3 APPROVAL SIGNATURES

STUDY TITLE: PSMA-Directed Endoradiotherapy Of Castration-Resistant Prostate Cancer (RESIST-PC). A Phase II Clinical Trial
PROTOCOL NUMBER: PSMA-617-02
SAP Final version 2.0, 15May2020

PSI:

Author: [redacted]

Signature: ..... DocuSigned by: [redacted] ..... Date: 20-May-20 | 7:01:31 PM IST .....

[redacted]

Signature: ..... DocuSigned by: [redacted] ..... Date: 20-май-20 | 7:10:50 PM IST .....

Endocyte, Inc.:

Reviewed/Approved By: [redacted] Biostatistician

Signature: [redacted] Digitally signed by [redacted] DN: dc=com, dc=novartis, ou=people, ou=PH, serialNumber=2223545, cn=He Belle Reason: I am approving this document Date: 2020.05.19 09:49:13 +02'00' ..... Date: .....

Reviewed/Approved By: [redacted]

Signature: [redacted] Digitally signed by [redacted] DN: dc=com, dc=novartis, ou=people, ou=PH, serialNumber=2319892, cn=Camahan Natalie Reason: I am approving this document Date: 2020.05.19 08:20:48 -04'00' ..... Date: .....

Reviewed/Approved By: [redacted]

Signature: ..... DocuSigned by: [redacted] ..... Date: 20-May-20 | 7:39:37 PM IST .....

Reviewed/Approved B[redacted] M.D., M.H.S., M.Sc., [redacted]

Signature: [redacted] ..... Date: 05-19-2020.

Final

STATISTICAL ANALYSIS PLAN

Study PSMA-617-02

Title: *(as per protocol/amendment)*	PSMA-Directed Endoradiotherapy Of Castration-Resistant Prostate Cancer (RESIST-PC). A Phase II Clinical Trial
Version:	Final, Version 2.0
Date:	15-May-2020

CONFIDENTIAL

DOCUMENT HISTORY

1 VERSION HISTORY

Version #	Version Date
Final v1.0	24Sep2019
Final v2.0	15May2020

2 REVISION HISTORY

Version #	Chapter	Revision Summary	Reason(s) for Revision
Final v1.0	N/A	Initial release	N/A
Final v.2.0	2.3.2	Definition of secondary objectives updated PSA progression is defined as the date that a ≥ 25% increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance). and PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment	To be in line with the Prostate Cancer Clinical Trials Work Group 3 (Scher et al 2016) and to have comparable data for the two main studies in this indication, VISION and RESIST-PC.
	2.5	MedDRA version changed from 22.0 to 22.1	The clinical database was updated to the most current version of MedDRA; to correctly reflect the MedDRA version used in the study.
	3.4.1	Rules for imputation of missing dates clarified.	To be consistent with the SAP sections 3.11.8-9.
	3.4.2	Rules for visit assignment for laboratory tests, PSA, Epic-26, ECG, vital signs, ECOG and AE questionnaire were added.	To account for the CRF structure, where data collected at different timepoints is presented under the same visit name,
	3.4.2	Baseline definition: If there is no time, only date of assessment is collected, then the last non-missing assessment prior or on date of first administration of Lu-PSMA-617 is used.	To clarify how baseline for assessments for which only date is collected is derived.
	3.5	Selection of the first result for the same assessment collected during a visit extended to all assessments.	To account for the changes in section 3.4.2, visit assignment.
	3.9	Clarification on data analyzed as Prior Cancer Related Therapy added.	To clarify based on the CRF structure.

	3.9	Best overall response categories removed from the summaries for Other Treatment and Radiotherapy,	Patients could have multiple therapies recorded; therefore, a summary of best overall response would not be informative.
	3.10.2	PSA progression-free survival (PFS): PSA PFS is measured from date of randomization until death or PSA progression. date that a ≥ 25% increase in PSA and an absolute increase of 2 ng/mL or more from the nadir (from all visits prior to the current visit being evaluated) is documented and confirmed by a second value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks of date of first dose will be ignored and PSA progression is defined as a ≥ 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks from the date of first dose of treatment (without confirmation) as specified in PCWG3 guidelines. PSA PFS is calculated as the time from randomization to the date of first documentation of PSA progression or date of death due to any cause, whichever occurs first: PSA PFS = Date of PSA progression or death - date of randomization + 1 Additional analysis for PSA PFS was added: Median follow-up (months) with 95% CI, censoring for deaths or PSA Progression, and range will be provided.	To be in line with the Prostate Cancer Clinical Trials Work Group 3 (Scher et al 2016) and to have comparable data for the two main studies in this indication, VISION and RESIST-PC.
	3.10.2	Change in ECOG-PS The changes in ECOG from baseline will be evaluated over time at treatment visit 1, 2, 3 and 4, and at follow-up visits.	Data for ECOG was captured in CRF with each ^{177}Lu-PSMA-617 treatment visit and during follow-up
	3.11.3	MedDRA version changed from 22.0 to 22.1	The clinical database was updated to the most current version of MedDRA; to correctly reflect the MedDRA version used in the study.
	3.11.8-11	Best overall Response removed from the summaries for Concurrent and Post-Treatment Radiotherapy and Other Treatments, and for the Post-Treatment Chemotherapy	Patients could have multiple therapies recorded; therefore, a summary of best overall response would not be informative.
	2.1	The PSA related efficacy will not be analyzed. Only listing will be presented	The PSA related efficacy will not be analyzed due to the significantly smaller sample size and investigator's inconsistent timing of PSA data collection. PSA data will only be able to be listed

	2.4.1-2.4.2, 3.10	Efficacy endpoints associated with efficacy objectives will not be analyzed.	The PSA related efficacy will not be analyzed due to the significantly smaller sample size and investigator's inconsistent timing of PSA data collection. PSA data will only be able to be listed

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Author: [redacted], [redacted]

Signature: ..... Date: .....

[redacted]: [redacted]

Signature: ..... Date: .....

Endocyte, Inc.:

Reviewed/Approved By: [redacted], Biostatistician

Signature: ..... Date: .....

Reviewed/Approved By: [redacted]

Signature: ..... Date: .....

Reviewed/Approved By: [redacted]

Signature: ..... Date: .....

Reviewed/Approved By: [redacted], M.D., M.H.S., M.Sc., [redacted]

Signature: ..... Date: .....

Abbreviations

Abbreviation	Description
AE	Adverse event
ALT/SGPT	Alanine aminotransferase/Serum glutamic-pyruvic transaminase
ANC	Absolute neutrophil count
AST/SGOT	Aspartate aminotransferase/Serum glutamic-oxaloacetic transaminase
ATC	Anatomic Therapeutic Chemical Classification
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CI	Confidence interval
CMP	Comprehensive metabolic panel
CR	Complete response
CRF	Case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
eGFR	estimated Glomerular Filtration Rate
EPIC	Expanded prostate cancer index composite
FT	Frequency table (prototype)
GBq	Gigabecquerel
Gy	Gray
IND	Investigational New Drug (application)
ITT	Intent-to-treat
i.v.	Intravenous
^{177}Lu	Lutetium 177
mCRPC	Metastatic castration-resistant prostate cancer
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume

Abbreviation	Description
MedDRA	Medical Dictionary for Regulatory Activities
ND/UNK/NA	Not determined / unknown / not applicable
PASS	Power Analysis and Sample Size (PASS
PCWG3	Prostate Cancer Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
PT	Preferred term
RBC	Red blood cell
RDW	Red cell distribution width
RECIST	Response evaluation criteria in solid tumors
RLT	Radioligand therapy
rPFS	(radiographic) Progression-free survival
SAE	Serious adverse event
SD	Stable disease
SOC	System organ class
TEAE	Treatment emergent adverse event
UCLA	University of California at Los Angeles
WBC	White blood cell

Table of Contents

1 Relevant Documents and Standards

1.1 Protocol Version and Amendments

The statistical analysis plan is based on version 5.0 of the study protocol of study PSMA-617-02 dated 01 June 2018.

1.2 Changes from Protocol

The protocol does not include any planned interim analyses. Enrollment was ceased when Endocyte acquired the Investigational New Drug (IND) application in order to do a phase 3 study of ^{177}Lu-PSMA-617, now currently under way. The RESIST-PC study (NCT03042312), now identified as PSMA-617-02, was ongoing when Endocyte acquired global development rights to the clinical development of PSMA-617 and to the PSMA-617 IND. It was agreed with the two principal investigators that the study was to stay open until the start of the Phase 3 VISION study (NCT03511664) in the USA. On 23 May 2018, the first site for the Phase 3 VISION study was opened to enrollment; therefore, the investigators were notified that enrollment to PSMA-617-02 would end on 22 June 2018, prior to full enrollment of the study. All enrolled patients were to continue to follow the protocol visit schedule.

To support the phase 3 study, a database lock of the RESIST phase 2 study is to occur after randomized patients have completed the treatment phase and 2 years follow-up period of the study.

Using the locked database, protocol analyses will be performed to summarize only safety. Most of the objectives will not be able to be met due to the early stopping of enrollment into the study; the modeling approaches stated in the protocol cannot be carried out as there is insufficient data to perform the analyses. Limited imaging data is available, and thus the endpoints associated with it will not be analyzed nor described with summary statistics (i.e., radiographic Progression-free survival [rPFS] and disease control rate [DCR]). The PSA related efficacy will not be analyzed due to the significantly smaller sample size than the planned 200 and investigator's inconsistent timing of PSA data collection. PSA data will only be able to be listed. Statistical testing will also not be applied to EPIC 26 Quality of life (QoL) questionnaire results and ECOG performance status, but summary statistics will be presented for these endpoints. Bone level pain data will only be able to be listed due to the nature of the data (i.e., free text pain levels).

For the laboratory parameters listed in Table 6 in the protocol, there is no data for white blood cell (WBC) differential (percentage), mean corpuscular hemoglobin concentration (MCHC), BUN/creatinine, and glucose; however, there is additional data for white blood cell (WBC) differential (absolute), sodium, chloride, potassium and albumin. All laboratory parameters for which most patients have data will be included in the summary tables. All laboratory parameters for which there is any data will be listed.

Section 2.3.2 and 3.10.2 - Definition and algorithm of PSA Progression Free Survival was updated to be in line with the Prostate Cancer Clinical Trials Work Group 3 (Scher et al 2016) and to have comparable data for the two main studies in this indication, VISION and RESIST-PC.

Section 3.10.2 – Timepoints for Changes in performance status (ECOG) from baseline was to be evaluated over time at 3, 6, 9, 12, 18 and 24 months after start of ^{177}Lu-PSMA-617 RLT; however, the eCRFs only captured ECOG with each ^{177}Lu-PSMA-617 treatment visit and during follow-up.

2 Study Design and Objectives

2.1 Study Design

This is an open-label, multicenter, prospective trial. Upon inclusion patients will be randomized in a 1:1 ratio into two treatment doses. Radioligand therapy (RLT) will be performed by repeated intravenous (i.v.) injection of 6.0 gigabecquerel (GBq) (±10%) or 7.4 GBq (±10%) ^{177}Lu-PSMA-617 every 8±1 weeks until reaching four cycles or threshold maximum dose to the kidneys of 23 Gray (Gy). All doses after labeling will be presented in buffered solution for i.v. injection.

In the initial plan for the study design a total of 200 patients with histologically proven prostate cancer and metastatic castration-resistant prostate cancer (mCRPC) were to be enrolled, however due to early stopping of enrollment only 71 patients were enrolled at time of data base lock. Salivary protection will be accomplished by applying ice pack starting 30 minutes prior to infusion of radiopharmaceutical and will continue for 4 hours. Patients will be recruited at up to 3 Nuclear Medicine sites selected for this project. Each patient will undergo a screening visit within 14 days prior to receiving study drug.

Dosimetry was required to be performed in the initial versions of the study according to dosimetry protocol (Appendix VI of the protocol) provided by Prof. [redacted] to determine dose to the kidneys. Dosimetry data for 20 patients on study (16 from University of California at Los Angeles (UCLA) and 4 from Excel Diagnostics) was analyzed and it was found that the permitted renal dose of 23 Gy was not exceeded in any patient after 4 cycles demonstrating overall favorable renal dosimetry and dosimetry is no longer required per protocol.

Treatment was continued until either of the following conditions applied:

- Prostate-specific antigen (PSA)/radiographic progression at ≥12 weeks
- Completion of four RLT cycles
- 23 Gy kidney dose would be exceeded by the next cycle as estimated by dosimetry
- Patient withdrawal (e.g. appearance of intolerable adverse events)

2.2 Sample Size Determination

Per the protocol, sample size calculation was based on the primary endpoint of this protocol, i.e. baseline to 12- week decline in tumor marker level (prostrate-specific antigen; PSA) ≥50% [3]. Based on a recent publication [2], we estimate that the proportion of patients who meet the primary endpoint will range between 38% and 65% for both treatment doses combined. We thus define the following null hypothesis: Less than 40% of patients will reach the endpoint after ^{177}Lu-PSMA RLT. ^{177}Lu-PSMA RLT would therefore be considered worthy of further study if 50% or more patients met the endpoint and not worthy of further study if 40% or less achieved the endpoint. This rationale was adapted from a single-arm study on mCRPC patients with same endpoint definition, published in 2010 in the Journal of Clinical Oncology [53]. We have performed power analysis for the two-sided binomial test (beta 0.2, alpha 0.05) to measure the efficacy of ^{177}Lu-PSMA RLT. A sample size of 200 achieves 78% power (beta 0.2) at a given alpha of 0.05 to distinguish between 40% versus 50% response rates. The power analysis was performed by a trained Biostatistician from the Department of Biostatistics, UCLA using Power Analysis and Sample Size (PASS) 14 software (NCSS LLC).

At the time of study enrollment stoppage only approximately 71 of the planned 200 patients were enrolled. The exact number of patients at the time of study enrollment stoppage will be reported in the tables and all analyses will be performed on this number of patients, and not the 200 patients originally planned.

2.3 Study Objectives

2.3.1 Primary objectives

1. To assess the clinical safety of ^{177}Lu-PSMA-617 by evaluation of adverse events (AE) using severity (mild moderate and severe). SAE will be assessed by Common Terminology Criteria for Adverse Events (Common Terminology Criteria for Adverse Events (CTCAE)
2. To assess the efficacy as defined by proportion of patients with PSA-response of ≥50% decline at 12-weeks from baseline

2.3.2 Secondary objectives

1. Maximum PSA response: Maximal baseline to follow-up PSA decline, at any time during or after therapy [1].
2. PSA Progression Free Survival (PFS): To determine the time to PSA progression, separate for treatment doses: time from inclusion (date of randomization) to date of PSA progression or death (whichever occurs first) [1].
    a. For patients with PSA decline from baseline at any time during or after therapy: PSA progression is defined as the date that a ≥ 25% increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance).
    b. For patients without PSA decline from baseline: PSA progression is defined as a ≥25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.
3. rPFS: To determine the radiographic progression free survival (rPFS), for each treatment dose: time from randomization to date when first site of disease is found to progress or death (whichever occurs first).
    a. Nodal and visceral disease is evaluated on cross-sectional imaging using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1/ Prostate Cancer Working Group (PCWG3) criteria.
    b. Bone metastases are evaluated using bone scintigraphy and new lesions have to be confirmed on a second scan (2+2 rule) using PCWG3 criteria.
4. To determine disease control rate (DCR) defined as the proportion of patients achieving RECIST 1.1/PCWG3 criteria stable disease (SD), partial response (PR) or complete response (CR).
5. Change in Bone Pain Level and Quality of Life: Pain and Expanded prostate cancer index composite (“Epic-26”) Questionnaires will be completed at baseline and at 3, 6, 9, 12, 18 and 24 months. Pain response will be determined in accordance with PCWG3 [1].
6. Change in Eastern cooperative oncology group (ECOG) performance score.

2.4 Primary and secondary endpoints

2.4.1 Primary endpoints

1. Safety of ^{177}Lu-PSMA-617RLT will be assessed by analysis of toxicity through adverse events. Both results from laboratory tests, physical examination and patient surveys will be included.
2. Efficacy of ^{177}Lu-PSMA-617 will be assessed at week 12 by means of number and percentage of patients with ≥50% decline in PSA at 12 weeks from baseline. Due to not enough patients to ensure the statistical power, and investigator’s inconsistent timing of PSA data collection. PSA data will only be able to be listed.

2.4.2 Secondary endpoints

1. Maximum PSA response, time to PSA nadir, PSA PFS (Due to not enough patients to ensure the statistical power, and investigator’s inconsistent timing of PSA data collection. PSA data will only be able to be listed.

2. Radiographic progression-free survival (rPFS) (only limited imaging data is available for this endpoint)
3. Disease control rate (DCR) (only limited imaging data is available for this endpoint)
4. Bone pain level (as measured in the Baseline and Follow-Up Questionnaire for Pain and Adverse Events CRF)
5. Quality of Life by the Quality of life questionnaire “EPIC-26”
6. Performance status (ECOG)

Due to the early stopping of enrollment into the study an abbreviated CSR will be written primarily concentrating on the primary endpoints.

2.5 Coding dictionaries

- Adverse events: Medical Dictionary for Regulatory Activities (MedDRA) version 22.1, CTCAE version 4.0

3 Statistical Evaluation

The analysis cut-off date for the final analysis of study data will be established after all randomized patients have completed last follow-up visit or have discontinued study. All statistical analyses will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations. The cutoff date for the final analysis is database lock date.
All events with start date before or on the cut-off date and end date after the cut-off date will be reported as ‘ongoing’. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

3.1 Populations for Analysis

Population	Description
Intention-to-Treat (ITT) Population	All randomized patients. Patients will be included in the treatment arm to which they were randomized regardless of actual treatment received.
Safety Population (SAF)	The subset of patients in the ITT population who received at least one dose of randomized therapy. Patients will be included in the treatment arm corresponding to the actual treatment received.

Baseline summaries will be presented for the Safety and ITT populations.
All efficacy analyses will be performed on the ITT population.
Safety analyses will be presented for the Safety population.

3.2 Interim analyses

None are planned in the protocol, however due to the early stopping of the study enrollment a database lock is to occur at some time after randomized patients have completed the treatment phase of the study. Using the locked database, the analyses described in this SAP will be performed to summarize

efficacy and safety (see section 1.2 for more details). At end of study, the safety summary will be updated to include all data collected during follow-up.

3.3 Subgroup analyses

All Safety endpoints will have summary statistics provided by the following subgroup:

1. Age (<65 years old, >= 65 years old)

3.4 Derived Data and Data Sets

3.4.1 Rules for incomplete data

Missing data will not be replaced. Only partial dates as described below will be imputed for purposes of assignment of adverse events to treatment emergent. The imputed dates will not be listed.

For the calculation of the time since initial cancer diagnosis, the following imputation rules will be applied when the date of initial diagnosis is incomplete:

- If the day is missing: first day of the month.
- If the day and month are missing: first day of January.

For the assignment of AEs to treatment emergent, the following rules will be applied in case of incomplete dates:

- If start date is incomplete:

Missing Element	**Rule**
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  ○ Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

day	• If available month and year = month and year of study treatment start date then
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  ○ Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month year of study treatment start date then 15MONYYYY

Any adverse events and concomitant medications with partial/missing dates will be displayed as such in the data listings.

Also, any adverse events and concomitant medications which are continuing as per data cut-off will be shown as ‘ongoing’ rather than the end date provided.

3.4.2 General Analysis Definitions

Study day

The study day describes the day of the event or assessment date, relative to the reference date.

The study day is defined as:

- Study Day= Assessment date – Reference date +1 if assessment date is after or on the reference date
- Study Day= Assessment date – Reference date if assessment date is before the reference date

For visit's assignment during treatment phase for the laboratory tests and PSA, and for Epic-26, for both treatment and follow-up phase, the reference date is defined as specified below in the table.

For visit's assignment during follow-up phase for the laboratory tests and PSA the reference date is defined the reference date for FU should be date of last dose + 1, as specified below in the table.

Data collected for the following procedures according to the visit windows as specified below in the table:

Parameters	Analysis visit	Reference day	Target day of assessment compare to the reference day	Time interval start (>=) end (<)
Lab test	Baseline			The last assessment on or before first injection
	Week 2	First dose Day 1	14	Day 7 to day 21
	Week 4		28	Day 21 to day 35
	Week 6		42	Day 35 to day 49
	Week 2k (till week 36)		D=7*2k	Day D-7 to day D+7
	FU week 2	Day 1 is the day after treatment end date, treatment end date is defined as the date of last injection	14	Day 7 to day 21
	FU week 4		28	Day 21 to day 35
	FU week 6		42	Day 35 to day 49
	FU week 2k (till FU week 12)		D=7*2k	Day D-7 to day D+7
	FU Month 6		168	Day 140 to day 196
	FU Month 9		252	Day 224 to day 280

Parameters	Analysis visit	Reference day	Target day of assessment compare to the reference day	Time interval start (>=) end (<)
	FU Month 12		336	Day 308 to day 364
	FU Month 3k (till FU MONTH 24)		D=28*3k	Day D-28 to day D+28
PSA	Baseline			Safety analysis with SAF: the last assessment on or before treatment start date (PSA baseline disease characteristic uses last assessment on or before randomization for both ITT and SAF)
	Week 6	SAF:First dose Day 1	42	Day 35 to day 49
	Week 12		84	Day 77 to day 91
	Week 18		126	Day 119 to day 133
	Week 6k (till end of the last dose)		D=7*3k	Day D-7 to day D+7
	FU Week 6	Day 1 is the day after treatment end date	42	Day 35 to day 49
	FU month 3		84	Day 56 to day 112
	FU month 6		168	Day 140 to day 196
	FU month 9		252	Day 224 to day 280
	FU month 3k (Till early termination of study or 24 month after the first treatment)		D=28*3k	Day D-28 to day D+28
ECOG	Baseline			the last assessment before treatment start date

Parameters	Analysis visit	Reference day	Target day of assessment compare to the reference day	Time interval start (>=) end (<)
	Treatment visit 1			Treatment visit +-7days
	Treatment visit 2			
	Treatment visit 3			
	Treatment visit 4			
	FU month 3	Day 1 is the day after treatment end date	84	Day 56 to day 112
	FU month 6		168	Day 140 to day 196
	FU month 9		252	Day 224 to day 280
	FU month 3k (Till early termination of study or 24 month after the first treatment)		D=28*3k	Day D-28 to day D+28
Epic-26	Baseline			the last assessment before or on treatment start date
	Month 3	First dose Day 1	84	Day 56 to day 112
	Month 6		168	Day 140 to day 196
	Month 9		252	Day 224 to day 280
	Month 3k		D=28*3k	Day D-28 to day D+28
	FU month 3	Day 1 is the day after treatment end date	84	Day 56 to day 112
	FU month 6		168	Day 140 to day 196
	FU month 9		252	Day 224 to day 280
	FU month 3k (Till early termination of study or 24 month after the first treatment)		D=28*3k	Day D-28 to day D+28

Parameters	Analysis visit	Reference day	Target day of assessment compare to the reference day	Time interval start (>=) end (<)
Pain and AE questionnaire	Baseline	Injection 1	Day of the first injection	Cycle 1 pre-dose
	Cycle 1 Post Dose	Injection 1	Day of the first injection +1	For pre dose, a window of 10 days before will be applied and the last assessment within this window will be used for the table, For post dose, a window of 10 days after will be applied and the earliest assessment within this window will be used for the table
	Cycle 2 Pre Dose	Injection 2	Day of the second injection	
	Cycle 2 Post Dose	Injection 2	Day of the second injection +1	
	Cycle 3 Pre Dose	Injection 3	Day of the third injection	
	Cyce 3 Post Dose	Injection 3	Day of the third injection +1	
	Cycle 4 Pre Dose	Injection 4	Day of the fourthe injection	
	Cycle 4 Post Dose	Injection 4	Day of the fourth injection +1	
	FU month 3	Day 1 is the day after treatment end date	84	Day 56 to day 112
	FU month 6		168	Day 140 to day 196
	FU month 9		252	Day 224 to day 280
	FU month 3k (Till early termination of study or 24 month after the first treatment)		D=28*3k	Day D-28 to day D+28
Vital sign	Baseline			Treatment visit 1, pre-dose,
	Treatment visit 1, 30 mins post dose, 60 mins post dose	Injection 1		Treatment visit x is from injection x to the day before injection

Parameters	Analysis visit	Reference day	Target day of assessment compare to the reference day	Time interval start (>=) end (<)
	Treatment visit 2, pre-dose, 30 mins post dose, 60 mins post dose	Injection 2		x+1. For the last injection Treatment visit y is from the last injection to last injection + 28 days.
	Treatment visit 3, pre-dose, 30 mins post dose, 60 mins post dose	Injection 3		
	Treatment visit 4, pre-dose, 30 mins post dose, 60 mins post dose	Injection 4		
	FU month 3	Day 1 is the day after treatment end date	84	Day 56 to day 112
	FU month 6		168	Day 140 to day 196
	FU month 9		252	Day 224 to day 280
	FU month 3k (Till early termination of study or 24 month after the first treatment)		D=28*3k	Day D-28 to day D+28
12 lead ECG	Baseline			Treatment visit 1, pre-dose
	Treatment visit 1, post-dose	Injection 1		Treatment visit x is from injection x to the day before injection x+1. For the last injection Treatment visit y is from the last injection to last injection + 28 days.
	Treatment visit 2, pre-dose, post-dose	Injection 2		
	Treatment visit 3, pre-dose, post-dose	Injection 3		
	Treatment visit 4, pre-dose, post-dose	Injection 4		

If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If two assessments within a time window are equidistant from the target date, then the earlier of the two assessments will be used. If multiple assessments on the same date

then the worst case will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed. For those parameter analysis at timepoints should be analyzed separately at timepoints, not be considered as multiple test within one window.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375; if duration is provided in days, duration in months will be multiplied by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For safety evaluations, the last available assessment on or before the date of start of study treatment is taken as ‘‘baseline” assessment. Evaluation of EPIC-26 will use safety definition for baseline.

For PSA relevant safety analysis, baseline for safety evaluation definition will be used with SAF population. PSA data will only be able to be listed.

ECOG Baseline is defined as last assessment before treatment start date

3.4.3 Rules for adverse events

Intensity
AE is collected in eCRF based on severity (mild, moderate and severe), SAE is based on CTCAE Grading.

Body System
Adverse events will be categorized by MedDRA preferred term (PT) and system organ class (SOC).

Attribution of the AE to Study Drug
A frequency table will be presented showing the information on attribution of the AE to study drug using the categorization given on the case report forms (CRFs):

1 ≈ ‘none’, **2** ≈ ‘unlikely’, **3** ≈ ‘possible’, **4** ≈ ‘probable’, **5** ≈ ‘definite’.

Moreover, this categorization will be used in data listings.

3.4.4 Rules for vital signs

Systolic blood pressure
Following categories will be used for analysis of changes:

1 ≈ 'Decrease (Dec) >40 (i.e. Difference (D) < -40 mm Hg)'
2 ≈ 'Dec >20-40 (i.e. -40 mm Hg ≤ D < -20 mm Hg)'
3 ≈ 'Difference (+/-) 0-20 (i.e. -20 mm Hg ≤ D ≤ 20 mm Hg)'
4 ≈ 'Increase (Inc) >20-40 (i.e. 20 mm Hg < D ≤ 40 mm Hg)'
5 ≈ 'Inc >40 (i.e. D > 40 mm Hg)'.

Diastolic Blood Pressure
Following categories will be used for analysis of changes:

1 ≈ 'Dec >30 (i.e. D < -30 mm Hg)'
2 ≈ 'Dec >15-30 (i.e. -30 mm Hg ≤ D < -15 mm Hg)'
3 ≈ '+/- 0-15 (i.e. -15 mm Hg ≤ D ≤ 15 mm Hg)'
4 ≈ 'Inc >15-30 (i.e. 15 mm Hg < D ≤ 30 mm Hg)'
5 ≈ 'Inc >30 (i.e. D > 30 mm Hg)'.

Heart Rate
Following categories will be used for analysis of changes:
1 ≈ 'Dec >30 (i.e. D < -30 beats/min)'
2 ≈ 'Dec >15-30 (i.e. -30 beats/min ≤ D < -15 beats/min)'
3 ≈ '+/- 0-15 (i.e. -15 beats/min ≤ D ≤ 15 beats/min)'
4 ≈ 'Inc >15-30 (i.e. 15 beats/min < D ≤ 30 beats/min)'
5 ≈ 'Inc >30 (i.e. D > 30 beats/min)'.

3.5 General Variable Definitions

Data will be analyzed using SAS version 9.4 or higher.

Descriptive statistics will be presented in tables as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages.
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, minimum, and maximum values.

Unless otherwise indicated, for frequency tables, patients with missing data will be excluded from the denominator of percentage calculations.

Individual patient listings will include all study-related data. The sort order of the listings will be by treatment, patient ID, and date of assessment (if available).

If multiple results for the same assessment are collected during a visit time window, the first result will be utilized unless indicated otherwise.

The following definitions will be used:

- Age (years): year of informed consent - year of birth
- Time since initial cancer diagnosis (years): (Date of randomization - Date of initial cancer diagnosis)/(365.25)
- Weight (kg) = weight (lb) * 0.45359237
- Height (cm) = height (in) * 2.54

3.6 Patient Disposition, Deviations, Demography

The following patient data will be summarized in tables for all patients:

- Number (%) of patients who signed informed consent
- Number (%) of patients in each analysis population

The following patient data will be summarized in tables for the ITT population:

- Number (%) of patients discontinued from study treatment
- Number (%) of patients discontinued from the study
- Number (%) for the primary reason for discontinuation for each of the above

For the ITT population, protocol deviations will be listed by treatment and patient ID.

Demographic data (age (years), age categorical (< 65 years, >= 65 years), ethnicity, race, weight (kg), height (cm), and pulse oximetry (%)) will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum and maximum for quantitative variables; frequency counts by category will

be given for qualitative variables). All demographic summary tables will be based on the ITT and Safety populations. An individual listing will be provided for demographic data for the ITT population.

For demographic and baseline characteristics, the last available assessment on or before the date of start of study treatment is taken as ‘‘baseline” assessment for both ITT and safety population analyses.

3.7 Baseline Disease Characteristics

Descriptive statistics of patient disease characteristics at baseline will be presented for the following variables for the ITT and Safety population:

- Time since initial cancer diagnosis (years)
- Initial Histopathological Classification (type of prostate cancer tumor)
- Initial Gleason score
    - Categorical: 2-3,4-7,8-10, unknown
- Baseline PSA doubling time (months): continuous and categorical (≤ 6 months vs. >6 months)

  Baseline PSA doubling time (months): PSA doubling time will be calculated as natural log of 2 (0.693) divided by the sum of the fixed slope (common to all patients) and the random slope (specific for the patient) of the random coefficient linear model between the natural log of PSA and time of PSA measurement (Svatek et al., 2006). If the PSA doubling time is less than zero (i.e. stable, nonincreasing, or decreasing PSA levels as defined by a negative slope from the random coefficient linear model), the PSA doubling time is set to 0. PSA is collected at screening visit and for the most recent 2 PSA measurements available prior to screening. Calculations will be performed only for subjects with (1) all 3 PSA values with each value ≥ 0.2 ng/mL and (2) for which the interval between the first and last PSA values are ≥8 weeks but ≤ 12 months as stated in PCWG3 guidelines (Scher et al., 2016; Pound et al., 1999).

For interpretation of PSA doubling time it should be noted that PCWG3 guidelines state the calculation should be based on the most recent PSA values during androgen deprivation therapy, and that 3 PSA values ≥ 0.2 ng/mL should be consecutive. These additional criteria will not be applied since the information is not available.

- Baseline PSA

For Baseline PSA as baseline disease characteristic, the last available assessment on or before the date of randomization is taken as ‘‘baseline” assessment for both ITT and safety population analyses.

Listings of baseline disease characteristics will be provided for the ITT population.

3.8 Medical History

A medical history listing will be provided for the ITT population.

3.9 Prior Cancer Related Therapy

Descriptive statistics with respect to prior therapy collected on the Prostate Cancer Treatment History CRF pages (Chemotherapy, Other Treatment, and Radiotherapy) will be displayed for the ITT population. A listing of data recorded on the Prostate Cancer Treatment History CRF pages (Chemotherapy, Other Treatment, and Radiotherapy) will also be provided for the ITT population.

The variables to be summarized in tables are:

- Prostate Cancer Treatment History: Chemotherapy

- Prior number of therapies
- Prior number of taxane-containing regimens
- Number of unique agents

- Prostate Cancer Treatment History: Chemotherapy - Last Taxane Therapy
  - Number of cycles
  - Duration of therapy (months)
  - Best overall response (BOR) to last taxane-therapy (Complete response (CR), Partial response (PR), Stable disease (SD), Progressive Disease (PD), Missing)

- Prostate Cancer Treatment History: Chemotherapy - Last Therapy
  - Type of last prior therapy
  - Number of cycles
  - Duration of therapy (months)
  - Best Response (CR, PR, SD, PD, Missing)

- Prostate Cancer Treatment History: Other Treatment
  - Number of patients with at least one prostate cancer-related other treatment
  - Type of other treatment
  - Prior number of other treatments

- Prostate Cancer Treatment History: Radiotherapy
  - Number of patients with at least one prostate cancer-related radiotherapy
  - Type of prior radiotherapy
  - Prior number of radiotherapies

3.10 Efficacy Analysis

All efficacy analyses will be based on the ITT population.

Due to not enough patients to ensure the statistical power, and investigator's inconsistent timing of PSA data collection. PSA efficacy endpoints will not be analyzed and therefore are not described in this SAP. PSA results will be listed by visit for all patients in the SAF population

Due to only limited imaging data being available, the relevant endpoints (i.e., rPFS and DCR) will not be analyzed and therefore are not described in this SAP.

Bone pain level

Bone pain level will be listed by visit for all patients in the ITT population.

QoL: EPIC-26

Quality of Life questionnaire "EPIC-26" item value will be transformed into score as below. HRQOL domain score will be calculated as below. If >20% of the items that comprise a domain summary score or subscale score are missing a response, the corresponding domain summary or subscale score cannot be calculated. Domain scores at each time point, along with the change from baseline, will be summarized as continuous variable at baseline and at treatment visits and follow-up 3, 6, 9, 12, 18 and 24 months after start of ^{177}Lu-PSMA-617 RLT. Results will be presented separately for both treatment groups (6.0 vs. 7.4 GBq ^{177}Lu-PSMA-617) and overall. Item value with standardized score will also be listed.

There are 2 steps involved in scoring EPIC-26:
Step 1. The response for each item is standardized to a 0 to 100 scale according to the table below.

Item Number	Item Response Value	Standardized Value
23.57.58.60.64	1	0
	2	25
	3	50
	4	75
	5	100
26.59	1	0
	2	33
	3	67
	4	100
27	0	100
	1	67
	2	33
	3	0
28.29.30.31.33.49.50.52.53. 54.74.75.77.78.79	0	100
	1	75
	2	50
	3	25
	4	0
34.55.68	1	100
	2	75
	3	50
	4	25
	5	0

Step 2. Using the item groupings listed below for each HRQOL Domain Score, average the standardized values (see Step 1, above) for all items within a group to create the summary or subscale score. (If ≥20% of the items that comprise a domain summary score or subscale score are missing a response, the correspondin domain summary or subscale score can not be calculated).

To calculate the following HRQOL domain Summary Score or Subscale Score:	Determine the average of the Standardized Values (see Step 1, above) for the following items:	Number of non-missing items needed to compute score (otherwise, set score to missing)
HRQOL Domain Summary Scores		
Urinary Incontinence	23, 26-28	4
Urinary Irritative/Obstructive	29-31, 33	4
Bowel	49, 50, 52-55	5
Sexual	57-60, 64, 68	5
Hormonal	74, 75, 77-79	4

Item numbers are indicated along the right border of the questionnaire (question numbers on left of questionnaire pages are not used for scoring because some questions contain multiple items).

Change in ECOG-PS

The changes in ECOG from baseline will be evaluated over time at treatment visit 1, 2, 3 and 4 administration, and at follow-up visits. Shift tables will be provided for each post administration time point and FU visits compared to baseline. Results will be presented separately for both treatment groups (6.0 vs. 7.4 GBq ^{177}Lu-PSMA-617) and overall. Results will also be listed for the ITT population.

Exploratory efficacy analysis not planned.

3.11 Safety Analysis

The safety analysis will be based on the safety population. Tables will show results by treatment arm and for all patients combined. Listings will be created by treatment arm.

For all safety summary tables, the tables will also be provided by age (<65 years old, >= 65 years old).

Reference date is the date of first dose of Lu-PSMA-617 unless otherwise noted.

3.11.1 Safety Variable Definitions

- **^{177}Lu-PSMA-617 exposure variables:**
  Duration of exposure/study treatment (months) = (Date of last study drug administration – Reference date + 1)/30.4375

Dose per cycle

Dose for each cycle/overall (GBq/cycle) = (actual total dose during the cycle/study) / (1 or actual # of cycles)

Planned dose for each cycle/overall (GBq/cycle) = (planned total dose during the cycle) / (1 or planned # of cycles)
Note: Planned number of cycles = received number of cycles unless there was a missed dose

Relative dose per cycle/overall (%) = (dose by cycle/overall) / (planned dose by cycle/overall)

3.11.2 Extent of Exposure

A listing of study drug administration will be provided.

Randomized Treatment Exposure, Summary of Cycles

For the Safety population, summary of treatment cycle variables to be included are:

- Duration of study treatment (months)
- Number of cycles started per patient (both as categorical and continuous variable)
- Average duration of treatment cycles (months)

Randomized Treatment Exposure, By Cycle and Across Cycles Combined

For the Safety population, ^{177}Lu-PSMA-167 exposure variables to be summarized for the entire study and for each cycle are:

- Cumulative dose (GBq) of patient
- Dose per cycle/overall (GBq/cycle)
- Relative dose per cycle/overall (%)

To convert from mCi units to GBq units the conversion 1 mCi = 0.037 GBq will be used.

3.11.3 Adverse Events

Safety of ^{177}Lu-PSMA-617 RLT will be assessed by analysis of toxicity.

Adverse events (AE) will be coded using MedDRA version 22.1, by SOC and PT. Serious AEs will be graded according to the NCI CTCAE criteria version 4.0 while AEs will be described by severity (i.e., Mild, Moderate, Severe).

In case a patient experienced the same event more than once, the maximum toxicity grade will be presented.

In all AE tables, multiple occurrences of the same adverse events occurring in one individual are counted only once.

Definition of Treatment Emergent Adverse Event (TEAE)

A randomized treatment TEAE is defined as an AE that was not present prior to initiation of randomized treatment, defined as first dose of 177Lu-PSMA-617, but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated).

Any event that is considered study drug-related (stated as possible, probably, definite relationship, or missing assessment of relatedness), regardless of the start date of the event, or any event that worsens in toxicity grade while on treatment or is subsequently considered study drug-related by the investigator is also defined as a treatment-emergent adverse event.

The treatment-emergent period will be defined as the period from the date of initiation of randomized treatment up to 30 days after date of last administration of study treatment or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

Randomized Treatment Adverse Events

A summary table including the number of patients with at least one event, will be presented for the AE variables below.

- TEAE[1, 3]
- Serious TEAE[1, 2, 3]
- Drug-related TEAE[1]
- Serious drug-related TEAE[1]
- TEAE leading to reduction of ^{177}Lu-PSMA-617 dose[1]
- TEAE leading to permanent discontinuation of ^{177}Lu-PSMA-617 treatment[1]
- Fatal TEAE[1]

[1]AE variables to be tabulated by SOC and PT.

[2]Serious AE variables to be tabulated by SOC and PT by CTCAE grade.

[3]AE variables are to be tabulated by SOC and PT, CTCAE grade (serious AEs) or severity grade (TEAEs), and cycle.

A listing for each patient will include the same variables as mentioned above and will also include action taken regarding ^{177}Lu-PSMA-617.

Deaths

All deaths will be summarized by treatment groups (6.0 vs. 7.4 GBq ^{177}Lu-PSMA-617) and overall with the End of Treatment status table; deaths will also be listed.

Specific Adverse Events Questionnaire

Adverse events as captured on the pain and adverse events questionnaire form will be summarized and listed by treatment arm. A listing will also be created.

3.11.4 Laboratory Data

Laboratory parameters will be analyzed descriptively by summary tables.

Hematology	**Clinical Chemistry**
Hematocrit	eGFR
Hemoglobin	Bilirubin
Red blood cell (RBC) count (Erythrocytes)	Creatinine
WBC count (Leukocytes)	Sodium
Absolute Monocyte count	Urea nitrogen (BUN)
Platelets	Chloride
Absolute neutrophil count (ANC)	AST/SGOT
Mean corpuscular volume (MCV) / Mean corpuscular hemoglobin (MCH)	ALT/SGPT
Absolute Eosinophil count	Alkaline phosphatase
Absolute Basophil count	PSA*
Absolute Lymphocyte count	Albumin
RDW (Erythrocytes Distribution Width)	Potassium

**PSA will be done only at the time intervals called by the protocol (see Schedule of Events in Section 3.13).*

Laboratory values and, for assessments measured over time, change from baseline will be summarized by visit. Frequency statistics for qualitative laboratory parameters will also be presented by visit.

Shift tables of high-normal-low laboratory values from baseline to each measurement time point will be provided for each parameter that has a reference range. The abnormal flag be derived based on the upper and lower limits of normal range. Reference ranges are taken from the Merck Manual Professional Version, 2018 and the Merck Manual Consumer Version for Complete Blood Count for all parameters except estimated Glomerular Filtration Rate (eGFR; reference range from National Kidney Foundation).

The mean (±standard error) values over time will be plotted for PSA by treatment arm.

Patient listings of all lab values will be provided, values outside of the laboratory's reference range will be flagged for all parameters with ranges. The patient listings will indicate the CTCAE grade if one is provided in the data.

3.11.5 Vital Signs

Systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm), temperature (C), and respiratory rate (breaths per min) will be analyzed descriptively by summary tables noting observed values and change from baseline. Transition tables will be provided for the transitions from baseline to each follow-up time point.

3.11.6 12-Lead ECG Data

Overall ECG interpretation will be summarized. Heart rate (bpm), PR (msec), QRS (msec), QT (msec) and QTc (msec; measured by both sites as QTcB using Bazett's formula) intervals will be summarized as continuous variables. All ECG variables will also be listed.

3.11.7 Physical Exam

Physical examination results will be listed for the Safety population

3.11.8 Concomitant Medications

Medications as recorded on the Concomitant Medications CRF will be listed.
Medications will be classified as prior and/or concomitant. Prior medications are all medications taken or occurring prior to first dose of ^{177}Lu-PSMA-617. Concomitant medications are all medications continued or started on or after the date of the first randomized study drug administration

3.11.9 Concurrent and Post Chemotherapy

Descriptive statistics for Concurrent Chemotherapy and Post-Treatment Chemotherapy will be displayed using the data collected on the Treatment Visit Concomitant Cancer-related Therapy Chemotherapy CRF and Follow-up Concomitant Cancer-related Therapy Chemotherapy CRF, respectively. Separate listings of Concurrent Chemotherapy and Post-Treatment Chemotherapy will be provided.

The variables to be summarized in the table are:

- Number of patients with at least one chemotherapies
- Number of chemotherapies
- Type of chemotherapies

3.11.10 Concurrent and Post Radiotherapy

Descriptive statistics for Concurrent Radiotherapy and Post-Treatment Radiotherapy will be displayed using the data collected on the Treatment Visit Concomitant Cancer-related Therapy Radiotherapy CRF and Follow-up Concomitant Cancer-related Therapy Radiotherapy CRF, respectively. Separate listings of Concurrent Radiotherapy and Post-Treatment Radiotherapy will be provided.

The variables to be summarized in the table are:

- Number of patients with at least one radiotherapy
- Number of radiotherapies
- Type of radiotherapies

3.11.11 Concurrent and Post Other Treatments

Descriptive statistics for Concurrent Other Therapy and Post-Treatment Other Therapy will be displayed using the data collected on the Treatment Visit Concomitant Cancer-related Therapy Other Therapy CRF and Follow-up Concomitant Cancer-related Therapy Other Therapy CRF, respectively. Separate listings of Concurrent Other Therapy and Post-Treatment Other Therapy will be provided.

The variables to be summarized in the table are:

- Number of patients with at least one other treatments
- Number of other treatments
- Type of other treatments

3.12 Other Analyses

None.

3.13 Schedule of Events

7	Screening	Therapy													F/U																								30
Month					1		2		3		4		5		6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	Month
Week		-2	0	2	4	6	8	10	12	14	16	18	20	22	24																								Week
Therapy			1				2				3				4																								Therapy
Signing informed consent form	*																																					Signing informed consent form
Randomization		*																																				Randomization
1 Evaluation of blood tests (CBC, CMP with eGFR)	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	Every 2 weeks			*			*			*			*			*								Evaluation of blood tests (CBC)
2 PSA determination		*				*			*				*		*			*			*			*			*			*								PSA determination
3 Evaluation of Imaging studies (CT, MRI, bone imaging)	*										*							*			*			*			*			*								Evaluation of Imaging studies (CT, MRI)
4 Ga-68 or Lu-177 PSMA imaging	*																																						Ga-68 or Lu-177 PSMA PET/CT
5 Medication & Hypersensitivity assessment	*																																						Medication & Hypersensitivity assessment
6 Current Disease (somatic or psychiatric)	*																																						Current Disease(somatic or psychiatric)
7 Histopathology evaluation	*																																						Histopathology evaluation
8 Relevant medical history & demographics	*																																						Relevant medical history & demographics
9 Physical exam	*		*				*				*				*			*			*			*			*			*								Physical exam
10 Concomitant cancer-related therapies since last visit			*				*				*				*			*			*			*			*			*								Concomitant cancer-related therapies since last visit
11 Vital Signs (BP, HR, T, RR)	*		*				*				*				*			*			*			*			*			*								Vital Signs (BP, HR, T, RR)
12 Evaluation of life-expectancy	*																																						Evaluation of life-expectancy
13 Prior therapy for Prostate cancer	*																																						Prior therapy for Prostate cancer
14 Continuous ECG monitoring			*				*																																ECG and continues ECG monitoring
15 12 lead static ECG	*		*				*				*				*																								
16 Quality of life assessment (EPIC-26) & ECOG	*								*						*			*			*						*											Quality of life assessment (EPIC-26) & ECOG
17 Whole body (Anterior And Posterior) scan			*				*																																Whole body (Anterior And Posterior) scan
18 Follow up calls for AE Monitoring		+7 days					+7 days				+7 days				+7 days			*			*			*			*			*								Follow up calls for AE Monitoring
days	-10	-7	0	14	28	42	56	70	84	98	112	126	140	154	168	196	224	252	280	308	336	364	392	420	448	476	504	532	560	588	616	644	672	700				

1 Only at first or second treatment, several blood and urine samples will be required for dosimetry purposes. Blood: before injection, 5 (±1) min, 30 (±3) min, 60 (±5) min, 4 (±10 min), 18-30, 42-54, and 66-78 hours post injection. 7 to 9 days sample is optional. Urine collection will include 0-4 hrs and 4 hrs until discharge
1 Laboratory tests will be acceptable only if performed within two weeks of each scheduled visit. Screening visit and week -2 can be combined if screening visit performed within 2 weeks of the first cycle
1 CBC/CMP with eGFR will be performed at least once every other week continued for 12 weeks after the last treatment and then continued every 3 (±1) months during follow-up for 24 months or until disease progression as per clinical routine
2 PSA will be measured every 6 weeks during the treatment and every 3 (±1) months after the last treatment until reaching endpoint or 24 months after the first treatment.
3 Baseline imaging within 12 weeks of start of therapy including (a) Chest CT preferably with contrast & CT or MRI of the Abdomen- pelvis preferably with contrast, (b) bone imaging, (c) or equivalent as per clinical routine
3 Relevant imaging studies will be done at baseline, before 3rd RLT cycle, 3 (±1) months after last RLT cycle, and then every 3 (±1) months during follow-up until reaching the endpoint or 24 months after the first treatment as per clinical routine
11 For safety assessment, vital signs will be measured within 20 minutes before and for up to an hour after administration of 177Lu-PSMA 617
14 Continuous ECG monitoring (only in first 2 RLT cycles) starts at least 15 minutes prior to administration of the study drug and lasts at least 1 hour after administration.
15 Two 12 lead ECGs: one before injection and one after 4 hr scan in dosimetry RLT and after completion of salivary gland protection in non-dosimetry RLT
16 Quality of life questionnaire (EPIC-26) and ECOG will be completed at baseline, and at 3, 6, 9, 12, 18 and 24 months from first RLT cycle
17 Only at first or second treatment, whole body scintigraphy will be performed several times (4 hrs ±10 min), 18-30, 42-54 , and 66-78 hours) after injection for dosimetry purposes. For non-dosimetry RLTs, only one (optional) post therapy WB scan will be performed. Please refer to dosimetry schedule of events.
18 Telephone follow up: 7 (± 3) days after each treatment cycle until completion of 4 cycles and for follow up phase , every 3 months (± 1 month) until the end of follow up visits (24 months).
In each time point that the therapy stops follow up visits will be started.

Note: ECOG was done at every treatment visit then every three month FU visits

3.14 References

1. Scher, H.I., et al., Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol, 2016. 34(12): p. 1402-18.

2. Rahbar, K., et al., *German multicenter study investigating 177Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients.* J Nucl Med, 2016.

3. Danila, D.C., et al., *Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer.* J ClinOncol, 2010. **28**(9): p. 1496-501.

Appendix I Generalized Reference Ranges

Laboratory Test	Units	Merck Low	Merck High	National Kidney Foundation Low	National Kidney Foundation High
Albumin	g/dL	3.5	5.4		
Alkaline Phosphatase	U/L	36	150		
Alanine Aminotransferase	U/L	0	35		
Aspartate Aminotransferase	U/L	0	35		
Bilirubin	mg/dL	0.3	1.2		
Chloride	mEq/L	98	106		
Creatinine	mg/dL	0.7	1.3		
Glomerular Filtration Rate, Estimated*	mL/min/1.73 m2			>90	
Potassium	mEq/L	3.5	5		
Sodium	mEq/L	136	145		
Urea Nitrogen	mg/dL	8	20		
Basophils	x10^3/mcL	0	0.3		
Basophils/Leukocytes	%	0	3		
Eosinophils	x10^3/mcL	0	0.9		

Eosinophils/Leukocytes	%	0	8
Hematocrit	%	41	51
Hemoglobin	g/dL	14	17
Lymphocytes	x10^3/mcL	1.0	4.8
Lymphocytes/Leukocytes	%	22	44
Ery. Mean Corpuscular Hemoglobin	pg	28	32
Ery. Mean Corpuscular Volume	fL	80	100
Monocytes	x10^3/mcL	0.2	1.2
Monocytes/Leukocytes	%	4	11
Neutrophils	x10^3/mcL	1.8	7.7
Neutrophils/Leukocytes	%	40	70
Platelets	x10^3/mcL	150	450
Erythrocytes	x10^6/mcL	4.2	5.9
Erythrocytes Distribution Width	%	11.5	14.5
Leukocytes	x10^3/mcL	4.5	11
Prostate Specific Antigen	ng/mL	0	4
Prostate Specific Antigen	ng/mL	0	4

Ranges taken from Merck Manual Professional Version, 2018 and the Merck Manual Consumer Version for Complete Blood
*estimated Glomerular Filtration Rate (eGFR) taken from the National Kidney Foundation

Final

STATISTICAL ANALYSIS PLAN ADDENDUM 1

Study PSMA-617-02

Title: *(as per protocol/amendment)*	PSMA-Directed Endoradiotherapy Of Castration-Resistant Prostate Cancer (RESIST-PC). A Phase II Clinical Trial
Version:	Final Addendum 1
Date:	15-Dec-2020

CONFIDENTIAL

1 APPROVAL SIGNATURES

STUDY TITLE: PSMA-Directed Endoradiotherapy Of Castration-Resistant Prostate Cancer (RESISTPC). A Phase II Clinical Trial
PROTOCOL NUMBER: PSMA-617-02
SAP Addendum 1 Final, 15-Dec-2020

Endocyte, Inc.:

Reviewed/Approved By: [redacted], [redacted]

[redacted]

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Date: 2020.12.16 19:38:11 +01'00

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Date: 2021.01.11 16:10:41 -05'00'

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2 Abbreviations

Abbreviation	Description
CR	Complete response
DCR	Disease control rate
ITT	Intent-to-treat
PCWG3	Prostate Cancer Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PSA	Prostate-specific antigen
RECIST	Response evaluation criteria in solid tumors
rPFS	(radiographic) Progression-free survival
SD	Stable disease

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4 Reason for addendum

The original statistical analysis plan (SAP), Version 2.0, dated 15-May-2020, describes the analyses planned for the abbreviated clinical study report (aCSR) that summarized the safety data and listed the efficacy data. The efficacy data was not summarized for the aCSR due to the significantly smaller sample size than the planned 200 patients since enrollment into the study was stopped early. The modeling approaches stated in the protocol could not be carried out as there was insufficient data to perform the analyses that would allow for appropriate evaluation of effectiveness.

Clinicaltrials.gov requires all available data for primary and secondary endpoints to be disclosed. The purpose of this SAP addendum is to describe the analyses planned for clinicaltrials.gov using the limited data available. Due to only limited imaging and PSA data being available, some secondary endpoints could not be analyzed as planned in the protocol and the changes to the analyses are described in this SAP addendum. The source of the data is the clinical database.

5 Objectives and Endpoints for SAP Addendum

5.1 Study Objectives

5.1.1 Primary objectives

1. To assess the efficacy as defined by proportion of patients with PSA-response of ≥50% decline at 12-weeks from baseline

5.1.2 Secondary objectives

1. Maximum PSA response: Maximal baseline to follow-up PSA decline, at any time during or after therapy.
2. PSA Progression Free Survival (PFS): To determine the time to PSA progression, separate for treatment doses: time from inclusion (date of randomization) to date of PSA progression or death (whichever occurs first). SAP Addendum Note: Time to PSA progression will not be analyzed; only number of PSA progression or death events can be summarized for this objective.
    a. For patients with PSA decline from baseline at any time during or after therapy: PSA progression is defined as the date that a ≥ 25% increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance).
    b. For patients without PSA decline from baseline: PSA progression is defined as a ≥25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.
3. rPFS: To determine the radiographic progression free survival (rPFS), for each treatment dose: time from randomization to date when first site of disease is found to progress or death (whichever occurs first). SAP Addendum Note: rPFS cannot be analyzed; only investigator assessment of RECIST 1.1 overall response by each follow-up assessment and investigator assessment of PCWG3 bone scan clinical impression by visit can be summarized for this objective.
    a. Nodal and visceral disease is evaluated on cross-sectional imaging using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1/ Prostate Cancer Working Group (PCWG3) criteria.

b. Bone metastases are evaluated using bone scintigraphy and new lesions have to be confirmed on a second scan (2+2 rule) using PCWG3 criteria.

4. To determine disease control rate (DCR) defined as the proportion of patients achieving RECIST 1.1/PCWG3 criteria stable disease (SD), partial response (PR) or complete response (CR). SAP Addendum Note: Only RECIST 1.1 disease control rate by each follow-up assessment can be summarized for this objective.

5.2 Primary and secondary endpoints

5.2.1 Primary endpoints

1. Efficacy of ^{177}Lu-PSMA-617 will be assessed at week 12 by means of number and percentage of patients with ≥50% decline in PSA at 12 weeks from baseline.

5.2.2 Secondary endpoints

1. Maximum PSA response
2. PSA-PFS
3. Radiographic progression-free survival (rPFS)
4. Disease control rate (DCR)

6 Analyses

Tables will show results by treatment arm and for all patients combined. The following patient data will be summarized in tables for the ITT population: • PSA Response at Week 12

- Percent change in PSA from baseline to Week 12
- Maximum PSA response
- PSA Progression and Death Events
- RECIST 1.1 Overall Response by Follow-up Assessment Visit
- RECIST 1.1 Disease Control Rate by Follow-up Assessment visit
- PCWG3 Bone Scan Clinical Impression by Visit

7 Statistical Methods and Definitions for Addendum

The same statistical methods as described the original SAP will be followed, with any exceptions noted below. Table shells are created along with this document.

- Baseline PSA is defined as the last available assessment prior to or on first dose date of ^{177}LuPSMA-617.
- PSA response at Week 12: PSA response is defined as the proportion of patients who have a ≥50% decrease in PSA from baseline at Week 12.
- Maximum PSA response includes all available PSA results, including unscheduled, up to and including the last assessment visit.
- PSA progression is defined as:
  (a) For patients with PSA decline: PSA progression is defined as the date that a ≥ 25% increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored (PCWG3 Guidance),

(b) For patients without PSA decline: PSA progression is defined as a ≥25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.

- RECIST 1.1 Overall Response = Number of patients with an overall response of Complete Response (CR), Partial Response (PR), Stable Disease (SD), or Progressive Disease (PD) according to RECIST v1.1 using investigators assessments.
    - There is no minimum time after first dose of ^{177}Lu-PSMA-617 to when first assessment is included in analysis.
    - Data is summarized by assessment visit; therefore, the data presented is unconfirmed response.
- RECIST 1.1 Disease Control Rate = Proportion of patients with Overall Response of CR, PR, or SD according to RECIST v1.1 using investigators assessments.
- PCWG3 Bone Scan Clinical Impression = Number of patients with a clinical impression of Improved, Stable or Progression according to PCWG3 using investigators assessments.

As stated in the original SAP, the investigator's had inconsistent timing of PSA data collection; therefore PSA-PFS will not be derived because censoring rules are not applicable given this inconsistent timing of PSA data collection. Instead, number and percentage of patients with a PSA progression event or death event will be summarized.

As stated in the original SAP, limited imaging data is available. The date of radiographic tumor assessment for the RECIST 1.1 follow-up assessments is not available; therefore, the rPFS analysis cannot be performed. Instead, the available RECIST v1.1 overall response and disease control rate will be summarized by number and percentage of patients at each follow-up assessment and the available PCWG3 bone scan clinical impression will be summarized by number and percentage of patients at each visit.