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 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 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 rescreened. The Participant No. consists of the Site Number (Site 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.

6.4.2 Treatment assignment, randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased 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 randomization will be stratified according to the stratification factors detailed in Section 4.1.

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

6.5 Treatment blinding

Treatment will be open to participants, investigator staff, persons performing the assessments, and the Novartis study team. However, in order to minimize the potential impact of knowledge of treatments, the randomization list will be kept strictly confidential, until the primary analysis is conducted, no aggregate statistical analyses (efficacy or safety across the study) by treatment shall be performed prior to the database lock/interim analysis. BIRC will remain blinded to the treatment assigned.

6.6 Dose escalation and dose modification

The dose of ARDT, ADT therapy as a part of Standard of Care may be adjusted as per local package insert and/or guidelines.

The dose of ^{177}Lu-PSMA-617, starting at a dose of 7.4 GBq (±10%), may be reduced or delayed as described in Section 6.6.1.

6.6.1 Dose modifications

Dose adjustments are not permitted for the investigational imaging agent during study. Dose must be administered as outlined in Section 6.1.1

For participants who do not tolerate the protocol-specified ^{177}Lu-PSMA-617 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 of ^{177}Lu-PSMA-617 treatment are summarized in Table 6-2 and Table 6-3. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent discontinuation of study treatment is mandatory for specific events indicated as such in Table 6-2 or listed in Section 9.1.1.

These dose changes must be recorded on the appropriate CRF.

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

Every effort should be made to keep the treatment cycle of 6 weeks (±1 week) at the prescribed doses. Physical exams, assessment of toxicities, along with hematology and chemistry results (cross refer to Section 8.4.1) must all be assessed prior to dosing with ^{177}Lu-PSMA-617. Table 6-2 provides dose modification criteria and guidance on dose management, which must be followed when causal relationship between ^{177}Lu-PSMA-617 and adverse event is confirmed by the investigator Table 6-3 provides the corresponding dose levels in GBq or mCi. In case of adverse events not related, in opinion of the investigator, 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.

Discontinuation of ^{177}Lu-PSMA-617 treatment is mandated regardless of the relationship between ^{177}Lu-PSMA-617 and toxicity coming from adverse event in case of:

- Any AE that requires drug discontinuation or treatment delay for >4 weeks (dose interval between the cycles more than 10 weeks)
- Any unacceptable toxicity when it may not be corrected with appropriate concomitant treatment

Only one AE/toxicity-related dose reduction is permitted. If a patient has further toxicity that would require an additional reduction in administered activity, treatment with ^{177}Lu-PSMA-617 must be discontinued.

Once a dose is reduced by 20%, treatment with ^{177}Lu-PSMA-617 should not be re-escalated.

If the treatment is delayed due to an AE or toxicity management persists for more than 4 weeks, 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 6-4 Criteria for dose reduction / interruption and re-initiation of ^{177}Lu-PSMA-617 treatment for adverse drug reactions

Dose modifications for ^{177}Lu-PSMA-617	
CTCAE Grade (lab values)[a] during a cycle of therapy	**Dose management**
Investigations (Hematologic)	
Anemia, Leukopenia, Neutropenia	
Grade 1	Recommendation: Maintain dose level and administration schedule
Grade 2 (Hemoglobin <10.0 – 8.0 g/dL White Blood Cell (WBC) count <3.0 – 2.0 × 10^9/L ANC < 1.5 – 1.0 × 10^9/L)	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 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 (dose level -1), except lymphocytopenia that responds to medical intervention. Recommendation as for grade 2
Thrombocytopenia	
Grade 1 (Platelet count < lower limit of normal (LLN) – 75 × 10^9/L)	Recommendation: maintain dose and administration schedule
≥ Grade 2 (Platelet count < 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.

Dose modifications for ^{177}Lu-PSMA-617	
CTCAE Grade (lab values)[a] during a cycle of therapy	**Dose management**
	Recommendation: platelet transfusions may be given as clinically indicated.
Investigations (Renal)	
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 next administration, 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.
Investigations (Hepatic)	
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) 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 ^{177}Lu-PSMA-617. 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 – 3.0 x ULN	Recommendation: maintain dose and administration schedule.
<u>If normal at baseline:</u> > 5.0 x ULN for more than 2 weeks, OR >10 x ULN <u>If elevated at baseline:</u> > 3.0 x baseline AND > 10 x 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

Dose modifications for ^{177}Lu-PSMA-617	
CTCAE Grade (lab values)[a] during a cycle of therapy	**Dose management**
	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 >3.0xULN 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 >2 x baseline AND >2.0 x ULN* *Note: For participants with Gilbert's syndrome, at least 2-fold increase in direct bilirubin.	Mandatory: hold ^{177}Lu-PSMA-617 and assess for Drug-Induced Liver Injury (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 6.6.2.1 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.
Investigation (metabolic)	
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) OR (> 5.0 x ULN and asymptomatic))	Recommendation: hold ^{177}Lu-PSMA-617 until resolved to Grade ≤,1 or baseline then: If resolved in ≤ 7 days, 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*

Dose modifications for ^{177}Lu-PSMA-617	
CTCAE Grade (lab values)[a] during a cycle of therapy	**Dose management**
Gastro intestinal	
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.
All dose modifications should be based on the worst preceding toxicity. [a] Common Toxicity Criteria for Adverse Events (CTCAE Version 5.0)	

Dose modifications for ^{177}Lu-PSMA-617	
CTCAE Grade (lab values)[a] during a cycle of therapy	**Dose management**
[b] Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (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: 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 6-5 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.			

In case a dose reduction is needed, full dose will be provided by the manufacturing site to the clinical site and it will be Investigator or delegates' responsibility for measuring the activity in vial and pulling out and administering the current dose activity based on the planned dose for the participant, i.e. 5.9 GBq (160 mCi) in this case. Another option for the site is to let activity decay and dose the patient later but not after the expiry date and time of the dose which is stated on the label and on the product batch release certificate.

6.6.2 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 the last dose of ARDT and 42 days after the last dose of ^{177}Lu-PSMA-617 whichever is longer. In addition, safety follow up will be continued in long-term follow up period as described in Section 9.1.1.2.

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

Participants with transaminase increase combined with elevations of total bilirubin may be indicative of potentially severe DILI. These events should be considered as clinically important 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 to be 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, GGT, prothrombin time (PT)/INR, alkaline phosphatase (ALP), albumin, and creatine kinase (CK). If feasible, 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.

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 6-6 Guidance for further assessment of drug-induced liver injury

Disease	Assessment
Hepatitis A, B, C, E	• IgM Serum antibody to hepatitis A virus (anti-HAV); Hepatitis B surface antigen (HbsAg), IgM & IgG Antibody to hepatitis B core antigen (anti-HBc), Hepatitis B Virus (HBV) DNA; Serum antibodies to Hepatitis C Virus (anti-HCV), Hepatitis C Virus (HCV) RNA, IgM & IgG Anti Hepatitis E Virus (anti-), Hepatitis E Virus (HEV) RNA
CMV, Herpes simplex virus (HSV), EBV infection	• Immunoglobulin M (IgM) & Immunoglobulin G (IgG) anti Cytomegalovirus (anti-CMV), IgM & IgG anti-HSV; IgM & IgG anti-Epstein-Barr virus (anti-EBV)
Autoimmune hepatitis	• Antinuclear Antibodies (ANA) & Anti-smooth muscle antibody (ASMA) titers, total IgM, IgG, Immunoglobulin E (IgE), Immunoglobulin (IgA)
Alcoholic hepatitis	• Ethanol history, GGT, MCV, Carbohydrate-Deficient-Transferrin (CD-transferrin)
Nonalcoholic steatohepatitis	• Ultrasound or 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, 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 mellitus / 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 DILI case and should be reported as an SAE. All potential cases of Hy's law must be reported as an SAE. For more details regarding potential Hy`s law case SAE reporting and definition please refer to Section 10.1.2 and Section 10.1.3 of the protocol.

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 a SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

6.7 Additional treatment guidance

6.7.1 Treatment compliance

For the Standard of Care, 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. Note, that the same should apply to investigational imaging radiopharmaceutical ^{68}Ga-PSMA-11 given during screening period. Administration of ARDT, ADT, ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617 must be recorded in the corresponding eCRF pages.

Participants on investigational arm will have the ^{177}Lu-PSMA-617 administered during site visits as per schedule of events, Table 8-1. 177Lu-PSMA-617 administrations must be recorded in the Drug Accountability Log and in the corresponding eCRF pages.

6.7.2 Treatment of overdose

In the event of an overdose, the Investigator/treating physician should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study treatment should be interrupted or whether the dose should be reduced.
- Document the quantity of the excess dose as well as the duration of the overdose.
- Follow standard clinical practice for overdose of systemically administered radionuclide therapy with radioligands.
- For overdose of ARDT, ADT, follow instructions as per local label

In the event of administration of a radiation overdose with ^{177}Lu-PSMA-617 or ^{68}Ga-PSMA-11, 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.

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 participants' 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 Harmonization of Technical Requirements for Pharmaceuticals for Human Use (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 medicinal products can be found in the Investigator's Brochures and/or Core Data Sheet for marketed drugs. This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also 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 (IN) or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

Participants who are rescreened are required to sign a new ICF.

The following informed consents are included in this study:

- Main study consent, which also included:
  - [redacted]
  - 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

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]. It is required as part of this protocol that the Investigator presents this option to the participants, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these optional assessments will in no way affect the participant's ability to join the main research study.

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, 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 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 8-1 lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

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. Participants should be seen for all visits/assessments as outlined in the assessment schedule Table 8-1 or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit 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 CRF.

In extraordinary situations of e.g. a potential supply disruption and/or a quality incident, the investigator may immediately be

- informed to withhold doses from impacted batch and not administer them to the participant,

and/or

- asked to closely monitor participants who have received a dose from an impacted batch for adverse events.
- advised how to manage participants in screening or on treatment in case of supply disruption.

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 by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site

again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

For participants randomized to the ^{177}Lu-PSMA-617 + SoC arm 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 8-1.

For participants randomized to the SoC treatment where COVID-19 pandemic limits or prevents on-site study visits, delivery of SoC and any alternative methods as described above may be used with approval from Novartis to continue with the study assessments as per Table 8-1 and Table 8-2. The Principal Investigator and Novartis will assess the possibility to cross-over to the ^{177}Lu-PSMA-617 treatment under COVID-19 circumstances.

Screening	-28 days from randomization in IRT system
Cycle 1 Day 1	Within [redacted] days after randomization in IRT system – (Maximum time needed to provide ^{177}Lu-PSMA-617 to the site)
Cycle 1 (all visits)	[redacted] days
Cycle 2-6 (all visits) and all subsequent cycles (all visits)	[redacted] days
Imaging evaluations	[redacted] days
EOT	[redacted] days
30-Day Safety FUP	[redacted] days
Long-term safety follow-up	[redacted] days
Long-term efficacy follow-up	[redacted] days
Survival FUP	[redacted] days

For participants randomized to the ^{177}Lu-PSMA-617 + SoC arm, C1D1 will be the day of injection of the 1st dose of ^{177}Lu-PSMA-617 and because of on demand supply will be scheduled within [redacted] after randomization.

For participants randomized to the SoC arm, C1D1 should occur within [redacted] after randomization, independently of ARDT initiation date. Every effort must be made to follow the schedule of assessments within the windows outlined in the assessment schedule Table 8-2 or as close to the designated day/time as possible.

If a given visit is out of window, the next visit should be performed with reference to the day of first dose in order to get the participant back on schedule for participant enrolled in SoC arm.

For participant enrolled in the investigational arm, next ^{177}Lu-PSMA-617 administration visit and all assessments (except imaging assessment) should be performed with reference to the previous administration of ^{177}Lu-PSMA-617 + 6 weeks [redacted]

If an off-schedule imaging assessment is performed, subsequent imaging assessments should be performed in accordance with the original imaging schedule based on [redacted] as defined in Section 8.3.1.

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

Participants who discontinue from study 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 (EOT) will be performed.

If they agree, participants who withdraw their consent/oppose the use of their data/biological samples should complete a final evaluation visit, at the time of the withdrawal, with all of the assessments listed for the final visit (EOT).

At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously recorded must be recorded on the eCRF.

Cycle 1 to 6 are 6 full weeks long. Cycle 2 D1 start 42 days after C1D1. After Cycle 6 is completed, visits will occur every 12 weeks until EOT.

Table 8-1 Assessment Schedule, ^{177} Lu-PSMA-617 + SoC and SoC arms

Period	**Screening Period / ^{68}Ga-PSMA-11 Safety follow up**		**Period 1**						**Period 2**				**Period 3**				**Period 4**	**End of Treatment**	**Post-treatment follow-up**	
Cycle			**Cycle 1**						**Cycle 2-5**				**Cycle 6**							
Visit Name	**Screening and PSMA eligibility by ^{68}Ga-PSMA-11**	**Randomization**	**C1 W1**	**C1 W2**	**C1 W3**	**C1 W4**	**C1 W5**	**C1 W6**	**C2W1, C3W1 etc..**	**C2 W3, C3 W3 etc. .**	**C2 W5, C3 W5 etc. .**	**C2 W6, C3 W6 etc. .**	**C6 W1**	**C6 W3**	**C6 W5**	**C6 W 6**	**After Cycle 6**	**End of Treatment**	**30 days safety FUP**	**24 and 48 weeks**
Days	**-42 to -14**	**-14**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**36**	**-**	**-**	**-**	**-**	**Every 12 weeks $**	**-**	**-**	**-**
Informed consent	X																			
Demography	X																			
Inclusion/exclusion criteria	X[5]																			
Medical History	X																			
Diagnostic and extend of cancer	X																			
Prior medications	X																			
Directed Physical Exam	S		S						S				S			S	S	S	S	S
Body Height	X																			
Body Weight	X								X				X			X	X	X		
ECOG	X		X					X	X			X	X			X	X	X		
Vital Signs	X		X[1]					X	X[1]			X	X[1]			X	X	X		
Electrocardiogram (ECG)	X	ECG as clinically indicated and at week 3 after last dose of ^{177}Lu-PSMA-617 or as soon as feasible thereafter																X		
Adverse Events	X***	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X***	X	X[9]

Period	**Screening Period / ^{68}Ga-PSMA-11 Safety follow up**		**Period 1**						**Period 2**				**Period 3**				**Period 4**	**End of Treatment**	**Post-treatment follow-up**	
Cycle			**Cycle 1**						**Cycle 2-5**				**Cycle 6**							
Visit Name	**Screening and PSMA eligibility by ^{68}Ga-PSMA-11**	**Randomization**	**C1 W1**	**C1 W2**	**C1 W3**	**C1 W4**	**C1 W5**	**C1 W6**	**C2W1, C3W1 etc..**	**C2 W3, C3 W3 etc. .**	**C2 W5, C3 W5 etc. .**	**C2 W6, C3 W6 etc. .**	**C6 W1**	**C6 W3**	**C6 W5**	**C6 W 6**	**After Cycle 6**	**End of Treatment**	**30 days safety FUP**	**24 and 48 weeks**
Days	**-42 to -14**	**-14**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**36**	**-**	**-**	**-**	**-**	**Every 12 weeks $**	**-**	**-**	**-**
Serious Adverse Events	Continuously from signing of screening ICF up to and including 30 days safety FUP, , or start of new post treatment anti-neoplastic medication, whichever is sooner, irrespective of relationship to study treatment***.																			X[10]
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Clinical Chemistry[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Coagulation Panel[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis, macroscopic (microscopic when indicated)	X																	X		
PSA	X								X				X			X	X	X		
Radiographic imaging (CT with contrast/MRI and bone scan)	X[3]		Every 12 weeks [redacted] - independent of dose delays - during 24 months, then every 16 weeks [redacted] until radiographic disease progression, death, WD of consent, loss to FUP, participant/guardian decision																	
EQ5D-5L[4]			X						X				X			X	X	X		X
FACT-P[4]			X						X				X			X	X	X		X
BPI-SF[4]			X						X				X			X	X	X		X

Period	**Screening Period / ^{68}Ga-PSMA-11 Safety follow up**		**Period 1**						**Period 2**				**Period 3**				**Period 4**	**End of Treatment**	**Post-treatment follow-up**	
Cycle			**Cycle 1**						**Cycle 2-5**				**Cycle 6**							
Visit Name	**Screening and PSMA eligibility by ^{68}Ga-PSMA-11**	**Randomization**	**C1 W1**	**C1 W2**	**C1 W3**	**C1 W4**	**C1 W5**	**C1 W6**	**C2W1, C3W1 etc..**	**C2 W3, C3 W3 etc. .**	**C2 W5, C3 W5 etc. .**	**C2 W6, C3 W6 etc. .**	**C6 W1**	**C6 W3**	**C6 W5**	**C6 W 6**	**After Cycle 6**	**End of Treatment**	**30 days safety FUP**	**24 and 48 weeks**
Days	**-42 to -14**	**-14**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**36**	**-**	**-**	**-**	**-**	**Every 12 weeks $**	**-**	**-**	**-**
Trial Feedback Questionnaire[4] (optional)			X						X				X			X	X	X		
IRT registration for screening	X																			
Radiolabeling - Dose Preparation ^{68}Ga-PSMA-11	X																	X**		
Administer ^{68}Ga-PSMA-11	Order/prepare Gallium same time as IRT registration																	X**		
^{68}Ga-PSMA-11 PET/CT scan	X																	X**		
IRT randomization		X[5]																		
Administer ^{177}Lu-PSMA-617			X						X				X							
[redacted]																				
Standard of Care	As per local package insert/guidelines refer to Section 6.2.1																			

Period	**Screening Period / ^{68}Ga-PSMA-11 Safety follow up**		**Period 1**						**Period 2**				**Period 3**				**Period 4**	**End of Treatment**	**Post-treatment follow-up**	
Cycle			**Cycle 1**						**Cycle 2-5**				**Cycle 6**							
Visit Name	**Screening and PSMA eligibility by ^{68}Ga-PSMA-11**	**Randomization**	**C1 W1**	**C1 W2**	**C1 W3**	**C1 W4**	**C1 W5**	**C1 W6**	**C2W1, C3W1 etc..**	**C2 W3, C3 W3 etc..**	**C2 W5, C3 W5 etc..**	**C2 W6, C3 W6 etc..**	**C6 W1**	**C6 W3**	**C6 W5**	**C6 W6**	**After Cycle 6**	**End of Treatment**	**30 days safety FUP**	**24 and 48 weeks**
Days	**-42 to -14**	**-14**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**36**	**-**	**-**	**-**	**-**	**Every 12 weeks $**	**-**	**-**	**-**
[redacted]																				
Antineoplasic therapy (medication, surgery, radiation) since discontinuation of study treatment																		X	X	X

Period	**Screening Period / ^{68}Ga-PSMA-11 Safety follow up**		**Period 1**						**Period 2**				**Period 3**				**Period 4**	**End of Treatment**	**Post-treatment follow-up**	
Cycle			**Cycle 1**						**Cycle 2-5**				**Cycle 6**							
Visit Name	**Screening and PSMA eligibility by ^{68}Ga-PSMA-11**	**Randomization**	**C1 W1**	**C1 W2**	**C1 W3**	**C1 W4**	**C1 W5**	**C1 W6**	**C2W1, C3W1 etc..**	**C2 W3, C3 W3 etc. .**	**C2 W5, C3 W5 etc. .**	**C2 W6, C3 W6 etc. .**	**C6 W1**	**C6 W3**	**C6 W5**	**C6 W 6**	**After Cycle 6**	**End of Treatment**	**30 days safety FUP**	**24 and 48 weeks**
Days	**-42 to -14**	**-14**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**36**	**-**	**-**	**-**	**-**	**Every 12 weeks $**	**-**	**-**	**-**
(See Section 9.1.1.1)																				
Survival																				
Disposition	X	X																X		

Period	**Post-treatment follow-up**	**Survival FUP**
Cycle		
Visit Name	**Long-term Efficacy FUP**	**Survival FUP**
Days	-	-
Informed consent		
Demography		
Inclusion/exclusion criteria		
Medical History		
Diagnostic and extend of cancer		
Prior medications		
Directed Physical Exam	S	
Body Height		
Body Weight		
ECOG		
Vital Signs[1]		
Electrocardiogram (ECG)		
Adverse Events	X[9]	
Serious Adverse Events	X[10]	
Concomitant medications		
Hematology[2]		
Clinical Chemistry[2]		
Coagulation Panel[2]		
Urinalysis, macroscopic (microscopic when indicated)		
PSA		
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 12 weeks [redacted] - independent of dose delays during 24 months, then every 16 weeks [redacted] until radiographic disease progression, death, WD of consent, loss to FUP, participant/guardian decision	

Period	**Post-treatment follow-up**	**Survival FUP**
Cycle		
Visit Name	**Long-term Efficacy FUP**	**Survival FUP**
Days	-	-
EQ5D-5L[4]	refer to Section 8.5.1	
FACT-P[4]	refer to Section 8.5.1	
BPI-SF[4]	refer to Section 8.5.1	
Trial Feedback Questionnaire[4]		
IRT registration for screening		
Administer ^{68}Ga-PSMA-11		
^{68}Ga-PSMA-11 PET/CT scan	Participants from both ^{177}Lu-PSMA-617+SoC and SoC arms with radiographic progression confirmed by BIRC during efficacy FUP, within 28 days of site notification	
IRT randomization		
Administer ^{177}Lu-PSMA-617		
Standard of Care		
[redacted]		
Antineoplasic therapy (medication, surgery, radiation) since discontinuation of study treatment	X	X
Survival		X
Disposition	X	

Period	Post-treatment follow-up	Survival FUP
Cycle		
Visit Name	Long-term Efficacy FUP	Survival FUP
Days	-	-

[X] Assessment to be recorded in the clinical database or received electronically from a vendor

[S] Assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database

[1] In ^{177}Lu-PSMA-617+SoC arm, temperature to be taken only once during the visit 15 (+/-5) mins prior to administration of ^{177}Lu-PSMA-617 administration. Blood pressure, pulse and respiratory rate to be assessed 15(+/-) 5 min before, 30 (+/-15) minutes post and 60 (+/-15) minutes post ^{177}Lu-PSMA-617 administration. In SoC arm, temperature, blood pressure, pulse and respiratory rate to be assessed only once during the visit approximately 15 (+/-5) mins prior to ARDT dose.

[2] Hematology, coagulation and chemistry to be done at screening before ^{68}Ga-PSMA-11 administration and pre ^{177}Lu-PSMA-617 administration (when applicable)

[3] Radiographic imaging for screening within 28 days prior randomization

[4] PRO to be completed prior to drug administration, when applicable

[5] Eligibility check to be completed prior randomization, Order ^{177}Lu-PSMA-617 the day of randomization -at the latest 2 weeks prior dosing

[6] [redacted]

[7] [redacted]

[8] [redacted]

[9] [redacted]

[10] [redacted]

[11] [redacted]

For patients enrolled in investigational arm [redacted]

For patients enrolled in SoC arm, [redacted] is defined by:

- If ARDT is initiated prior ICF signature, [redacted]
- If ARDT is initiated after randomization, [redacted]

[$]Switch from 12 weeks interval to 16 weeks interval in imaging assessments will occur at approximately Post-Cycle 6, Visit 5 (Week 96).

** PET/CT with ^{68}Ga-PSMA-11 scan should be performed in both ^{177}Lu-PSMA-617+SoC and SoC arms participants with radiographic progression confirmed centrally, within 28 days after the site receives a notification about confirmed radiographic progression and submitted to BIRC. Results will not be communicated back to the sites. In SoC arm participants who are the candidates for cross-over, this PET/CT should be preferably performed prior to initiation of ^{177}Lu-PSMA-617, and should not be used to assess potential eligibility for cross-over.

***For AE and SAE reporting after ^{68}Ga-PSMA-11 scan (performed during screening and after confirmation of radiographic progression), refer to Section 9.1.1.1

Table 8-2 Assessment Schedule, cross-over to ^{177} Lu-PSMA-617 treatment

Period	**Cross-over baseline**	**Cross-over C1**						**Cross-over C2-C5**				**Cross-over Cycle 6**				**Cross-over End of Treatment**	**Post-treatment follow-up**		**Survival FUP**
Cycle	**(SCREENING)**	**Cycle 1**						**Cycle 2-5**				**Cycle 6**							
Visit Name	**CO baseline - upon rPFS**	**C1 W1**	**C1 W2**	**C1 W3**	**C1 W4**	**C1 W5**	**C1 W6**	**C2W1, C3W1 etc...**	**C2W3, C3W3 etc....**	**C2W5, C3W5 etc....**	**C2W6, C3W6 etc....**	**C6 W1**	**C6 W3**	**C6 W5**	**C6 W6**	**End of Treatment**	**30 days safety FUP**	**24 and 48 weeks**	**Survival FUP**
Days		**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**36**	**-**	**-**	**-**	**-**	**-**	**-**		**-**
Inclusion/exclusion criteria	X																		
Directed Physical Exam	S	S						S				S			S	S	S	S	
Body Height																			
Body Weight	X							X				X			X	X			
ECOG	X	X					X	X			X	X			X	X			
Vital Signs[1]	X	X					X	X			X	X			X	X			
Electrocardiogram (ECG)	X	ECG as clinically indicated and at week 3 after last dose of ^{177}Lu-PSMA-617 or as soon as feasible thereafter														X			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[9]	
Serious Adverse Events	Continuously from signing of screening ICF up to and including 30 days safety FUP, or start of new post treatment anti-neoplastic medication, whichever is sooner, irrespective of relationship to study treatment.																	X[10]	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Clinical Chemistry[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	

Period	**Cross-over baseline**	**Cross-over C1**						**Cross-over C2-C5**				**Cross-over Cycle 6**				**Cross-over End of Treatment**	**Post-treatment follow-up**		**Survival FUP**
Cycle	**(SCREENING)**	**Cycle 1**						**Cycle 2-5**				**Cycle 6**							
Visit Name	**CO baseline - upon rPFS**	**C1 W1**	**C1 W2**	**C1 W3**	**C1 W4**	**C1 W5**	**C1 W6**	**C2W1, C3W1 etc...**	**C2W3, C3W3 etc....**	**C2W5, C3W5 etc....**	**C2W6, C3W6 etc....**	**C6 W1**	**C6 W3**	**C6 W5**	**C6 W6**	**End of Treatment**	**30 days safety FUP**	**24 and 48 weeks**	**Survival FUP**
Days		**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**36**	**-**	**-**	**-**	**-**	**-**	**-**		**-**
Coagulation Panel[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Urinalysis, macroscopic (microscopic when indicated)	X															X			
PSA	X							X				X			X	X			
Radiographic imaging (CT with contrast/MRI and bone scan)	X[7]	Every 12 weeks [redacted] from first dose of ^{177}Lu-PSMA-617 - independent of dose delays during 24 months, then every 16 weeks [redacted] until radiographic disease progression, death, WD of consent, loss to FUP, participant/guardian decision[11]																	
EQ5D-5L[3]		X						X				X			X	X			
FACT-P[3]		X						X				X			X	X			
BPI-SF[3]		X						X				X			X	X			
Trial Feedback Questionnaire [3](optional)		X						X				X			X	X			
IRT registration for cross over	X																		

Period	**Cross-over baseline**	**Cross-over C1**						**Cross-over C2-C5**				**Cross-over Cycle 6**				**Cross-over End of Treatment**	**Post-treatment follow-up**		**Survival FUP**
Cycle	**(SCREENING)**	**Cycle 1**						**Cycle 2-5**				**Cycle 6**							
Visit Name	**CO baseline - upon rPFS**	**C1 W1**	**C1 W2**	**C1 W3**	**C1 W4**	**C1 W5**	**C1 W6**	**C2W1, C3W1 etc...**	**C2W3, C3W3 etc....**	**C2W5, C3W5 etc....**	**C2W6, C3W6 etc....**	**C6 W1**	**C6 W3**	**C6 W5**	**C6 W6**	**End of Treatment**	**30 days safety FUP**	**24 and 48 weeks**	**Survival FUP**
Days		**1**	**8**	**15**	**22**	**29**	**36**	**1**	**15**	**29**	**36**	**-**	**-**	**-**	**-**	**-**	**-**		**-**
Administer ^{177}Lu-PSMA-617[4]		X						X				X							
[redacted]																			
Standard of Care	As per local package insert/guidelines refer to Section 6.2.1																		
[redacted]																			
Antineoplastic therapy (medication, surgery, radiation) since discontinuation of study treatment (Refer to																X	X	X	X

Period	Cross-over baseline	Cross-over C1						Cross-over C2-C5				Cross-over Cycle 6				Cross-over End of Treatment	Post-treatment follow-up		Survival FUP
Cycle	(SCREENING)	Cycle 1						Cycle 2-5				Cycle 6							
Visit Name	CO baseline - upon rPFS	C1 W1	C1 W2	C1 W3	C1 W4	C1 W5	C1 W6	C2W1, C3W1 etc...	C2W3, C3W3 etc....	C2W5, C3W5 etc....	C2W6, C3W6 etc....	C6 W1	C6 W3	C6 W5	C6 W6	End of Treatment	30 days safety FUP	24 and 48 weeks	Survival FUP
Days		1	8	15	22	29	36	1	15	29	36	-	-	-	-	-	-		-
Section 9.1.1.1)																			
Survival																			X
Disposition																X			

[X] Assessment to be recorded in the clinical database or received electronically from a vendor

[S] Assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database

[1] Temperature to be taken only once during the visit 15 (+/-5) mins prior to administration of ^{177}Lu-PSMA-617. Blood pressure, pulse and respiratory rate to be assessed 15(+/-) 5 min before, 30 (+/-15) minutes post and 60 (+/-15) minutes post ^{177}Lu-PSMA-617 administration

[2] Hematology, coagulation and chemistry to be done pre ^{177}Lu-PSMA-617 administration (when applicable)

[3] PRO to be completed prior to drug administration, when applicable

[4] Order ^{177}Lu-PSMA-617 as per pharmacy manual guidance

[5] [redacted]

[6] [redacted]

[7] No new images will be required, and EOT images will be used for Cross-over baseline visit (incl. disease evaluation at cross-over baseline)

[8] [redacted]

[9] [redacted]

[10] [redacted]

[11] Radiographic imaging assessments for patients in cross-over will be assessed locally.

8.1 Screening

Screening

Written informed consent must be obtained prior to any study related 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-PSMA-11 requested for the PET/computed tomography (CT) scan to evaluate PSMA positivity. Participants who meet criteria for PSMA positivity and eligibility related to ^{68}Ga-PSMA-11 as evaluated by BIRC will be allowed to enter the study as defined in Section 3. Randomization will be stratified by Low vs high volume / age / Previous or planned treatment (prostatectomy or radiation) to primary (prostate) tumor (Yes vs No) as defined in Section 3.

All screening/baseline assessments should occur within 28 days before randomization. Assessments performed before the main study consent signature can be used as part of the screening procedures and for the confirmation of the eligibility criteria as long as they are within predefined time window of 28 days prior to randomization.

Screening blood samples (including chemistry, hematology and coagulation) must be collected before the ^{68}Ga-PSMA-11 administration.

Screening assessments include physical examination, vital signs, body height and weight, ECOG, ECG, laboratory (hematology, chemistry, urinalysis, PSA), evaluation of all relevant medical history including cardiovascular risk factors, prostate cancer disease history, including staging according to American Joint Committee on Cancer (AJCC) (Appendix 7, Buyyounouski et al 2017, prior antineoplastic medication, prior and concomitant medication, and must be performed prior to randomization. Imaging assessments at screening will include the following:

- ^{68}Ga-PSMA-11 PET/CT scan, to evaluate PSMA-positivity and eligibility as defined in Section 3
- CT with contrast/MRI imaging, to evaluate so-called “soft tissue” disease burden and document evidence of lymph node, visceral, other extraosseous metastases
- Bone scans with technetium-99m labeled diphosphonates, to evaluate bone disease burden and document evidence of bone metastases

Based on bone scan/CT/MR images, a disease will be qualified as high or low volume, it will be used for stratification (refer to Section 4.1 and Section 8.3). For details of assessments required during screening please refer to Section 8.3.1 and Table 8-1.

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

The results of the hematology and chemistry screen as well as the central reading of PET/computed tomography (CT) scan to evaluate PSMA positivity and eligibility related to ^{68}Ga-PSMA-11 PET/CT scan must be available prior to randomization to evaluate eligibility.

A participant who has a laboratory test (peripheral blood test) or ECG results that do not satisfy eligibility criteria may have the tests repeated. These tests may be repeated as soon as the

investigator considers but should be completed within the 28 day screening period. 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 the laboratory tests 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. 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 [redacted], should be performed when the participant is re-screened for participation in the study.

A participant may only be re-screened once for the study. If a participant undergoes re-screening following screen failure, the results of assessments (including, but not limited to images) performed prior to a decision to rescreen the participant, may be used for rescreening as long as they were performed within protocol-predefined timelines. 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-PSMA-11 positivity confirmed by BIRC), the investigator or designee may proceed with randomization in IRT system.

Please refer to Section 6.4.2 and Section 3 as well as comply with 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 and data will be handled in the same manner.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, Inclusion/Exclusion, withdrawal of consent (WoC) (if applicable) and death (if applicable) pages must also be completed for screen failure participants. For the participants who had PET/CT imaging assessment with ^{68}Ga-PSMA-11 prior to registration of screening failure the following information will be collected:

- Data related to PET/CT with ^{68}Ga-PSMA-11 (dose preparation, dose administration, adverse events if applicable)

- Data about mHSPC treatment prior to PET/CT with ^{68}Ga-PSMA-11 (ADT, ARDT given for metastatic disease, radiotherapy on distant metastases) if the participant does not meet criteria for PSMA positivity and eligibility related to ^{68}Ga-PSMA-11 by BIRC

Other data will not be collected in the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening period (see Section 10.1.2 and Section 10.1.3 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 CRF.

Participant demographic 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 condition (until date of signature of informed consent) will be recorded. Where possible the 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 on the appropriate page of the eCRF. Investigators will have the discretion to record abnormal test findings on the appropriate CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

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

- ECOG PS, height and Weight, Body temperature, BP and Pulse measurements
- Laboratory evaluations: Hematology, Chemistry and Urinalysis test, PSA

Assessment that will be used for stratification:

- Age (full years at time of signed inform consent)
- Low/High Volume Disease based on bone scan/CT/MR images
- Previous or planned treatment (prostatectomy or radiation) to primary (prostate) tumor

Medical history:

- Prostate cancer prior history incl. date of initial diagnosis, AJCC stage (Buyyounouski et al 2017), pathology, Gleason Score etc. of prostatic cancer and PSMA result with ^{68}Ga-PSMA-11 PET/CT scan. Please refer to Appendix 7 and Appendix 8
- Prior and concomitant medications which related to the prostate therapy and best supportive care/ standard of care, date of response

- Date and type of progression (e.g. PSA, radiographic, metastasis to bone, Soft tissue or no clinical benefit) and date of progressive disease (PD)
- 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.
- All other clinically important medical/surgical interventions, and medical conditions 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

8.3.1 Radiographic imaging for tumor assessment

Tumor response of soft tissue, lymph node, and visceral lesions to treatment will be assessed locally and centrally according to Novartis guideline version 3.2 (Appendix 2 Section 16.2) based on RECIST 1.1 (Eisenhauer et al 2009) with caveats outlined in the PCWG3 recommendations (e.g., to optimally identify at least 1 target lesion from each major site of metastatic spread, and up to 5 target lesions per site of metastatic spread in total, distinguishing pelvic from extrapelvic nodes, etc. as well as 2+2 rules for progression and assessment of bone disease) (Appendix 3 Section 16.3). The imaging assessment collection plan is presented in Table 8-5. Details of the central review process will be described in the independent review charter.

Radiologic assessment should follow RECIST 1.1 with the caveats as outlined in PCWG3 guidelines. The modification used for this trial is limited to the periodicity of the scan schedule (i.e., q 12 weeks x 2 years, and q 16 weeks thereafter). Periodic radiographic imaging will include both:

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

At Screening/Baseline, the sites of disease present will be identified.

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/MR images. The distribution of the target and non-target lesions should be representative of the participant’s overall disease. Note, that for the purpose of the study a maximum of five (5) target lesions per site of metastatic spread (per PCWG3, disease site; 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 the 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 soft tissue component of bone metastasis, 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 and should not be selected as target or non-target (except soft tissue component as described above) even when detectable on CT/MRI images.

For more details on imaging assessment collection plan, please refer to Table 8-5.

For more details on adjustments of RECIST 1.1 criteria based on the caveats outlined in PCWG3 and used in this study, please refer to the Appendix 9.

Bone disease response will be assessed locally and centrally according to PCWG3 recommendations. Disease progression by bone scan criteria (2+2 PCWG3 criteria, Scher et al 2016) will be met if

- For scan at Week 12: at least 2 new bone lesions at the first on-treatment scan (i.e., the week 12 scan), that persist on the next scan, with at least two additional lesions on the next (confirmatory) scan
- For scans after the [redacted] flare window: the first observation of at least two new lesions relative to the baseline scan confirmed on a subsequent scan

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

Table 8-3 Bone Disease response

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	Time window when pre-existing lesions become more visible because of the tumor flare phenomenon; 1st on-treatment scan performed at Week 12 (or any time within [redacted]) is within flare window
Outside Flare Window	Any time points after the 1st On-Treatment Scan and beyond [redacted] flare window

Table 8-4 Bone 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
[redacted] of treatment	Two (2) or more new lesions within the flare window	At least [redacted] after progression is initially identified	Two (2) or more additional new lesions outside the flare window compared to the prior scan
[redacted] of treatment	Two (2) or more new lesions outside the flare window	At least [redacted] after progression is initially identified	Persistence of bone lesions compared to prior scan

A superscan is defined as a bone scan which demonstrates markedly increased skeletal radioisotope uptake relative to soft tissue in association with absent or faint activity in the kidneys and genitourinary system, and characterized by diffuse uptake throughout the bones, little to no kidney uptake, and reduced sensitivity for detecting metastatic osteoblastic lesions and determining new sites of bone disease.

- The participants with superscan at screening/baseline may be enrolled when meet other eligibility criteria.
- If baseline superscan is identified, subsequent timepoints are limited to UNK, Non-PD, or PD (based on appearance of new lesions in the areas not affected on superscan).
- If superscan has not seen at baseline, and identified first during the study, on-study superscan will be assessed as PDu, confirmatory scan required

Radiographic imaging assessments are to be scheduled based on the following [redacted]:

- For patients enrolled in ^{177}Lu-PSMA-617 + SoC arm, [redacted]. C1D1 date in investigational arm does not depend on ARDT initiation date.
- For patients enrolled in SoC arm, [redacted] to schedule post-baseline scans is defined by:

  - If ARDT is initiated prior ICF signature, [redacted]
  - If ARDT is initiated after randomization, [redacted]
- For patients who cross-over to receive ^{177}Lu-PSMA-617, [redacted]
- Radiographic imaging assessments are:
  - to be performed from [redacted] as defined above every 12 weeks [redacted] for the first 24 months, then every 16 weeks [redacted]
  - independent of dose delays,
  - to be continued, as per above schedule, for participants who discontinue treatment for reasons other than documented radiographic progression, death, lost to follow-up or withdrawal of consent.
  - must be completed at end of treatment (EOT/EOT2) Visit if the last scan was done more than 12 weeks (for patients in the study for less than 24 months), or more than 16 weeks (for patient in the study for more than 24 months).

The disease progression will be assessed via blinded centralized review of radiographic images provided by the treating physician for participants randomized in either arm.

Upon the occurrence of radiographic progression confirmed by BIRC, 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.

Participants randomized to SoC only 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. Subsequent images collected as per the schedule for patients who cross-over to ^{177}Lu-PSMA-617 will not be assessed by BIRC.

For cross-over participants on ^{177}Lu-PSMA-617, upon the occurrence of the second progression, participants may enter the long-term follow up period and continue to receive any other therapy per the discretion of the treating physician.

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 for primary analysis 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 patient to another imaging center, when feasible. Those visits might be scheduled as close as possible to study schedule.

Table 8-5 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 12 weeks [redacted] for the first 24 months and then every 16 weeks until confirmation of radiographic progression by BIRC
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 12 weeks [redacted] for the first 24 months and then every 16 weeks until confirmation of radiographic progression by BIRC
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 (i.v.) 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. brain, neck), if clinically indicated

Whole body bone scan with technetium-99m labeled diphosphonates should be performed per institutional standard of care. If clinically indicated, CT or MRI of other areas (e.g. brain, neck, 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. Other methods, including but not limited to X-Ray and/or ultrasound of any area will not be used in this study to evaluate disease burden at screening/baseline and to assess response.

Post-baseline imaging assessments

Imaging assessments as described in Table 8-5 should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 8-1). Imaging assessments for response evaluation will be performed every 12 weeks [redacted] during the 24 months, and every 16 weeks [redacted] thereafter until disease progression, death, lost to follow-up or withdrawal of consent, as applicable.

Frequency of response assessment should be respected regardless any delays in study treatment, date of previous response assessment, or unscheduled assessments. Time points of response assessment should be calculated from [redacted] as described above with consideration of recommended intervals and regardless of any shift in study treatment administration.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the response assessment for a participant, as necessary. For "soft-tissue" disease, an additional confirmatory CT or MRI scan of chest, abdomen and pelvis is not mandated to confirm complete or partial response. 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 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 compliment the documentation of radiographic progression per the Prostate Cancer Working Group 3 (PCWG3) Guidelines, but will not be used 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 BIRC as per investigator's request. 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 this request to the imaging CRO on a designated form or by alternative means. 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 continues 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 8-1) 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.

In summary, for expedited timepoints (assessed as PD by local):

Rapid image transmission to the central imaging CRO may be accomplished by uploading all digital images acquired by the Investigator in a secured website, while preserving the blinded status of the images.

- If BIRC determines PD, the study site will be informed. Study drug may continue to be administered beyond BIRC-confirmed PD until such time as the patient is no longer clinically benefiting, as determined by the investigator.
- If BIRC does not conclude PD, the study site will be informed. As long as it is clinically acceptable, every effort should be made to continue the participant on study drug until PD is determined by BIRC or for at least one subsequent radiological timepoint.

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 except expedited review requests to confirm radiographic progression suspected by the site.

For patients who cross-over to ^{177}Lu-PSMA-617 after their first rPFS event, imaging timepoints will not be submitted to the designated imaging CRO, those assessments will only be read as per local procedure.

Once the number of rPFS events determined by BIRC have been reached and the cut-off date for the primary anaylsis has been confirmed, only images done during the treatment period will be send to the designated imaging CRO.

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.

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, home nursing visits directed by investigator might be considered (as close as possible to the visits as per schedule) until the participant can again visit the site.

8.3.3 Clinical Progression

Clinical progression will be assessed by the investigator and will be declared when a participant has met at least one of the following criteria used to determine unequivocal evidence of clinical progression:

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

For participant requiring palliative therapy within 12 weeks after randomization and beyond refer to Section 6.2.1.

8.3.4 PSA levels

Central lab will measure PSA levels (Section 8.4.1). Increases and decreases will be tracked to assess PSA responses as per PCWG3 (Appendix 3 Section 16.3).

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, 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 revised RECIST guideline, version 1.1 (Eisenhauer et al 2009) with the caveats as outlined in PCWG3 recommendations. PCWG, Prostate Cancer Working Group is an international working group of clinical and translational research experts in prostate cancer who developed internationally recognized recommendations on trial design and objectives. For the purpose of the study updated recommendations from PCWG3 will be utilized (Scher at al 2016).

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 can 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 Section 10.1.

Table 8-6 Assessments & Specifications

Assessment	Specification
Directed Physical examination	A complete physical examination will include the examination of general appearance, eyes, ears, nose, throat, skin, neck (including thyroid), lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, will be performed. 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 CRF 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 blood pressure (supine position preferred when ECG is collected), respiratory rate, pulse measurement, and body temperature. Temperature needs to be recorded only once during the visit prior study treatment.
Height and weight	Height in centimeters (cm) or inches and body weight (to the nearest 0.1 kilogram (kg) or pounds in indoor clothing, but without shoes

Performance status:

ECOG Performance status scale will be used as described in Table 8-7.

Table 8-7 ECOG status

Grade	ECOG 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 e.g., light house work, 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 self-care. Totally confined to bed or chair
5	Dead

8.4.1 Laboratory evaluations

Central laboratory will be used for analysis of hematology, chemistry, urinalysis and PSA testing (safety monitoring) according to the schedule of assessments as described in Table 8-1 and Table 8-2 and collection plan outlined respectively. 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 [redacted] to confirm a dose reduction or a dose delay. The samples need to be taken prior 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 [CAAA617C12301 Laboratory Manual]. If local laboratory is used for the analysis of samples, the local procedures will be followed (note, that when local laboratory is used for eligibility evaluation, eGRF (estimated glomerular filtration rate) should be calculated locally using MDRD equation, the local laboratory/investigator may use available MDRD calculators such as // calculator.net/gfr-calculator.html).

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 Common Terminology Criteria for Adverse events (CTCAE) version 5 (Section 16.1). Additional analyses are left to the discretion of the investigator.

If local laboratories are used, 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 CRF via the lab normal range (LNR) form. 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.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, ie. Pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site for protocol specified safety lab assessments, a, alternative lab (local) collection site may be used.

Table 8-8 Laboratory evaluation

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Erythrocytes, Leukocytes, 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, Creatine kinase (CK), Direct Bilirubin, Total Bilirubin, Urea Nitrogen and Urea, Uric Acid, Amylase, Lipase, Glucose , eGFR (calculated using MDRD equation) at screening
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Occult Blood, Macroscopic Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) if needed Microscopic Panel (Erythrocytes, Leucocytes, Casts, Crystals, Bacteria, Epithelial cells) will be added
Coagulation	International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
PSA	PSA

Hematology

Hematology tests are to be performed according to the Visit Schedules outlined in Table 8-1 and Table 8-2. For details of the hematology panel refer to Table 8-8. Hematology should be assessed on the actual scheduled day, even if study drug is being withheld.

Hematology test should be done pre ^{68}Ga-PSMA-11 and pre ^{177}Lu-PSMA-617 administration, when applicable.

More frequent hematology testing may also be performed as medically necessary. Additional results from unscheduled hematology lab evaluations should be recorded on the appropriate unscheduled visit eCRF.

Clinical chemistry

Clinical chemistry tests are to be performed according to the visit schedule outlined in Table 8-2. For details of the biochemistry panel see Table 8-8. Biochemistry should be assessed on the actual scheduled day, even if study drug is being withheld.

Clinical chemistry test should be done pre ^{68}Ga-PSMA-11 and pre ^{177}Lu-PSMA-617 administration, when applicable.

More frequent chemistry testing may also be performed as medically necessary. Additional results from unscheduled chemistry lab evaluations should be recorded on eCRF as unscheduled visit.

Urinalysis

Urinalysis Dipstick measurements will be performed as per Table 8-8 and according to the schedule of assessments (Table 8-2). Any significant findings on dipstick will be followed up with microscopic evaluation.

8.4.2 Electrocardiogram (ECG)

Electrocardiograms (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 appropriately signed must be collected and archived at the study site. If heat sensitive paper is used, a certified copy on non-heat sensitive paper must be also 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.

Any identifier details must be redacted e.g. participant initials, date of birth.

Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or adverse events as appropriate.

A standard 12 lead ECG will be performed at least:

- at screening and/or baseline
- at week 3 after last dose of ^{177}Lu-PSMA-617 or as soon as feasible thereafter
- at the end of treatment visit

Interpretation of the tracing must be made by a qualified physician and documented on the appropriate eCRF. Each ECG tracing should be labeled with the study number, participant initials (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.

8.4.2.1 Cardiac imaging - MRA (magnetic resonance angiography), MUGA (multiple gated acquisition) scan or echocardiogram

Not applicable

8.4.2.2 Cardiac enzymes

Not applicable

8.4.3 Pregnancy

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 ^{177}Lu-PSMA-617 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 day of the ^{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).

Participant receiving standard of care treatment (ADT and ARDT) must follow contraceptive requirements as detailed in the local SmPC for the respective drug.

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.

All PRO data will be collected on an electronic 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(s) must be reviewed and assessed by the investigator 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.

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.

The PRO measures used in this study will be the BPI-SF, Fact-P and the EQ-5D-5L, further described below.

PRO measures will be assessed at C1D1, then at D1 of each cycle up to cycle 6, at week 6 of cycle 6 and then decrease to every 12 weeks thereafter, up to End of Treatment. Assessments will be collected during post treatment follow up at W24, and W48. Patients who prematurely discontinued for any reason other than disease progression, lost of follow-up or withdraw consent, will continue PRO assessments at the same timepoint as the radiographic assessments during the long term efficacy follow up. See Table 8-1 and Table 8-2.

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, telephone interviews) depending on local regulations, technical capabilities, and following any applicable training in the required process.

8.5.1.1 Brief Pain Inventory- Short Form (BPI-SF)

The Brief Pain Inventory - Short Form (BPI-SF) is a 9 item self-administered questionnaire used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning. The patient is asked to rate their worst, least, average, and current pain intensity, list current treatments and associated relief, as well as to rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 10 point scale. The BPI-SF has become the standard for use in clinical trials.

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

A copy of the BPI-SF questionnaire is provided in Appendix 6, Section 16.6.

8.5.1.2 EQ-5D-5L

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 and de Charro 2001). EQ-5D was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (The EuroQoL Group 1990).

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

EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics and face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete.

Instructions to respondents are included in the questionnaire. The most recent version of EQ-5D is the EQ-5D-5L, which was developed to improve the instrument's sensitivity and to reduce ceiling effects. The number of dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) has not changed, however the new version includes five levels of severity in each of the existing dimensions in place of three (EuroQoL 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. A copy of the EQ-5D-5L questionnaire is provided in Appendix 4, Section 16.4.

8.5.1.3 FACT-P

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/FACITOrg/Questionnaires.

A copy of the questionnaire (FACT-P version 4) is provided in Appendix 5 Section 16.5.

8.5.1.4 Trial Feedback questionnaire

This study includes an optional questionnaire, 'Trial Feedback Questionnaire'(TFQ) for trial to 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 is not considered as trial data. TFQ data will be received electronically outside the clinical database.













[redacted]

[redacted]

9 Discontinuation and completion

9.1 Discontinuation from study treatment and 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 administration) and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

In addition to mandatory discontinuation of study treatment for toxicity listed in Section 6.6.1 and Table 6-2. Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Investigator decision
- Use of prohibited treatment as per recommendations in the prohibited treatment Section 6.2.2
- Any situation in which continued study participation might result in a safety risk to the participant
- Disease progression per modified RECIST 1.1 with caveats outlined in PCWG3 as determined by investigator and confirmed by BIRC. In some circumstances participants may be allowed to continue to receive study treatment beyond radiographic disease progression (as per RECIST 1.1 with caveats outlined in PCWG3) if they continue to derive clinical benefit, as determined by the investigator. These participants will continue assessments as outlined in Table 8-1 or Table 8-2 as applicable, and will complete the end of treatment visit only after permanent discontinuation of study treatment
- Adverse event requiring permanent discontinuation of study treatment
- Protocol deviation that results in a significant risk to participant's safety

- Withdraw of consent (see Section 9.1.2)
- Study is terminated by the sponsor (see Section 9.4)
- Death
- Lost to follow-up
- Any laboratory abnormalities that in the judgment of the investigator, prevents the participant from continuing participation in the study

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information.

^{68}Ga-PSMA-11

Since the ^{68}Ga-PSMA-11 PET investigational imaging agent is administered as a single intravenous injection, discontinuation of the investigational imaging agent is not applicable.

For participants randomized into the investigational arm

The End of Treatment visit will take place when both ^{177}Lu-PSMA-617 and ARDT (as standard of Care) are permanently discontinued. A first switch to ARDT prior to rPFS event by BIRC is not considered as permanent discontinuation of Standard of Care. If a second switch of ARDT occurs (from second to third ARDT prior to rPFS by BIRC), then it will be considered as permanent discontinuation of the Standard of Care in investigational arm. Note, that the participant remains on treatment as long as he remains on one of the treatment components (^{177}Lu-PSMA-617 or SoC/ARDT), while permanently discontinued from another. If ^{177}Lu-PSMA-617 is the last treatment to be permanently discontinued, the full cycle must be completed with regular safety visits. The EOT visit should take place <=7 days after the cycle is completed.

If ARDT is the last treatment to be permanently discontinued, the EOT visit should take place when ^{177}Lu-PSMA-617 is discontinued and the full cycle is completed + <=7 days or <=7 days after the last dose of ARDT, whichever occurs last.

When a participant in the investigational arm has radiographic progression confirmed by BIRC, PET/CT with ^{68}Ga-PSMA-11 should be performed within 28 days after the site received a notification about confirmed radiographic progression by BIRC (refer to Section 6.1.1 and Table 8-1).

For participants randomized in the control arm

End of Treatment visit will take place when the ARDT (as Standard of Care) is permanently discontinued. EOT visit must occur <= 7 days after the last dose of ARDT. A first switch to ARDT prior to rPFS event by BIRC is not considered as permanent discontinuation of Standard of Care. If a second switch of ARDT occurs, then it will be considered as permanent discontinuation of the Standard of Care in the control arm as described above for investigational arm.

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

When a participant in the control arm has radiographic progression confirmed by BIRC, PET/CT with ^{68}Ga-PSMA-11 should be performed within 28 days after the site received a notification about confirmed radiographic progression from a central reader (regardless of if considered for cross-over or not, refer to Section 6.1.1 and Table 8-1).

Study cross-over participants for whom ^{177}Lu-PSMA-617 is discontinued must have a second End of Treatment (EOT2) visit performed ≤ 7 days after the cycle is completed and enter the Post-treatment Follow-up as per the assessment indicated in Table 8-2.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2). **Where possible, they should return for the assessments indicated** in the Assessment Schedule. 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 as specified in the lost to follow-up section (Section 9.1.3). This contact should preferably 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, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

In some circumstances participants may be allowed to continue to receive study treatment beyond BIRC-confirmed radiographic progression. These participants will continue assessments as outlined in the assessments section and will complete the EOT visit only after permanent discontinuation of study treatment.

9.1.1.1 Follow up for safety evaluations

Regardless of the reason for discontinuation from study treatment (See Section 9.1.1), participants will be contacted for a safety follow-up 30 days after the EOT visit. All participants will have a 30 day [redacted] onsite safety follow-up visit. If on site safety visit is not possible, the site must put all effort to collect safety information remotely.

If the participant begins any post-treatment antineoplastic medication before the 30 day safety follow-up period is complete, the collection of new SAEs and AEs unrelated to ^{177}Lu-PSMA-617 will stop, and, thereafter, only suspected AEs and suspected SAEs will continue to be

collected up to day 30. Suspected SAEs and all AE/SAE linked to the study procedures will continue to be collected beyond the 30 day safety visit.

AEs, concomitant medications and antineoplastic therapies since discontinuation of study treatment will be recorded on the appropriate eCRFs during this follow-up period. Reasons for no administration of subsequent antineoplastic medications since discontinuation of study treatment will be collected in all participants who did not start new antineoplastic medication after study treatment permanent discontinuation.

For participants who undergo PET/CT with ^{68}Ga-PSMA-11 at time of radiographic progression confirmed by BIRC, AE monitoring will continue for 14 days after administration of ^{68}Ga-PSMA-11.

9.1.1.2 Follow-up for long term safety and efficacy evaluations

After the 30 days safety follow-up visit (FUP), all participants will be followed for a long-term safety follow-up, for a period of approximately 12 months; visits are to be done at 24 weeks and 48 weeks after the EOT visit [redacted] If a new antineoplastic therapy (e.g., docetaxel) is initiated after study treatment, safety follow-up will be made only on AE/SAEs suspected to be related to study treatments, [redacted]

For participants who discontinue treatment for reasons other than documented disease progression confirmed by BIRC, death, lost to follow-up, or withdrawal of consent as applicable, tumor assessments must continue to be performed every 12 weeks for the first 24 months, or every 16 weeks thereafter, until documented disease progression confirmed by BIRC, death, lost to follow-up, or withdrawal of consent as applicable, or if the total number of protocol-defined rPFS events has occurred triggering the primary analysis, whichever occurs first.

9.1.1.3 Survival Follow-up

Participants will enter the survival follow-up period once they complete the 30-day safety follow-up and/or long-term safety/efficacy follow-up after discontinuation of study treatment (whichever is longer). Participants will then be contacted by telephone every 12 weeks to follow-up on their survival status. Any new antineoplastic therapies that have been started since the last contact date will also be collected during these phone calls. At this time, the investigator will record any SAEs that may have occurred after discontinuation of study treatment if the investigator suspects a causal relationship to study treatment. This follow-up will allow medically significant long-term toxicities to be captured, such as long-term radiotoxicity. The telephonic visits will be carried out every 12 weeks (± 30 days) until death, lost to follow-up, withdrawal of consent or accrual of the number of events required for the planned analyses for OS for the study, whichever occurs first.

Every effort should be made to comply with the survival follow-up schedule and ensure collection of participant survival data.

9.1.1.4 Long term Follow-up study

Participants who have received ^{177}Lu-PSMA-617 and as soon as they enter the survival follow-up on the trial, will be asked to join a separate study (CAAA617A12402) of long-term safety

as requested by health authorities. This long-term follow-up study will last up to 10 years after their first day of treatment with ^{177}Lu-PSMA-617.

Participants who enter the separate long-term safety follow-up study (CAAA617A12402) will remain on long-term follow-up in this study (CAAA617C12301) as well. The participant's survival status, AEs, SAEs and anti-neoplastic therapy (as detailed in Table 8-1 and Table 8-2) will continue to be collected every 12 weeks in CAAA617C12301 study until its completion as per definition in Section 9.3.

9.1.2 Participant 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 or fail to respond to any site attempts to contact them without stating an intention to discontinue or withdraw, 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 participant's data privacy rights

Participants may voluntarily withdraw consent/opposition to use of data/ and/or biological samples to participate in the study for any reason at any time. Withdrawal of consent occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data
- 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 per local regulation (e.g.in writing) 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/exercise data/privacy rights and record this information. The Investigator shall clearly document if the

participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data/privacy rights should be made as detailed in the assessment table (refer to Section 8).

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

For an individual participant

Study treatment completion is defined when the participant completes all post-treatment follow-up (including 30-day safety follow-up after EOT, (or EOT2 if cross-over occurs) or tumor assessment until PD, whichever is longer). The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation. The appropriate disposition eCRF must be completed, giving the date and reason of post-treatment follow-up discontinuation. After this, participant will enter survival follow-up and will be asked to join the long term safety follow-up study in parallel (CAAA617A12402). The visits will be carried out every 12 weeks (± 30 days) until death, lost to follow-up, withdrawal of consent or accrual of the number of events required for the planned analyses for OS for the study, whichever occurs first.

For the study

The primary analysis will occur when approximately the required [redacted] of rPFS events is reached (refer to Section 12.8.1). At this time, the primary clinical study report (CSR) will be produced. After the primary analysis of rPFS, the study will remain open provided the rPFS demonstrates treatment benefit. Participants still being followed on the study after the primary analysis time point will continue as per the schedule of assessments.

The study will end once the final OS analysis is performed, approximately when the [redacted] deaths are observed or when statistical significance is reached for OS analysis, (see Section 12.8.2) and the final analysis of study data is conducted. All available data from all participants up to this cutoff date will be analyzed.

Post-trial access

At the end of the study and 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, and until such time as the product is launched or reimbursed (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.

Post-Trial Access (PTA) will be provided until one of the following is met: participant no longer derives clinical benefit, Investigator discontinues treatment, launch or reimbursement (where applicable), treatment fails to achieve registration in the trial participant's country, or the clinical program is discontinued for any other reason.

Mechanisms for provision of PTA may include an extension period to this study, a separate extension protocol, a rollover protocol, provision of the Novartis investigational product in a non-trial setting (known as post-study drug supply [PSDS]) when no further safety or efficacy data are required, or any other mechanism appropriate for the country.

The PTA mechanism must comply with local laws and regulations in the participating trial countries. If Novartis discontinues the PTA for this trial, Novartis will work with Investigators to transition participants onto locally available alternative treatment or standard of care.

Participants continuing to derive benefit from the comparator treatment (SoC) in the opinion of the Investigator may continue such treatment at the Investigator's discretion according to local clinical practice outside of this clinical trial. If the primary analysis of rPFS does not demonstrate treatment benefit, the follow-up for OS will end.

9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (including but not limited to):

- 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 rPFS analysis is statistically not significant (at IA2 and final rPFS analysis), 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 rPFS analysis is statistically significant (at IA2 or final rPFS analysis), 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, reporting and committees

10.1 Definition of adverse events and other safety 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. Patient-Reported Outcomes are considered as other assessments to detect adverse events, see Section 8.5.1.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 or severity grade when CTCAE grading does not exist.

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 (5.0).
2. Its relationship to the study treatment (^{68}Ga-PSMA-11 or ^{177}Lu-PSMA-617) and to the SoC. 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 if the event is ongoing, an outcome of not recovered/not resolved 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:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/permanently discontinued

6. Its outcome (not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF 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 CRF 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.

Participants receiving ^{177}Lu-PSMA-617 in investigational and cross over arm will continue to be followed for safety every 24 weeks for a period of 48 weeks from the EOT/EOT2 (long-term safety follow-up). During this long-term follow-up, sufficient information will be obtained to permit an adequate determination of the outcome of the event and an assessment of the casual relationship between the AE and study treatment.

For patients who received ^{68}Ga-PSMA-11 during screening but were not randomized or patients who received ^{68}Ga-PSMA-11 at radiographic progression confirmed by BIRC, 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 casual relationship between the AE and study treatment.

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, 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 drugs can be found in the Investigator's Brochures (IB) and for the SoC in package insert.

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.

During the long-term safety follow-up at Week 24 and Week 48 safety visits, the following will be captured in the study case report forms, as per Section 10.1.3:

- Selected AEs [redacted]

Reporting of AEs related to AxMP(s)

All AEs related to any authorized auxiliary medicinal product used in this study must be reported to Novartis.

In assessing causality, the investigators will use the points as described above in Section 10.1.1.

If a suspicion that medical occurrence could be related to study treatment (and/or interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply.

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).

- 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
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and 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 (second primary malignancy) 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.

All potential Hy's law cases will be assessed as serious under "medically significant" if other seriousness criteria are not met. Please refer to section 10.1.3 for additional information.

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 event has occurred (Section 10.1.5).

During the long-term safety follow-up, the following SAEs will be captured in case report forms, as per Section 10.1.3.

- All [redacted].
- Any SAEs [redacted].

Reporting of SAEs related to AxMP(s)

All SAEs related to any auxiliary medicinal product used in this study must be reported to Novartis within 24 hours of the site becoming aware of it. In assessing causality, the investigators will use the points above. If a suspicion that the medical occurrence could be related to study treatment (or and interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply.

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 the EOT visit (or EOT2 visits if cross-over occurs) 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 (Note: if more stringent, local regulations regarding reporting timelines prevail). An exception is detailed in Section 9.1.1. Follow up for safety evaluations, when antineoplastic medication has been started before Day 30 after the EOT visit. Detailed instructions regarding the submission process and requirements 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, but under no circumstances later than 24 hours of the investigator receiving the follow-up information (Note: if more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. 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.

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 Patient 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.

Elevations in AST or ALT (>3x ULN) in combination with total bilirubin >2x ULN or jaundice in the absence of cholestasis (defined as ALP < 2 ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law). For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious unexpected adverse event. It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available

information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

The reporting of AEs and SAEs related to AxMP(s) are detailed in Section 10.1.1 and Section 10.1.2.

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. Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). 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 and overdose

Study treatment errors (including study treatment overdose) are unintentional errors in the prescribing, dispensing, and administration of study treatment .

Study treatment misuse refers to situations where the study treatment is intentionally and inappropriately used not in accordance with the protocol.

Study treatment abuse corresponds to the persistent or sporadic, intentional excessive use of a study treatment , which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol (including misuse, abuse, and study treatment overdose) must be reported on AE (or SAE, if the event meets the definition of an SAE) CRF, irrespective of it being associated with AE/SAE.

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

10.2 Committees

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 Novartis 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 Novartis 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 provide scientific leadership for the study including but not limited to research activities, analysis of clinical trial data and its sharing through medical publications, 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 executive 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 Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of federal regulation (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, and screen failures, as well as randomization codes and data about all study treatment(s) dispensed to the participant will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

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 that time 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/delegated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (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 GCP, 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. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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 [redacted] rPFS events as per BIRC review. The primary Clinical Study Report (CSR) will be produced after the primary rPFS analysis and will summarize data from the study. 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 [redacted] deaths (if this timing doesn't overlap with the primary analysis), 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.

The analysis for [redacted] will be conducted at the same time as planned analysis for the main study (i.e., interim and/or final analysis of rPFS, or final OS). The sample size is driven by feasibility. Please refer to the Statistical Analysis Plan (SAP) for more details.

At the time of analysis of participants from [redacted], supportive analyses will also be conducted including [redacted]

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 (FAS) 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 subset of participants in the FAS who received at least one dose of randomized treatment (i.e. at least one administration of ^{177}Lu-PSMA-617 for the ^{177}Lu-PSMA-617+SoC arm and one dose of ARDT on or after randomization for the SoC alone arm). Participants will be included in the treatment arm corresponding to the actual treatment received.

RECIST Analysis Set (RAS) consists of subset of participants in the FAS with evaluable soft tissue disease by PCWG-modified RECIST 1.1 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, ORR, DCR, DOR, TTR, TTSTP, etc.).

The **Ga-PSMA-11 Full Analysis set** (Ga-FAS) includes all participants who received the administration of ^{68}Ga-PSMA-11. This analysis set will include all participants with ^{68}Ga-PSMA-11 PET/CT scan during screening assessment and will be the basis of the safety and imaging summaries for the ^{68}Ga-PSMA-11 specific analyses. This includes screened participants who received ^{68}Ga-PSMA-11 and were randomized, and those who received ^{68}Ga-PSMA-11 but not randomized.

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

The **Cross-over Analysis Set (CAS)** consists of participants randomized to the SoC arm who crossed over after BIRC-confirmed radiographic progression to receive at least one dose of ^{177}Lu-PSMA-617.

[redacted]

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be 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 in to ^{177}Lu-PSMA-617, ARDT and ADT 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 summarized, 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 disease progression as outlined in PCWG3 or death due to any cause. rPFS will be assessed via blinded independent central review of radiographic images provided by the treating physician.

Patients who are alive without radiographic progression at the analysis data cut-off or are lost to follow-up at the time of analysis will be censored for rPFS at the time of their last radiographic assessment or at the data cut-off date. 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 + SoC arm versus SoC 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. tumor volume (high vs low volume), age≥70 years (yes/no), Previous or planned treatment (prostatectomy or radiation) to primary (prostate) tumor (yes/no). High-volume disease defined as presence of visceral metastases and/or at least four bone lesions with at least one lesion outside of the vertebral bodies and pelvis.

The primary efficacy variable, rPFS, will be analyzed at the interim analyses (IA) and final analysis of a group sequential design, using a [redacted] function. 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 primary intent of the first interim rPFS analysis is to determine if the trial should be stopped early for futility. There is no intent to carry out an analysis to declare superior efficacy at the time of the first Interim Analysis (IA). The first rPFS IA is to be performed at approximately [redacted] rPFS events ([redacted] information fraction). If the study continues to the 2nd IA for rPFS, it will be performed when approximately [redacted] rPFS events ([redacted] information fraction) have been documented. If the study continues to the final rPFS analysis, the final rPFS analysis will be performed when approximately [redacted] rPFS events have been documented. Details of these analyses are provided in Section 12.7.

The primary analysis of rPFS for [redacted] participants will be based on [redacted] participants in the FAS of the main study. The analysis will be performed at the same time as global planned analysis (i.e., 2nd interim and/or final analysis of rPFS or final OS). The analysis will be conducted as for the main study, except that the log-rank test will not be performed (since the subgroup of [redacted] participant could not be adequately powered).

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 from study treatment will be used for the analysis (treatment policy strategy).
2. 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 BIRC 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 BIRC 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 BIRC 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 BIRC) 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 SAP.

Additional analysis will be performed in the FAS, will obtain the hazard ratio and 95% CI for rPFS per BIRC review accounting for change in SoC.

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 (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 rPFS 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 + SoC arm versus SoC 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.

If a participant is not known to have died, then OS will be censored at the latest date the participant was known to be alive (on or before the cut-off date).

A three-look group sequential design is considered for OS. The type I error probability will be controlled by using a [redacted] 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 hierarchically tested in the following way:

- The time point for the first OS IA will be at the time of second IA for rPFS analysis. At this point, approximately [redacted] deaths (i.e. approximately [redacted] information fraction) are expected to have been recorded in the clinical database. If rPFS is statistically significant at this stage, OS will also be tested. If rPFS is not statistically significant at this stage, then OS will not be tested.
- If OS is not statistically significant at the first OS IA, the second OS analysis will be planned at the time of final rPFS analysis. At this point, approximately [redacted] deaths (i.e.

approximately [redacted] information fraction) have been recorded in the clinical database. If rPFS is statistically significant at this stage, OS will also be tested. If rPFS is not statistically significant at this stage, then OS will not be tested at this or any later timepoint.

- If OS is not statistically significant at the time of final rPFS analysis, a final OS analysis is planned at the time when approximately [redacted] deaths have been recorded. Details of the interim analysis are also provided in Section 12.7.

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 main OS analysis (based on ITT principle) will be performed without accounting for cross-over, by considering 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. Start of a new anti-neoplastic therapy prior to radiographic progression or death: OS data collected irrespective of initiation of new anti-neoplastic therapy will be used for the analysis (treatment policy strategy)
3. cross-over to ^{177}Lu-PSMA-617 in combination with SoC arm for patients in the SoC alone arm: OS data collected irrespective of cross-over (treatment policy strategy).

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

Supplementary OS analysis based on FAS will be performed accounting for cross-over: since participants in the SoC alone arm are allowed to cross-over to ^{177}Lu-PSMA-617 in combination with SoC upon confirmation of radiographic progression by BIRC, adjustment for the effect of cross-over on OS will be performed based on recognized methods, e.g., a two-stage method or the Rank Preserving Structural Failure Time (RPSFT) model proposed by (Robins and Tsiatis 1991). RPSFT is intended to be used as a supplementary analysis, and other methods will also be used based on an examination of the appropriateness of the data to the assumptions required by the methods.

The supplementary OS 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. Start of a new anti-neoplastic therapy prior to radiographic progression or death: OS data collected irrespective of initiation of new anti-neoplastic therapy will be used for the analysis (treatment policy strategy)
3. cross-over to ^{177}Lu-PSMA-617 in combination with SoC arm for patients in the SoC alone arm: survival time will be re-calculated based on time spent on ^{177}Lu-PSMA-617 based on appropriate methods as described above (hypothetical strategy).

Supplementary analysis performed in the FAS, will obtain the hazard ratio and 95% CI for OS accounting for change in SoC.

Further details of sensitivity analyses will be described in the SAP as needed.**OS monitoring guidelines for assessing potential harm**

OS monitoring guidelines to consider ruling out any potential OS harm and to help evaluate the benefit/risk profile of ^{177}Lu-PSMA-617 in this study will be considered at each milestone (interim/final OS analyses). Details about such guidelines will be described in the SAP.

12.5.1.2 Other secondary efficacy endpoints

PFS defined as the time from date of randomization to the date of first documented progression by investigator's assessment (radiographic progression, clinical progression, PSA progression defined as ≥25% increase and ≥2 ng/mL above the nadir, confirmed by a second value ≥3 weeks later if there is PSA decline from baseline, or ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks if there is no PSA decline from baseline) or death from any cause, whichever occurs first. PFS will be censored if no PFS event is observed before the first to occur the analysis cut-off date. The censoring date will be the date of the last adequate tumor assessment prior to cut-off.

PFS will be analyzed in the FAS population according to the randomized treatment group and strata assigned at randomization. The PFS 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 PFS will be calculated, along with its 95% confidence interval, using a stratified Cox model. Restricted Mean Survival Time (RMST) method may be conducted for PFS to account for the possible non-proportional hazards effect.

As a supportive analysis, PFS will be censored if no PFS event is observed before the first to occur between the analysis cut-off date and the date when a new antineoplastic therapy is started. The censoring date will be the date of the last adequate tumor assessment prior to cut-off/start of new antineoplastic therapy. PFS will be analyzed using a stratified Cox model, 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.

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 PD (i.e. as captured on the anti-neoplastic therapy after discontinuation of 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 of 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.

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 cross-over 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 SoC arm are allowed to cross-over to ^{177}Lu-PSMA-617 in combination with SoC after progressive disease, adjustment for the effect of cross-over on PFS2 may be performed based on recognized methods, e.g., a two-stage method or the RPSFT model proposed by (Robins and Tsiatis 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.

Time to development of mCRPC (TTDm) is defined as the time from date of randomization to disease progression despite androgen deprivation therapy (ADT) presenting as either a continuous rise in serum prostate specific antigen (PSA) levels, the progression of pre-existing

disease, and/or the appearance of new metastases. TTDm will be summarized with the same analysis conventions as TTSSE , except it will be censored at the last assessment date.

Overall response rate (ORR) is defined as the proportion of participants with best overall response (BOR) of complete response (CR) or partial response (PR) in soft tissue, as per BIRC and according to RECIST 1.1 with the caveats outlined in PCWG3 (Section 16.2 and Section 16.3 for details), in the absence of bone progression as per PCWG3. CR and PR must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met. ORR will be calculated based on the RAS. ORR and its 95% confidence interval will be presented by treatment arm. As a supplementary analysis, ORR in soft tissue only, as per RECIST v1.1 with the caveats outlined in PCWG3 review will be presented by treatment group, along with 95% confidence intervals.

BOR for each participant 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.
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD = at least one SD assessment (or better) > 11 weeks after randomization (and not qualifying for CR or PR).
- PD = progression ≤ 25 weeks after randomization (and not qualifying for CR, PR or SD).
- Non-CR/Non-PD = at least one non-CR/non-PD assessment (or better) > 11 weeks after treatment start (and not qualifying for CR or PD).PD = progression ≤ 25 weeks after treatment start (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 11 weeks or early progression within the first 25 weeks)

As a supplementary analysis, ORR in soft tissue only, as per RECIST v1.1 with caveats outlined in PCWG3 review will be presented by treatment group.

Disease control rate (DCR) is defined as the proportion of participants with BOR of CR, PR, or stable disease (SD) in soft tissue, as per BIRC and according to RECIST 1.1 with the caveats outlined in PCWG3. DCR will be analyzed using the same analytical conventions as ORR.

Duration of response (DOR) is defined as the duration of time between the date of first documented BOR (CR or PR) in soft tissue according to RECIST 1.1 with the caveats outlined in PCWG3, based on tumor response data per BIRC and the date of first documented progression or death due to any cause. If a participant has not had an event, DOR is censored at the date of last adequate tumor assessment. Participants who never achieved a BOR of CR or PR will be excluded from the analysis. The distribution function of DOR will be estimated using the Kaplan-Meier method. The median DOR along with 95% CIs will be presented by treatment arm.

Time to response (TTR) is defined as the time from the date of randomization to the date of first documented BOR (CR or PR, which must be confirmed subsequently). CR and PR (in soft tissue) are based on tumor response data as per BIRC and according to PCWG3-modified RECIST 1.1 (see Section 16.2 and Section 16.3 for details). Participants who did not achieve a confirmed CR or PR will be censored at the last adequate tumor assessment date when they did

not have a PFS event or at maximum follow-up (i.e. FPFV to LPLV used for the analysis) when they did have a PFS event. The distribution function of TTR will be estimated using the Kaplan-Meier method. The median TTR along with 95% CIs will be presented by treatment arm.

Time to soft tissue progression (TTSTP) defined as time from randomization to radiographic soft tissue progression per PCWG3-modified RECIST 1.1 assessed by BIRC. 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.

As a supplementary analysis, ORR, DCR, DOR, TTR and TTSP will also be analyzed based on the data from FAS per PCWG3-modified RECIST1.1 based on investigator's assessment.

PSA90 response is defined as the proportion of patients who have a ≥90% decrease in PSA from baseline (defined as last value on or before randomization date) that is confirmed by a second (the next) PSA measurement ≥4 weeks later. All scheduled and unscheduled PSA assessments will be used to determine and confirmed PSA response.

PSA90 response will be calculated at 12, 24 and 48 weeks after C1D1 based on the FAS and according to the ITT principle. PSA response at 12, 24 and 48 weeks 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.

Similarly, response in terms of proportion of participants with PSA nadir levels < 0.2 ng/mL at 12, 24 and 48 weeks will be summarized with the same analysis conventions as PSA90 response.

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 prior to
    a. Day of first dose of ARDT on or after the date of randomization for SoC alone arm.
    b. Day of first administration of ^{177}Lu-PSMA-617 for ^{177}Lu-PSMA-617 + SoC arm.

Note that SoC may start before informed consent.

2. On-treatment period:
    a. For patients in SoC alone arm - from day of first dose of ARDT on or after the date of randomization to earlier of
        1. latter of 30 days after last dose of ARDT or 30 days after end of treatment per End of Treatment (EOT) or
        2. day before start of cross-over to ^{177}Lu-PSMA-617 injection

b. For patients in ^{177}Lu-PSMA-617 + SoC arm - from day of first administration of ^{177}Lu-PSMA-617 injection to latter of
    3. 30 days after last dose of ARDT or
    4. 30 days after end of treatment per End of Treatment (EOT) or
    5. 41 days after date of last administration of ^{177}Lu-PSMA-617.

A change in SoC can occur according to the protocol. In this case, the end of study treatment refers to the end of treatment of the last SoC.

3. Post-treatment period:
    a. For SoC alone arm - starting from the earlier of
        1. latter of 31 days after last dose of ARDT or 31 days after end of treatment per End of Treatment (EOT) or
        2. start of cross-over to ^{177}Lu-PSMA-617 injection for SoC arm
    b. For ^{177}Lu-PSMA-617 + SoC arm - from day of first administration of ^{177}Lu-PSMA-617 injection to latter of
        3. 31 days after last dose of ARDT or
        4. 31 days after end of treatment per End of Treatment (EOT) or
        5. 42 days after date of last administration of ^{177}Lu-PSMA-617.

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 (TEAE) (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 medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment.

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 consists 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 treatment group.

A ^{68}Ga-PSMA-11 treatment emergent adverse event (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. 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 patients with at least one event, and the total number of events will be presented.

During long-term follow-up, serious adverse events and [redacted] AEs related to ^{177}Lu-PSMA-617 [redacted] 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 summarized by treatment and visit/time.

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 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (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 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, serious adverse events related to Lu-PSMA-617 will be collected. Summary tables will be provided in the Safety Set.

12.5.3 Patient reported outcomes

Three patient-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 patients using the EQ-5D-5L and FACT-P questionnaires, and pain will be assessed by patients using the BPI-SF.

TTPP defined as time from randomization to pain progression. Pain progression will be assessed by participant responses to the BPI-SF questionnaire which is to be completed by the participants as per Schedule of Assessment Table 8-1 and Table 8-2.

TTPP will be estimated using the Kaplan-Meier method. The median time along with 95% confidence intervals will be presented by treatment group. A stratified Cox regression model will be used to estimate the hazard ratio of time to definitive deterioration, along with 95% confidence interval (using randomization stratification).

Other HRQoL endpoints (e.g. time to definitive deterioration) will be analyzed using a Cox regression model in the same manner as described for time to TTPP.

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.



[redacted]

12.7 Interim analyses

Primary endpoint: rPFS

A maximum of three analyses (two interim and one final) will be performed for rPFS.

The type I error probability will be controlled by using a [redacted] at 2.5% one-sided overall level of significance. A rho spending function ($\rho = 3$) as implemented in East 6.5.4 will be used as a beta-spending function to determine the non-binding futility boundary. The primary intent of the first IA is to determine if the trial should be stopped early for futility. A small alpha of 4.10^{-4} will be spent for rPFS at the futility analysis although there is no intention to stop for superior efficacy at this

interim analysis. Based on the choice of alpha-spending and beta-spending function described above and if the first interim rPFS analysis is performed exactly at [redacted] rPFS events, the futility boundary in terms of the p-value scale (or the Z-scale or HR (Hazard Ratio) scale) at the interim is calculated as [redacted]

The observed (i.e., nominal) p-value has to be greater than p-value scale futility boundary defined above to conclude (non-binding) futility. The data cut-off for the 1st interim rPFS analysis is anticipated to take place approximately [redacted] after the first participant is randomized.

If the study continues to the 2nd IA for rPFS, it will be performed when approximately [redacted] rPFS events have been documented. If exactly [redacted] rPFS events are observed at the 1st IA for rPFS, the study continued and exactly [redacted] events are obtained at the 2nd IA for rPFS, the observed p-value will have to be less than 0.01 ([redacted]) to declare superior efficacy (statistical significance at 2.5% one-sided overall alpha level). The data cut-off for the 2nd interim rPFS analysis is anticipated to take place approximately [redacted] after the first participant is randomized.

Since the observed number of events at the interim analyses may not be exactly equal to the planned [redacted] rPFS events at 1st interim rPFS analysis (or [redacted] rPFS events at 2nd interim analysis), the efficacy boundaries will need to be re-calculated using the pre-specified α-spending and β-spending functions and based on the actual number of observed events at the corresponding interim and the total number of targeted events to calculate the exact information fraction. The observed p-value (or Z-test statistic or HR estimate) at each interim analysis will then be compared against the re-calculated efficacy boundaries.

The interim analyses will be performed by an independent statistician (not involved with the conduct of the study). Further details will be described in the DMC charter. The results of the interim analysis will be provided to the DMC by the independent statistician. Safety analyses are planned for the monitoring of safety data and will be performed approximately every 6 months during the course of the study. Such safety analyses do not inflate the type I error for the primary efficacy hypothesis testing and thus no adjustment for multiplicity is required.

If the study continues to the final rPFS analysis, the final rPFS analysis will be performed when approximately [redacted] rPFS events have been documented. If exactly [redacted] events are observed at the first interim and exactly [redacted] events are observed at the second interim, the study continued and there exactly [redacted] events are obtained at the final analysis, the observed p-value will have to be less than [redacted] to declare statistical significance. In practice, the final rPFS analysis will be based on the actual number of rPFS events documented at the cut-off date for the final rPFS analysis and the alpha 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. The data cut-off for the final rPFS analysis is expected to occur approximately [redacted] after the first participant is randomized.

The statistical properties of the group sequential design are summarized in Table 12-1 below.



The analysis for the [redacted] main cohort from the main study will be conducted at the same time as planned analysis for the global main study (i.e., interim and/or final rPFS analysis) as part of the primary rPFS analysis. If rPFS data in the [redacted] subgroup is not mature, an additional rPFS analysis maybe conducted.

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 three analyses (two interim and one final) is planned for OS:

- at the time of the second IA for rPFS (provided rPFS is significant), at which point a total of approximately [redacted] deaths are expected
- at the final analysis for rPFS (provided rPFS is significant), when approximately [redacted] deaths are expected
- a final analysis for OS when approximately [redacted] deaths are expected (approximately [redacted] from date of first participant to be randomized)

[redacted] independent of the one used for the rPFS, 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 analysis (Glimm et al 2010).

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 for OS already spent at the time of earlier analyses.

[redacted]

12.8 Sample size calculation

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

12.8.1 Primary endpoint(s)

The hypotheses to be tested and details of the testing strategy are described in Section 12.4.2 and Section 12.7.

Based on available data, the median rPFS in the control arm (receiving SoC) is expected to be around 33 months as first-line treatment for participants with mHSPC (Fizazi et al 2017). It is expected that treatment with ^{177}Lu-PSMA-617 in combination with SoC will result in a [redacted] reduction in the hazard rate for rPFS compared to the control arm i.e., an expected hazard ratio of [redacted], which corresponds to an increase in median rPFS by [redacted] under the exponential model assumption ([redacted]).

In order to ensure at least 95% power to test any null hypothesis: rPFS hazard ratio = 1, versus the alternative hypothesis: rPFS hazard ratio = [redacted], it is calculated that a total of [redacted] rPFS events need to be observed at the final analysis. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, patients randomized to the two treatment arms in a 1:1 ratio, and a 3-look group sequential design with alpha spending function and beta spending functions as specified in Section 12.7 and using information fractions of [redacted] will be used for the rPFS interim efficacy analyses expected to occur approximately at [redacted]. The futility boundary is derived using the ρ=3 spending function.

Assuming that enrolment will continue for 22.5 months at a uniform rate of 50 patients per month and losses to follow-up for rPFS of approximately 15%, a total of 1126 patients will need to be randomized to observe the targeted [redacted] rPFS events at about [redacted] after the randomization date of the last patient, i.e., [redacted] after the randomization date of the first

patient. The sample size of approx.1126 patients will be randomly assigned to each treatment arm in a 1:1 ratio (approx 563 patients in ^{177}Lu-PSMA-617 in combination with SoC arm and approx 563 patients in SoC alone arm). These calculations were made using the software package East 6.5.4.

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 53 months (Fizazi et al 2019b). It is hypothesized that treatment with ^{177}Lu-PSMA-617 in combination with SoC will result in a [redacted] reduction in the hazard rate for OS compared to the control arm i.e., an expected hazard ratio of [redacted], which corresponds to an increase in median OS by [redacted] under the exponential model assumption ([redacted]).

Then in order to ensure 80% power to test the null hypothesis: OS hazard ratio = 1, versus the alternative hypothesis: OS hazard ratio = [redacted], it is calculated that a total of [redacted] deaths need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, patients randomized to the two treatment arms in a 1:1 ratio, and a 3-look group sequential design with alpha spending function as specified in Section 12.7 and using information fractions of (approximately [redacted]). The two interim OS analyses will be performed at the time of the 2nd IA/final analysis for rPFS.

Based on the 1126 of patients, and assuming losses to follow-up for OS of approximately 5%, it is estimated that the required [redacted] deaths will be observed approximately at [redacted] after the randomization date of the first patient. These calculations were performed using the software package East 6.5.4.

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, with applicable local regulations (including Clinical Trial Regulation (EU) No 516/2014, 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 (defined as last patient last visit) 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. Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

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.

13.5 Participant Engagement

The following participant engagement initiatives are included and will be provided, as available, for distribution to study participants:

Thank You letter, Plain language trial summary, Individual study results and Trial Feedback Questionnaires (TFQ)

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

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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: Response Evaluation Criteria in Solid Tumors

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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 ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 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 ≥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 et al 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 2012) 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

Situation		Options for end-date (progression or censoring)[1] **(1) = default unless specified differently in the protocol or RAP**	Outcome
D	No progression	(1) Date of last adequate assessment	Censored
E	Discontinuation of study treatment 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: Discontinuation of study treatment 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
- 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
- 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 Incomplete dates for last known date patient alive or death

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, 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 recommendations on baseline assessment, the criteria for radiographic response assessment. It is based on the PCWG3 recommendations. Please note that not all the recommendations listed below are applicable to this patient population or to the specifics of this study.

Recommendations for baseline assessment will apply to include

- Histology, to distinguish other histologies from adenocarcinomas
- Prior radiation therapy
- The timing and duration of, and (if available) response to all prior systemic treatment(s)
- Assessment of blood and tumor biomarkers
- Patient reported outcomes
- Imaging

Response should be categorized on the basis of post-therapy PSA or radiographic change pattern. The type of progression at trial entry should be defined.

Definition of PSA progression for eligibility:

- serum/plasma PSA progression defined as 2 increases of 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 is only indication of progression

Criteria for progression at trial entry, imaging:

- RECIST 1.1 for extraskeletal disease
- Two new bone lesions
- Measurable lesions are not required for entry

Imaging measures

For extraskeletal disease, RECIST 1.1 with the caveats will be followed:

- record the location of nodal disease (pelvic versus extrapelvic) and visceral disease (lung/liver/adrenal/CNS) separately
- monitor up to five individual lesions per site of spread (eg nodes, lung, liver as separate sites)
- bone lesions will be recorded separately

Bone lesions

- bone scintigraphy with technetium-99m labeled diphosphonate will be used as a standard for bone imaging
- bone lesions will be recorded with presence/absence, number, lesion area

Table 16-6 PCWG3 Criteria

Variable	PCWG3 (2016)
Soft tissue lesions	**For control/relieve/eliminate end points:** Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats: • Record up to 5 lesions per site of disease • Record changes in nodal, lung, liver adrenal and central nervous system (CNS) sites separately • Only report changes in lymph nodes that were ≥1.5 cm in diameter in short axis at baseline • Record changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separately • Only report changes in visceral lesions (liver, lung, adrenal, CNS) that were ≥1.0 cm in the longest dimension • Record complete elimination of disease at any site separately • Confirm favorable change with second scan • Record changes using waterfall plot **For delay/prevent end points:** • Record changes in nodal and visceral disease separately • Record up to 5 lesions per site of spread • Use RECIST 1.1 criteria for progression, but clearly record type of progression (growth of existing lesions vs development of new lesions) separately by site. • 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 • Note that for some treatments, a lesion may increase in size before it decreases. • Report the proportion who have not progressed at fixed time points (6 or 12 months)
Bone	**For control/relieve eliminate end points:** • Record outcome as new lesions, no new lesions or resolved lesion • First scheduled reassessment: • No new lesions: continue therapy • New lesions: perform a confirmatory scan 6 or more weeks later • Confirmatory scan: • No new lesions: continue therapy • Additional new lesions: progression • Subsequent scheduled reassessments: • No new lesions: continue • New lesions: progression • Changes in intensity or uptake do not constitute regression or progression **For prevent/delay end points (progression):** • Exclude pseudoprogression in the absence of symptoms or other signs of progression • At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)

Variable	PCWG3 (2016)
	• If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented • For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan • Date of progression is the date of the scan that first documents the second lesion • Changes in intensity of uptake alone do not constitute either progression or regression • Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)

16.4 Appendix 4: EQ-5D-5L (European Quality of Life (EuroQol) 5 Domain 5 Level scale), sample only, not for participant use



Health Questionnaire

English version for the UK

Sample

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

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

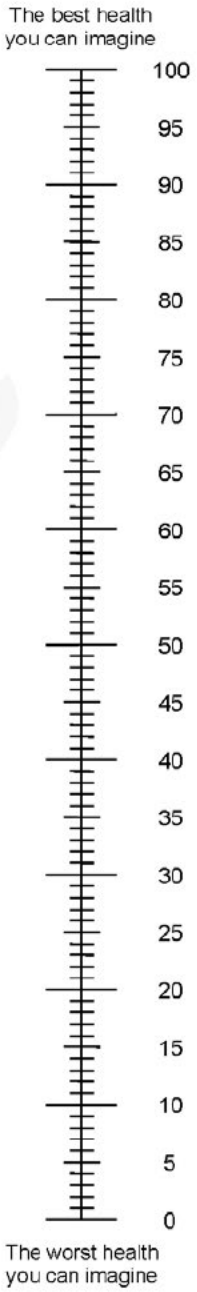
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Sample

- 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 = ☐



Sample

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

16.5 Appendix 5: FACT-P (Functional Assessment of Cancer Therapy Prostate), sample only, not for participant 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

English (Universal)
Copyright 1987, 1997

FACT-P (Version 4)

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

	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

16.6 Appendix 6: BPI-SF, sample only, not for participant use

1903

Date: ___ / ___ / ___ (month) (day) (year)

Subject's Initials : _____

Study Subject #: _____

Study Name: _____

Protocol # _____

PI: _____

Revision: 07.01.05

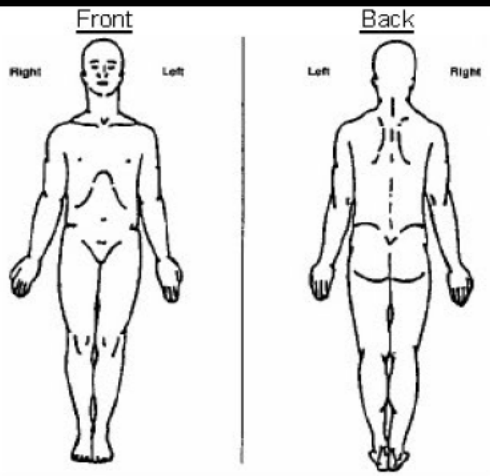
PLEASE USE BLACK INK PEN

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

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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

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16.7 Appendix 7: American Joint Committee on Cancer Prognostic Stage Grouping (8th Edition, 2017)

When T is...	And N is...	And M is...	And PSA is...	And Grade Group is...	Then the Stage Group is...
cT1a-c, cT2a	N0	M0	<10 ng/ml	1	I
pT2	N0	M0	<10 ng/ml	1	I
cT1a-c, cT2a	N0	M0	≥10, <20 ng/ml	1	IIA
pT2	N0	M0	≥10, <20 ng/ml	1	IIA
cT2b-c	N0	M0	<20 ng/ml	1	IIA
T1-2	N0	M0	<20 ng/ml	2	IIB
T1-2	N0	M0	<20 ng/ml	3	IIC
T1-2	N0	M0	<20 ng/ml	4	IIC
T1-2	N0	M0	≥20 ng/ml	1-4	IIIA
T3-4	N0	M0	Any	1-4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any	M1	Any	Any	IVB

Abbreviation: PSA indicates prostate specific antigen. Note that, when either PSA or grade group is not available, grouping should be determined by T category and/or either PSA or grade group, as available.

16.8 Appendix 8: Prostate Cancer Grading System

(adapted from Epstein et al., 2016)

Gleason Score	Grade Group	Histologic definition
3 + 3 = 6	1	Only individual discrete well-formed glands
3 + 4 = 7	2	Predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands
4 + 3 = 7	3	Predominantly poorly formed/fused/cribriform glands with lesser component of well-formed glands*
8	4	Only poorly formed/fused/cribriform glands OR Predominantly well-formed glands and lesser component lacking glands** Predominantly lacking glands and less component of well-formed glands**
9 - 10	5	Lack of gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands*
*For cases with >95% poorly formed/fused/cribriform glands or lack of glands on a core or at radical prostatectomy, the component of <5% well-formed glands is not factored into the grade ** Poorly formed/fused/cribriform glands can be a more minor component		

16.9 Appendix 9: 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 (App. 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)

RECIST 1.1 Response

- If participant does not have Target lesions, then Target response will be Blank in CRF
- If participant does not have Non- target lesions, Non-target response will be Blank in CRF
- **If participant has No target lesions AND No Non-target lesions AND no New lesions, then Overall response will be 'No evidence of Disease' (NED).**

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
- [redacted]
- 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.
- [redacted]
- 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