

PSMA-617 Sub-study manual

(VISION Sub-study)

Study Number:

PSMA-617-01

EudraCT N°:

2018-000459-41

IND N°:

133,661 (¹⁷⁷Lu-PSMA-617)

Title:

An international, prospective, open-label, multicenter, randomized phase 3 study of ¹⁷⁷Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration resistant prostate cancer (mcrpc).

Version:

4.4 DE

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Protocol; PSMA-617-01

PSMA-617 Sub-study manual

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Table of Contents

Table of Contents.....	3
History of Document.....	4
Abbreviations	5
1. Introduction	6
Study overview.....	6
Renal Function Surveillance.....	7
Scope of complete and simplified dosimetry assessments	7
2. Objectives.....	8
3. Electrocardiogram for dosimetry and QTc analysis	8
4. Image quantification	9
Necessary equipment for dosimetry data collection	9
General information.....	10
Data acquisition.....	11
Image processing.....	14
5. Biological samples for dosimetry and PK analysis.....	16
Blood analysis	16
General information and data collection of blood samples	16
Whole blood Pharmacokinetic Calculations.....	17
Urine analysis	18
General information and data collection time points	18
Urine collection for radioactivity	18
Equipment	19
Sample handling	19
Shipping	20
Urine Receipt and Processing	21
Urine Radioprofiling	21
Radioprofiling Data Analysis.....	22
6. Data analysis and radiation dosimetry calculations.....	23
7. References.....	27
8. Appendices	30
Appendix 1	31
Appendix 2	32
Appendix 3	34
Appendix 4	35
Appendix 5	38
Appendix 6	39
Appendix 7	40
Appendix 8	42
Appendix 9	43

History of Document

Version	Date	Summary of change
1.0	14-February-2020	Not applicable
2.0	16-June-2020	<p>Section 3:</p> <ul style="list-style-type: none"> - Add systolic and diastolic blood pressure - Modify Figure to include pre-dose PK sample collection - Clarify there is no restriction in water intake. If patients are dosed later in the day they should fast for three hours before dosing <p>Section 4:</p> <ul style="list-style-type: none"> - Provide clarification on scans collection and requirement for site to use the tool in Appendix 1 to help planning the subsequent scans acquisition. <p>Section 5:</p> <ul style="list-style-type: none"> - Add that ABX will provide CoA to Charles River - Add that blood sample can be collected following site procedures on how to handle blood withdrawal - Clarify that first timepoint for urine collection is not mandatory to be 0-2 hours but it is important to have complete urine collection up to first scan (e.g. up to 1 hour before the first scan is performed at 1 hr post-dose) - Requirement to maintain a temperature log for Urine storage until shipment added - There are no study supplies for urine collection. Vials were purchased locally and no need to return to sponsor - Blood and Urine back-up samples will be destroyed upon Sponsor request <p>Appendices:</p> <ul style="list-style-type: none"> - Appendix 1: add the PK/ECG/Urine/scans collection tool. - Appendix 3: add Certus Data Resolution Form. - Appendix 6: add total radioactivity to the HPLC transmittal form. - Appendix 7: add custom invoice template added; MARKEN booking form updated template added
3.0	23-Sep-2020	<ul style="list-style-type: none"> • Additional imaging procedures of whole body planar and 3D SPECT from cycle 2 through cycle 6 of ¹⁷⁷Lu-PSMA-617 treatment to align and comply with local radioprotection laws and established guidelines in Germany. • Implementation of assessment of estimated glomerular filtration rate (eGFR) using the MDRD equation from cycle 1 through cycle 6 of ¹⁷⁷Lu-PSMA-617 treatment to further monitor and assess potential renal toxicity.

Abbreviations

Bq	Becquerel
cpm	counts per minute
cps	counts per second
CRO	Contract Research Organization
CT	Computed Tomography
CRL-ASH	Charles River Laboratory - Ashland
DICOM	Digital Imaging and Communications in Medicine
EANM	European Association of Nuclear Medicine
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
GBq	Giga Becquerel
Gy	Gray
kBq	Kilo-Becquerel
mCRPC	metastatic Castration Resistant Prostate Cancer
MBq	Mega-Becquerel
MIRD	Medical Internal Radiation Dose
MEGP	Minimum Energy General Purpose
PK	pharmacokinetics
p.i.	post infusion
RDS	Radiation Dosimetry Systems, Inc.
RT	Retention Time
ROI	Region of Interest
SPECT	Single Photon Emission Computed Tomography
TAC	Time activity curve
TIAC	Time integrated activity coefficient
VOI	Volume of Interest
WB	Whole Body
HPLC	High-performance liquid chromatography

1. Introduction

Study overview

Treatment of mCRPC using ^{177}Lu -PSMA-617 is an attractive therapeutic option as it allows targeted tumor irradiation to PSMA-expressing cancer cells. The therapy not only provides a high radiation dose to the tumor as compared to normal tissue but the path length of the beta particle allows for bystander activity which also kills neighboring malignant cells that may not express the PSMA target.

While ^{177}Lu -PSMA-617 is a targeted therapy, exposure of normal tissues to radiation over the course of several treatment cycles does occur. A better understanding of the absorbed dose measures through the collection of additional dosimetry data may prove valuable in evaluating the acceptable number of treatment cycles or to increase the administered activity in a controlled setting. The patient to patient variability of these organ absorbed doses has been noted in previous dosimetry studies by [Kabaskal et al.](#) and others, which may indicate the utility of dosimetric-based dose optimization to improve outcomes. The experience from other molecular radiotherapies has shown that the common assumption of identical tolerance limits for PRT as for external beam radiation therapy often lead to an under-dosage of radiopharmaceuticals. This may be explained by different energies, the short range of the beta particles and the much lower dose rates of PRT. Dosimetric evidence for PRT regarding dose-effect curves, tolerance limits for normal tissue and the desirable absorbed dose to tumors are still lacking.

Besides the therapeutically relevant β -particles lutetium-177 also emits λ -particles with low energy (E γ : 113 keV, 208 keV), indeed with a relatively low transition probability of 6 % and 11 % respectively, but it enables imaging of the biodistribution of lutetium-177-labeled compounds in vivo by gamma camera. This allows the determination of the biokinetics for each patient specifically and to perform patient specific dosimetry during treatment. To perform calculations for post-therapeutic dosimetry gamma imaging of the patient at multiple time points during treatment is necessary to determine the kinetics of the biodistribution. From these images the time-activity-curve (TAC) for each organ and lesion of interest has to be extracted.

A full and simplified dosimetry, PK, urinary metabolism, and ECG sub-study will be conducted in a non-randomized cohort of approximately 30 patients administered ^{177}Lu -PSMA-617 (plus best supportive/best standard of care) at sites in Germany. In order to further assess renal function, estimated glomerular filtration rate (eGFR) must be calculated prior to ^{177}Lu -PSMA-617 dosing. Data from the patients in the sub-study will not be considered in the primary and secondary analysis of the main study. Patients participating in the sub-study will have been determined to be eligible for the main study and signed the informed consent specific to Germany. The treatment regimen and patient care management will be identical to that implemented in the main study. The results of this sub-study will be included in a separate reports (PK, ECG, urine HPLC and dosimetry) addendum that will accompany the main study report.

Due to local radioprotection laws and established guidelines in Germany, institutions are required to conduct additional imaging assessments following each given therapeutic dose of ^{177}Lu -PSMA-617 in order to investigate proper drug administration for patients participating

in clinical trials. In an effort to align and comply with these local guidelines, additional assessments have been added to include imaging assessments and further surveillance for evaluating renal function.

Renal Function Surveillance

In order to assess potential renal toxicity during the ^{177}Lu -PSMA-617 treatment phase of the study, the estimated glomerular filtration rate (eGFR) will be calculated with the most recent serum creatinine results collected using the Modification of Diet in Renal Disease (MDRD) equation. eGFR should be calculated prior to ^{177}Lu -PSMA-617 dosing in order to assess renal function. Please refer to [Appendix 4](#) or data collection requirements in the eCRF.

Scope of complete and simplified dosimetry assessments

During cycle 1 of the treatment, the 30 patients will undergo complete dosimetry assessment with extensive blood PK collection, urine collection, ECG collection as well as whole body planar and 3D SPECT at several time points in order to determine the absorbed radiation dose in critical organs, the metabolism and pharmacokinetics of ^{177}Lu -PSMA-617 and to evaluate possible effects of the compound on cardiac repolarization and on other ECG parameters.

From Cycle 2 through Cycle 6 of ^{177}Lu -PSMA-617 treatment, a simplified dosimetry assessment regimen will require a whole body planar, and 3D SPECT/CT localized to the abdomen to be performed at a unique time point (48 hrs post-dose).

Assessments will be performed at the defined time points in **Table 1** below. To better schedule these assessments, a tool was developed to support with the planning ([Appendix 1](#))

Table 1: Sub-Study Assessment timepoints

Timepoint	Cycle 1 only						Cycle 2 through Cycle 6		
	eGFR calculation	Whole body planar imaging	3D SPECT imaging	Blood sampling	BP & Intense ECG ^{b,d}	Urine	eGFR calculation	Whole body planar imaging	3D SPECT/CT imaging
Pre dose	X			X	X		X		
End of dose				X					
20 mins (+/- 5 mins)				X					
60 mins (+/- 5 mins)				X	X				
2 hr		X (1-2 hr) ^c	X (1-2 hr)+ CT	X (+/-30 mins)		X (start of dose to 1-2hr) cumulative collection ^a			
4 hr (+/- 30 mins)				X	X				
24 hr		X ^c (18-26 hr)	X (18-26 hr)	X (+/-2 hr)	X (+/- 2 hr)	X (+/-2 hr)			
48 hr		X (36-48 hr)	X (36-48 hr)	X (+/-2 hr)		X (+/-2 hr)		X (36-48 hr)	X (36-48 hr)
72 hr				X (+/-2 hr)		X (+/-2 hr)			
Day 6			X	X					
156-168 hr	X	X	X						

^a Whole urine collection required between end of infusion and 1 hr to 2hrs post infusion, before the first image

^b Intense ECG monitoring required on day 1 cycle 1 only. Predose (Typically the patient lies supine at least 30 minutes prior to dosing. The triplicate ECGs are collected at approximately 1.5-2 min intervals during the last 5 minutes of the 30 minutes. The next triplicate is collected 1hr post dose, typically the patient is supine for 15 minutes (45 minutes post dose) and 3 readings are taken in last 5 minutes. The next triplicate is at 4hrs and the final at 24hrs and patient is supine resting for 15 minutes – after 10 minutes take 3 readings. ECG monitoring should be performed prior to blood collection.

^c After urine collection

^d BP to be collect prior to each ECG

2. Objectives

Primary Objectives:

- Calculate whole body and organ radiation dosimetry of ¹⁷⁷Lu-PSMA-617 to further evaluate the dose to critical organs (e.g., kidney, bone marrow, salivary glands)

Secondary objectives:

- Define the whole blood pharmacokinetic profile of ¹⁷⁷Lu-PSMA-617;
- Evaluate ECGs during treatment with ¹⁷⁷Lu-PSMA-617;
- Evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617;
- Evaluate the metabolic stability of ¹⁷⁷Lu-PSMA-617

3. Electrocardiogram for dosimetry and QTc analysis

Systolic blood pressure, diastolic blood pressure and ECG data will be obtained at cycle 1. Systolic and diastolic blood pressure to be measured before each ECG recording.

ECG data will be transferred to central ECG lab eRT (eResearch Technology) using secure transfer and analyzed centrally to determine whether the drug has an effect on the QTc and if ECG is normal or abnormal, as well as the clinical relevance of abnormal ECGs.

ECGs results are assessed locally by the investigators. If the investigator observes a clinically significant changes in the ECGs, the event should be reported in the adverse event pages and ECG will need to be repeated at cycle 2 day1 and data transmitted to ERT.

ECG parameters to be collected in the eCRF will include: date/time of ECG, and ECG interpretation. The following parameters HR, RR interval, PR interval, QRS interval and QT interval will be read and analyzed by eRT. eRT will provide an overall evaluation of normal, abnormal or unable to evaluate. The evaluation items will include: rhythm, ectopy, conduction, ST segments, T waves, U waves, myocardial infarction, morphology.

Clinically significant abnormalities observed at eRT will be notified by the way of an alert to the site staff and to the study team.

Below is the sequence of events to follow for blood pressure/ECG collection when overlapping with PK collection timpoints (**Figure 1**):

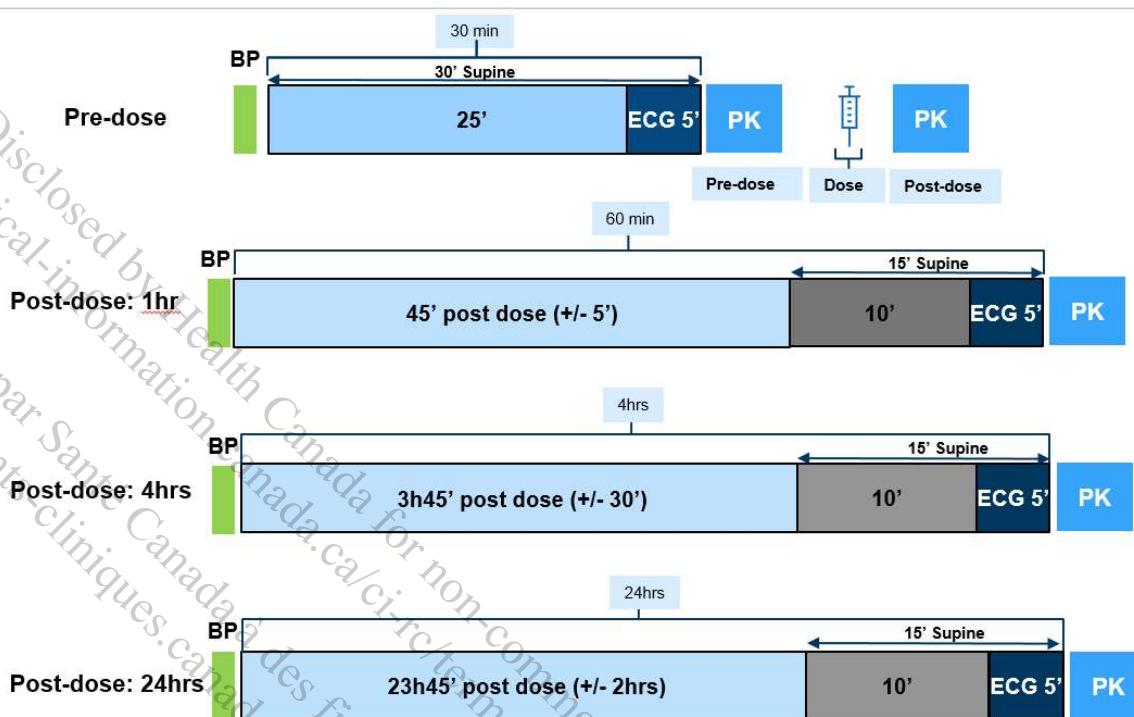


Figure 1: Blood pressure and ECG collection together with overlapping blood sampling for PK

Patients should be fasting overnight until one hour post dosing and overnight again until after the 24h ECGs. There is no restriction in water intake. If patients are dosed later in the day they should fast for three hours before dosing.

4. Image quantification

Each patient will have up to 4 whole body planar images and 4 3D SPECT acquired at cycle 1 over a period of approx 7 days (156-168 hours) from the ¹⁷⁷Lu-PSMA-617 administration for the purpose of dosimetry.

3D SPECT scans with CT imaging at 1-2 hours post infusion will also be performed in the upper abdomen to include the kidneys, liver, and spleen together.

In addition to performing complete dosimetry procedures at Cycle 1, simplified dosimetry assessment regimen will be performed from Cycle 2 through Cycle 6. Patients participating in the sub-study will be required to undergo whole body planar, and 3D SPECT/CT imaging localized to the abdomen during Cycle 2 through Cycle 6 of ¹⁷⁷Lu-PSMA-617 treatment

Necessary equipment for dosimetry data collection

The following equipment is requested in order to collect the data necessary for dosimetry evaluation:

- A gamma-camera with low and medium energy collimator
- Gamma-counter with multichannel analyzer to determine ¹⁷⁷Lu activity in blood and urine samples
- Dose calibrator (activimeter) to measure the radioactivity in the reference sources and the injected radioactivity
- CT scanner. Sites that do not have SPECT/CT equipment are requested to do a separate CT scan for attenuation correction of SPECT images

All the equipment has to be periodically checked for calibration accuracy as part of quality control according to published guidelines ([IAEA 2009; NEMA Standards Publication 2013; STUK 1/2010](#)).

The investigational sites must maintain records about the date of the last calibration / maintenance procedure applied.

General information

According to the RADAR method ([M. G. Stabin and J. A. Siegel, 2003](#)), the radiation dose to a target organ is the sum of the self-dose from that organ and the cross doses from all other source organs. In order to calculate the radiation dose to the various target organs the amount of radioactivity present in the source organs must be measured. The radioactivity uptake in each organ is determined at various time points. This uptake defines the kinetics of the radiopharmaceutical. By integrating the kinetic curve and dividing for the injected activity, the number of disintegrations from each source organ per injected activity dose is obtained, and this is the so-called time integrated activity coefficient TIAC.

Quantification of the ^{177}Lu radioactivity in liver, kidneys, and spleen will be performed by using serial SPECT images. Quantification of the ^{177}Lu radioactivity in the whole body and all other organs of interest will be performed by using serial conjugate WB planar images([Siegel JA et al., 1999](#)). Based on the outcome of the planar imaging, if deemed necessary, SPECT scans may also be performed in different regions at discretion of the investigational site.

Sites having the possibility to perform a SPECT/CT scan, are requested to provide raw tomographic data and reconstructed data with all available corrections applied (e.g. attenuation, resolution recovery) and conversion of counts to activity concentration using a calibration factor derived from a SPECT phantom. Sites are requested to provide spatially registered SPECT and fused CT scans for each time point..

Each patient image has to be acquired with the same dedicated gamma-camera for all the images of the therapy cycle. It is also requested that site use the same (or consistent) labeling scheme of acquisitions with descriptions of time point and technique for every patient.

The original images will be kept at the investigational sites, in the Institution's server (validation of the electronic system used should be provided, covering the IT functionality, back-up, and security, in particular under the perspective of data protection), with indication of the precise archiving location. Images and supporting documentation / diagnoses should be made available upon request of the Sponsor, its delegates (e.g. the appointed CRO), or Regulatory Authorities.

All acquired images per patient will be provided preferably at the same time to Certus International for organ count determination as DICOM files as directed by Certus International, with identification of the study number, site number, patient's enrollment number, and patient initials, at a minimum. Sites will be instructed on proper labeling and de-identification practices of DICOM files prior to transmittal to Certus International.

Refer to the **ShareFile guide** to upload DICOM files into the platform for further details.

An email will alert Certus International project team each time a new set of images has been uploaded. Certus International will centrally analyse the images and provide screenshots of the planar images (anterior & posterior) showing the ROIs to RDS (jpg format) and count data to measure organs activities.

Investigational sites must also provide to Certus International patient demographics and parameters used for subject imaging and attenuation correction for central analysis. IM forms to be completed for each patient and submitted to Certus International email address CertusICL@certusintl.com (see [Appendix 2](#) or the 02 and 03 IM form templates).

Data acquisition

Calibration Factor

A camera-specific SPECT calibration factor for ^{177}Lu and the imaging parameters described for patient imaging will be derived at each site. This will be used to convert the image counts from the patient scans to activity. The calibration factor will be determined through measurements of a SPECT phantom containing a known quantity of ^{177}Lu .

If a site will study more than one patient, only one SPECT calibration is required - if no special intervention on the gamma-camera occurs due to any break/anomaly.

Imaging Standard

An image standard, containing approximately 100 - 370 Megabecquerels (MBq) of ^{177}Lu will be placed in the field of view for each time point to correct the images for radioactive decay, changes in camera speed, and sensitivity.

^{177}Lu Standard Reference Aliquot Preparation

- The imaging standard is prepared by adding approximately 100 - 370 MBq of ^{177}Lu to the contents of a 100 mL saline bag. This would correspond to a specific activity of 1 MBq/ml to 3,7 MBq/ml for the 100 ml standard geometry.
- Measure and record the actual activity of ^{177}Lu used in the standard preparation in a dose calibrator before and after injection into the 100 mL saline bag.
- The standard will be placed next to the subject's right foot at each imaging session (see [Figure 2](#)).

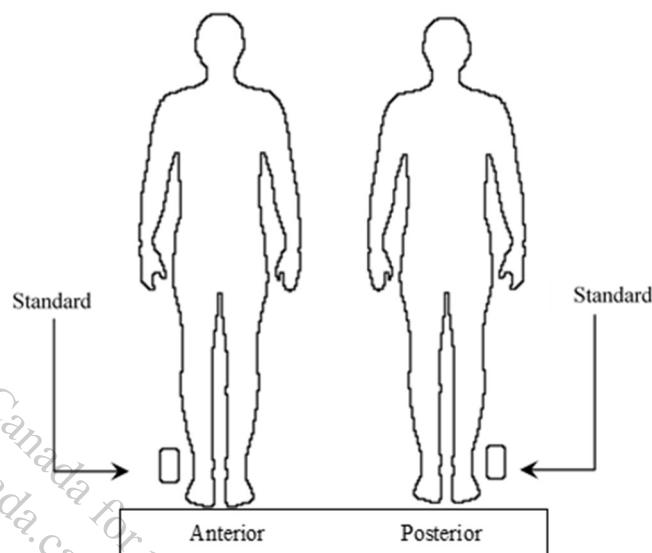


Figure 2: Positioning of Reference Standard

Acquisition of WB ^{177}Lu images

Patient measurements are performed with a medium energy collimator and the 208 keV peak (15% width) is used, with additional energy windows, including 170 (15% width) and 240 (10% width) keV for scatter correction, to be acquired as separate images, for a total of three anterior and posterior image pairs (total of six images/views in the same DICOM image series) as provided in **Table 2**. An example in order of Photopeak – Lower Energy – Higher Energy is provided in **Figure 3** below.

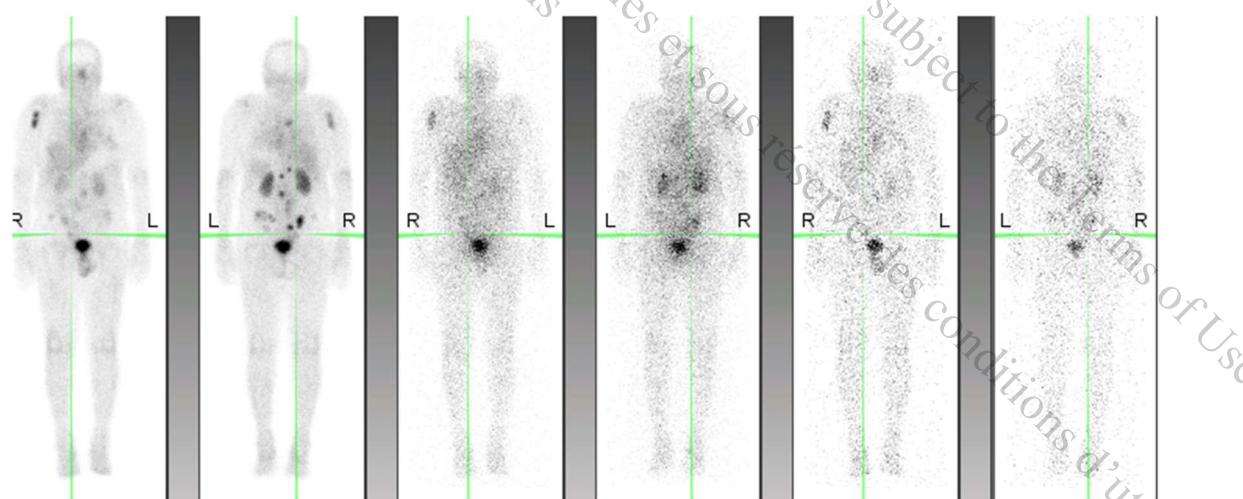


Figure 3: Example whole body scan using upper and lower energy peaks

The posterior and anterior views can be acquired as planar images with a fixed scan speed (10 cm/min).

Whole body planar images (head to feet) as well as 3D SPECT scans at the level of the abdomen (including liver, spleen and kidneys) have to be acquired at the following times after the end of the ¹⁷⁷Lu-PSMA-617 infusion:

• **Cycle 1:**

- 1-2 hour (post dose and after cumulative urine collection, **day 1**), please collect urine from injection time (if voided) until first WB image, AND place container with all excreted urine in field of view during first image. **An additional CT scan is also required at this time point only (after Whole body planar images and 3D SPECT)**
 - 24 hour (or within 18-26 hours post-dose; after urine collection)
 - 48 hour (or within 36-48 hours post-dose)
 - 168 hour (or within 156-168 hours post-dose).

• **Cycle 2 through Cycle 6: 48 hour (or within 36-48 hours post-dose)**

The time point ranges indicated above in parenthesis are to be considered if the specific time-point is not feasible.

The patient must void the urinary bladder before the acquisition of the whole body images, especially within the 24 h post injection.

Site is required to use the tool in [Appendix 1](#) to help planning the subsequent scans acquisition.

Table 2 – Image Acquisition Parameters

2A - Acquisition of the emission images	
<i>Acquisition parameters</i>	<i>Suggested</i>
Peak energy	15% at 208 keV
Supplemental energy windows for scatter correction (to be set as separate image from the 208 peak image)	15% at 170 keV + (¹⁷⁷ Lu) 10% at 240 keV (¹⁷⁷ Lu)
collimator	MEGP
WB speed (continuous)	10 cm/min
WB matrix	256 x 1024
WB body contouring	if available (emission only)
SPECT matrix	128x128
SPECT setting	120 projections (60 per head), 20 s /projection Zoom 1.0
SPECT body contouring	if available
SPECT attenuation correction	CT – 130 kV, 50 mAs (dose modulation) 3 mm slice thickness
SPECT reconstruction	iterative reconstruction specifying the number of iterations and subsets (e.g. 8 iter. and 6 sub. recommended) with all available corrections applied Gaussian post-reconstruction filter of 0.9 cm at FWHM
2B - Image Collection	
Cycle 1	
SPECT Calibration Scan (initial submission only)	Raw / AC CT / Reconstructed + Corrected Axial Slices
WB 1-2 h after end of infusion	Anterior / Posterior
WB 18-26 h after end of infusion	Anterior / Posterior
WB 36-48 h after end of infusion	Anterior / Posterior
WB 156-168 h after end of infusion	Anterior / Posterior
SPECT 1-2 h after end of infusion + CT	Raw / Scout / AC CT / Reconstructed + Corrected Axial Slices
SPECT 18-26 h	Raw / AC CT / Reconstructed + Corrected Axial Slices
SPECT 36-48 h	Raw / AC CT / Reconstructed + Corrected Axial Slices
SPECT 156-168 h	Raw / AC CT / Reconstructed + Corrected Axial Slices
Cycle 2 through Cycle 6	
WB 36-48 h after end of infusion	Anterior / Posterior
SPECT 36-48 h	Raw / AC CT / Reconstructed + Corrected Axial Slices

Image processing

ROI construction and generation of ROI statistics will be performed centrally at Certus International. Image quantification and dosimetry data analysis will be performed by RDS.

To quantify the absolute amount of ¹⁷⁷Lu radioactivity in the liver, kidneys, and spleen, the ROI statistics obtained from the SPECT scans, along with SPECT calibration factor will be utilized. For whole body and all other organs, the activity will be quantified using a modified method based on relative calibration ([Cremonesi M et al., 2007](#)). The conjugate-view technique will be applied to anterior and posterior images and physical decay corrections. Counts in whole-body images will be normalized based on first image counts, and accounting for the injected activity eliminated in the urine before the first image acquisition.

The digital images sent to Certus International will be loaded by Certus International in a secure dedicated access-limited folder protected by password. Certus will perform quality review

Protocol: PSMA-617-01

PSMA-617 Sub-study manual

upon receiving the images and raise queries using a Data Resolution Form ([Appendix 3](#)) to the sites.

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5. Biological samples for dosimetry and PK analysis

At cycle 1, **blood and urine samples** will be taken from all 30 patients participating in the trial in Germany to provide data for bone marrow radiation dose calculations and for PK evaluations. The results of the activity concentration in the blood and urine samples (only for the interval 0-2hrs) will be provided to RDS via data extract from the eCRF on an ongoing basis for PK and dosimetry calculations.

The radioactivity of blood and urine samples collected will be counted in the well- or gamma counter and compared to the count rate from a representative percentage of the injected activity inside the same counter.

Blood analysis

Radioactivity in blood will be measured at the investigational sites with a properly calibrated gamma counting system (**not decay corrected**) to calculate the results of the activity concentration in the blood.

Caution is recommended to avoid counting in the dead-time window of the detector.

General information and data collection of blood samples

Primary and back-up whole blood samples (**1 mL** in heparinized tubes) will be collected from each patients receiving ¹⁷⁷Lu-PSMA-617 infusion at the following time-points (with a tolerance of approximately $\pm 10\%$) following site procedures on how to handle blood withdrawal:

- immediately before the infusion
- just before the end of infusion
- after the end of infusion at:
 - 20 mins (+/- 5 mins)
 - 60 mins (+/- 5 mins)
 - 2 hours (+/- 30 mins)
 - 4 hours (+/- 30 mins)
 - 24 hours (+/- 2 hours)
 - 48 hours (+/- 2 hours)
 - 72 hours (+/- 2 hours)
 - Day 6 post end of infusion

Samples will be counted in a gamma-counter detector (e.g. NaI spectrometer) properly calibrated with a reference source of ¹⁷⁷Lu of known activity counted in the same geometry as that of the biological samples (e.g. **1 ml** in a vial). The count rate of the reference source will be **measured 5 times**. The calibration factor is the ratio between the activity of the reference source (kBq) and the mean count rate (counts per second – cps, or counts per minute cpm).

Data of the reference source, the date and time as well as the Calibration Factor should be recorded in the eCRF as per the checklist in [Appendix 4](#).

N.B.: *The calibration for blood and urine can be the same if the same detector and the same kind of vials/ same geometry are used.*

If a site will perform assessments for more than one patient, only one calibration is required - if no special intervention on the gamma-counter occurs due to any break/anomaly.

The information of blood collection and measurement must be reported in the eCRF ([Appendix 4](#)) and will be provided to Certus International, RDS and CRL for each patient.

A **second aliquot** (1 mL in heparized tube) will be collected as a backup sample. The sites can destroy the primary and back-up blood samples once CRL review PK data and advise if the data looks consistent with expectations. Before any sample destruction, sites are requested to wait for communication/confirmation by the Sponsor/Vendor/CRA.

Whole blood Pharmacokinetic Calculations

Blood radioactivity data will be converted into mass concentration data (e.g. ng/mL), considering the specific radioactivity of the product and its radioactive decay. Pharmacokinetic parameters will be estimated using Phoenix pharmacokinetic software (**Table 3**). A non-compartmental approach consistent with the intravenous infusion route of administration will be used for parameter estimation. All parameters will be generated from ^{177}Lu -PSMA-617 radioactivity in whole blood as data permits.

Table 3: Parameters to be Estimated from Whole Blood Data

Parameter	Description of Parameter
Tmax	The time after dosing at which the maximum observed concentration was observed
Cmax	The maximum observed concentration measured after dosing.
AUC(0-t)	The area under the concentration versus time curve from the start of dose administration to the last observed quantifiable concentration using the linear or linear/log trapezoidal method.
AUC(0-t)/D	The AUC(0-t) divided by the dose administered.

When data permits, the slope of the terminal elimination phase of each concentration versus time curve will be determined by log-linear regression, and the following additional parameters will also be estimated (**Table 4**):

Table 4: Additional Parameters to be Estimated from Whole Blood Data

Parameter	Description of Parameter
T _{1/2}	The apparent terminal elimination half-life.
AUC _{inf}	The estimate of the area under the whole blood concentration versus time curve from the time of dosing to infinity.
CL	The apparent clearance rate of parent test item from the analyzed test matrix.
V _d	The apparent volume of distribution of the parent test item in the test system.

Descriptive statistics (means and standard deviations) and ratios for appropriate grouping and sorting variables will be generated using Phoenix. PK tables and graphs will be generated by Phoenix, Microsoft Excel, and/or Graphpad Prism. Additional parameters generated by Phoenix may be included at the discretion of the Pharmacokineticist.

Urine analysis

Urine analysis will be collected at the investigational sites from all the 30 patients for radioactivity measurement (locally assessed) and for HPLC analysis at CRL. The **results of the activity concentration** in urine samples (**only for the interval 0-2hrs**) will be provided to RDS via data extract from the eCRF on an ongoing basis for dosimetry calculations.

The majority of the infused ^{177}Lu -PSMA-617 is excreted via the kidneys into the urine.

ABX advanced biochemical compounds will provide a copy of the Certificate of Analysis to CRL for each production lot of ^{177}Lu -PSMA-617 administered for each patient. The Specific Activity of Test Substance (MBq/mg), Radioactive Concentration of the Dosing Formulation (MBq/mL) and Net Administered Activity (MBq) will be calculated with the data collected on the ^{177}Lu -PSMA-617 Administration eCRF ([Appendix4](#)).

General information and data collection time points

Complete urine eliminated in the first 0-2 hours after infusion and before the first image will be collected with the last voiding immediately before the first body scan (cumulative collection).

Urine collection for less than 2 hours post-dose is acceptable, if no other urine is excreted from that point to the moment of the first image. It is important that all urine excreted **after ^{177}Lu -PSMA-617 infusion** and before the first scan (interval 1-2 hrs after infusion), is collected and the volume of aliquot, and the total volume of all urine voided is recorded.

Additional urine samples (10 mL) will be taken at the time points listed below:

- 24 hours (+/-2 hours)
- 48 hours (+/-2 hours)
- 72 hours (+/-2 hours)

No urine collections for central analysis are required at subsequent cycles.

Urine collection for radioactivity

The total radioactivity excreted **before the first image** acquisition will be determined at the interval between 0 and 2hrs post-dose, only at day 1 of cycle 1 and sent to RDS . The total cumulative volume of urine eliminated in that interval (from the administration to the first scan) will be measured and reported in the eCRF ([Appendix 4](#)). A urine sample (**1 ml**) will be taken from the total volume eliminated in that period for **local radioactivity measurement** and reported in the eCRF.

At the remaining timepoints (24hrs, 48hrs and 72hrs), the total radioactivity (10ml sample for each timepoint) will also be measured locally at site.

For shipment purpose the radioactivity measured in urine samples (each sample 10 ml) for the 4 timepoints (0-2 hrs, 24 hrs, 48 hrs and 72 hrs) will need to be reported in the HPLC transmittal form ([Appendix 4](#)).

Caution is recommended to avoid counting in the dead-time window of the detector.

Equipment

Before the start of sample collection, investigational sites must ensure the following are available:

- 50-mL Falcon tubes or similar screw-topped plastic tubes, pipettes, tube racks
- Scale
- Graduated cylinder
- Frozen (-20°C or -70°C) storage

The following materials will be provided:

- Vial labels provided by the courier
- Absorbent sheets, plastic baggies provided by the Courier
- Shipping boxes and box labels provided by the Courier
- Shipping forms and airway bill provided by the Courier
- Sub-study manual provided by the Sponsor
- Investigator's File provided by the Sponsor

Sample handling

Urine samples (10 ml) collected at 0-2h, 24 h, 48 h and 72 h will be sent to CRL for HPLC analysis purposes.

A (10 mL) urine aliquot will be withdrawn from each urine collection sample, at the end of the collection timepoint, placed into a 50-mL Falcon tube or similar screw-capped centrifuge tube, as shown in [Appendix 5](#), and shipped frozen (approximately -70°C) to CRL to be analyzed by HPLC (High-performance liquid chromatography) according to a validated procedure, in order to determine the elimination of ¹⁷⁷Lu-PSMA-617 and possible metabolites, if any, over time.

A **second aliquot** (10 mL or the remainder of the urine, whichever is less) will be collected as a backup sample. The sites can destroy the back-up samples after CRL receives the primary samples and perform the analysis. Before any sample destruction, sites are requested to wait for communication/confirmation by the Sponsor/Vendor/CRA. Primary and backup aliquot (10 mL each) of urine will be frozen, and shipped in separate shipments to CRL for HPLC analysis. Please maintain a temperature log for the sample storage period until shipment.

The vials will be labeled with the following information: patient number, date/time of start, and progressive number of sampling (#1 for the period 0-2 hours post-infusion, #2 for the period 24 hours post-infusion, #3 for the period 48 hours post-infusion, #4 for the period 72 hours post-infusion), see [Appendix 5](#). Labels will be provided to the sites by Marken.

The Investigator or investigator representative is requested to complete the label information, using a water-proof pen, before applying the label to the vial. Vials will be wrapped individually by the investigator or investigator representative in absorbent sheets, and placed individually in sealed plastic bags. Samples will be placed on dry ice in a Styrofoam box inside a cardboard box. The primary 10-mL aliquots will be shipped to CRL by a selected courier (Marken) on dry ice after the 72 hour collection. CRL will receive the samples Monday through Thursday 8 am to 3 pm. The backup samples will be shipped in a similar manner on Sponsor request.

A fully completed HPLC Transmittal Form ([Appendix 6](#)) will be placed in the package and a copy will be retained locally in the Investigator's file. The sample container should be labeled with code **UN3373 Category B, Biological Substances** and code **UN2910** for "radioactive material – excepted package, limited quantity of material".

Shipping

The courier for this sub-study is:

Marken Frankfurt
Monchhofallee 13
65451 Kelsterbach
Germany
Tel: +49 6142 301 820
Fax: +49 6142 301 8210
Email: marken.germany@marken.com

Instructions for ordering sample pick-up:

Contact the courier at the above telephone number or email address (Monday to Wednesday) at least one day before the scheduled pickup date and time. Please provide the Courier with the site address information, along with the number and size of vials so the Courier may provide the packaging and dry ice.

At the same time, a completed **booking form** and **customs invoice** ([Appendix 7](#)) should be sent to the courier by fax or email to confirm the request. The Courier will send back an Airway Bill (HAWB)that should be provided to the Courier at the day and time of the pick-up.

Alert to CRL-Ashland:

An email should also be sent by site to [Name] ([\[Contact\]](#)) and [Name] ([\[Contact\]](#)) to inform of imminent sample delivery and the date of pickup..

Instructions for sample delivery to the courier:

Documents (HPLC Transmittal form according to the template; and transport documents provided by the Courier) will be stapled together and included in the external pouch of the shipping box.

- A responsible person must be available at agreed pick-up time
- Use one pre-printed airway bill per day and collection
- Fill out the airway bill and shipment documentation before delivery
- Please prepare the package as described above, on the day of , but before, the courier arrival.

The shipping will be done at constant temperature (approximately -70°C on dry ice).

It is recommended that all primary urine samples be shipped by courier on the same day of the last sample collection, in order that all samples be delivered to the central laboratory within the next 2-5 days and processed immediately thereafter. Otherwise samples must be kept frozen (approximately -20°C or -70°C) at the site until the date of the pick-up (agreed with the Courier), if the immediate time for pick-up would determine the delivery to the central laboratory on Friday afternoon or during the weekend (no receipt times).

The sample storage temperature should be documented and checked on a daily basis. Temperature excursions should be reported in a Temperature Excursions Log ([Appendix 9](#)); excursions above -5°C should be reported in the HPLC Transmittal Form.

Backup samples will be stored at sites and shipped under the same conditions upon Sponsor request in the event something happens to the primary samples.

Boxes containing samples will be checked for dry ice by the recipient upon arrival. The temperature documentation will be archived at CRL. The corresponding box will be checked in the HPLC Transmittal form, otherwise a note will be added to comment about the out-of-range temperature.

Urine Receipt and Processing

Samples will be processed at CRL. The receipt of urine samples will be confirmed in the HPLC Transmittal Form with the date of receipt and signature of the Recipient, and all the shipping documentation will be archived at CRL. Upon receipt, the tubes received will be inspected by CRL personnel for correspondence with the HPLC Transmittal Form and integrity. In case any vial is missing or has broken, a note will be made in the HPLC Transmittal Form.

Samples will be processed as soon as possible, ideally within 24 hours of receipt. Samples will be stored frozen (-70°C) until processing and analysis.

Urine Radioprofiling

The scope of this analysis is to investigate whether ¹⁷⁷Lu-PSMA-617 is eliminated in urine as intact compound, by assessing if radioactivity in urine is represented by intact ¹⁷⁷Lu-PSMA-617 only, or also by potential metabolites ([Appendix 8](#)).

Analysis of radioactive species in urine samples will be performed using an Agilent 1200 series HPLC system (Agilent Technologies, Inc., Santa Clara, CA) equipped with an Agilent Quaternary Pump (G1311A), Agilent Degasser (G1322A), Agilent Variable Wavelength Detector (G1314B) set at 220 nm, and an Agilent Autosampler (G1329A) used in conjunction with Agilent Thermostat (G1330B). Radioactivity in the effluent will be monitored using an IN/US β-Ram Model 4B Radio-HPLC detector (IN/US Systems, Inc., Tampa, FL). Prior to entering the radioactive flow detector, the column effluent will be mixed with FlowLogic™ U scintillation cocktail (IN/US Systems, Inc.) pumped at a rate of 2 mL/minute. The radio-HPLC conditions are reported in **Table 5**, subject to modification during method development and validation:

Table 5: radio-HPLC conditions for urine radioprofiling

Flow rate:	1.0 mL/min		
Column type:	Aeris Peptide 3.6 XB-C18, 150 x 4.6 mm		
Injection volume:	10 µL		
Mobile Phase:	A: 0.1% Formic acid in Water; B: 0.1% Formic acid in Acetonitrile		
Program:	Time:	<u>A (%)</u>	<u>B (%)</u>
	0	90%	10%
	2	90%	10%
	27	65%	35%
	29	65%	35%
	29.1	10%	90%
	32	10%	90%
	32.1	90%	10%
	35	90%	10%
Column temp:	Ambient		
Detector time:	35 min		
Run time:	35 min		
UV Wavelength:	220 nm		

All the equipment will be periodically checked for calibration accuracy as part of quality control according to CRL SOPs. A reference solution of ^{177}Lu -PSMA-617 will be shipped by Endocyte to CRL.

Radioprofiling Data Analysis

Radiochromatograms will be integrated by manually selecting peaks substantially above baseline using the Laura Lite™ software package. For the parent compound and each metabolite, the following data will be determined at CRL:

- The relative amount of radioactivity in each peak will be reported as a percent of the total radioactivity in the selected peaks.
- Retention time (in minutes).
- Quantitative determination of each compound in MBq/mL and µg/mL ^{177}Lu -PSMA-617 equivalents, to be calculated in relation to the radioactivity detected.

The results of the urine determinations will be recorded in a separate file (Urine HPLC Results, [Appendix 8](#)) by patient and sampling period.

A separate protocol has been drafted by CRL for the validation of the HPLC method to be used for the analysis of ^{177}Lu -PSMA-617.

Based on preclinical data and activity excretion data in patients treated with similar urea-based compounds, it is expected that about 50% of the dose is eliminated within 4-12 hours and a cumulative 70-80% of the injected dose is eliminated within 12-24 hours. Starting from these data, the lowest volumetric activity expected is 0.25 MBq/mL and the highest volumetric activity should be close to 14 MBq/mL. Samples are collected more than 24 hours post-dosing,

samples are generally analyzed several half-lives after collection, and accurate quantitation of minor metabolites was desirable. Thus, the method will be validated over a range designed to cover the expected radioconcentration of parent and metabolites, if possible.

6. Data analysis and radiation dosimetry calculations

The analysis of data and radiation dosimetry calculations will be performed by Certus International and the Dosimetry Expert (RDS). Dosimetry Determination for Cycle 1:

Activity as a function of time in whole body and all other organs of interest (except red marrow), will be determined based on ROI/VOI image counts statistics. For the SPECT images, regions of interest (ROI) for kidneys, liver, spleen, will be drawn on every image slice containing these organs by Certus International. Counts from all slices will be summed to determine the total counts in the organ volume of interest (VOI). The SPECT calibration factor will then be applied to these counts to determine the activity in kidneys, liver, and spleen.

For the planar images, regions of interest (ROI) will be drawn around the whole body and other organs of interest by Certus International. The right salivary and parotid glands will be combined in a single ROI, as will the contralateral salivary and parotids. Image counts will be scatter and decay corrected. Activity in the whole body and organs will be determined by normalizing whole body/organ counts to those in the whole body at the first imaging time, and utilization of the known injected activity, after accounting for the activity lost in the urine prior to the first image. The result of these calculations will be activity as a function of time (time-activity curves) in the whole body and all organs of interest.

Activity in the red marrow will be estimated based on blood activity according to the blood-based method. ([Forrer F et al., 2009; Ferrer L et al., 2010; Hermann et al. 2015](#)). Patient specific blood masses will be estimated based on Nadler's formula (Nadler 1962). Patient specific red marrow mass will be determined using the patient specific blood mass and the ratio of the standard values of red marrow to blood mass. The time activity in the red marrow is then determined by application of the equation below.

$$TAC_{RM} = TAC_{blood} \cdot m_{RM} / m_{blood}$$

Time activity in the remainder tissues will be determined by subtraction of all other quantified organs/tissues from the whole body activity.

$$TAC_{RB} = TAC_{TB} - \sum_i TAC_i \quad \text{for each source organ } i.$$

Once the activities in the whole body and organs/tissues have been determined, the time integrated activity coefficients (TIACs) —mathematically equivalent to the number of decays per unit injected activity ([Stabin MG et al., 2005](#))— will be calculated from multi-exponential fits to the time-activity curves for the main source organs and remainder of body. By way of example, a bi-exponential clearance pattern can be used to simulate the source organ time-activity data an organ as follows:

$$A_{organ} = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t}$$

Parameter values A_1 , A_2 , λ_1 , and λ_2 , are determined via non-linear regression to complete the mathematical model.

Integration of these mathematical models results in the total number of radioactive decays (TIACs or normalized number of disintegrations or residence times) that occur in each of the organs, red marrow, and remainder tissues as follows:

$$\tilde{A}_{organ} = \frac{A_1}{\lambda_1 + \lambda_p} + \frac{A_2}{\lambda_2 + \lambda_p}, \text{ with } \lambda_p \text{ being the physical decay constant of } {}^{177}\text{Lu.}$$

The quotient of \tilde{A} and the injected activity (IA) will be calculated to yield the TIAC = \tilde{A}/IA .

To determine the TIACs in GI organs, the human alimentary model as implemented in OLINDA/EXM shall be utilized, assuming that the maximum activity seen in a general abdominal ROI (excluding visceral organs) enters the small intestine via the hepato-biliary pathway.

To determine the TIAC in the urinary bladder, the voiding bladder model as implemented in OLINDA/EXM shall be utilized, assuming that the bladder voiding interval is 3.5 hours. For the determination of the required urinary excretion parameters, a mono-exponential fit to the cumulative urinary excretion data will be performed to determine the fractions and elimination rate:

$$A_{Urine}(t) = A_0 - A_1 e^{-\lambda_{1t}}$$

Absorbed doses to target organs will be calculated by entering the TIAC values for all the source organs in the OLINDA/EXM software and adjusting the doses reported by the software as determined from CT for kidneys liver and spleen, and as described above for red marrow.

Dosimetry Determination for Cycles 2-6:

Dosimetry analysis in all therapy cycles after the first, will be based on a modified hybrid methodology (Dewaraja et al. 2012, Ljungberg et al. 2016, Squouros et al, 2003, and Koral et al. 2003), where the uptake and retention half-lives will be based on the determination made in the first therapy cycle, with the activity magnitude of the organ time activity curves scaled based on activity quantifications of a single conjugate whole body planar, and a single SPECT/CT image.

SPECT/CT and planar images will be collected at approximately 48 hours post injection. The planar and SPECT/CT images will be collected under exactly the same protocol as the original planar and SPECT/CT images were collected during the first cycle. For dosimetry purposes, urine collection and assay will not be required, blood collection and assay will not be required. The use of an imaging standard in the planar image will not be required, **but is strongly recommended**. Quantification of the organ activities in the liver, kidneys and spleen at the single imaging time (48 h) using the SPECT image data will be performed in exactly the same manner as done during therapy cycle one using the phantom derived calibration factor.

Additionally, whole body slice regions, which will encompass the entire patient in every SPECT image slice collected will be constructed. The total counts in the SPECT image will be determined by summation of the counts in each slice. Activity in the entire section of the body that is in the field of view of the SPECT image will be quantified in the same fashion as was performed for kidneys, spleen and liver in therapy cycle one.

A partial whole-body region of interest encompassing the same body area will be constructed on the whole body planar conjugate images. The previously determined activity in this body region in the SPECT image will be utilized to determine a calibration factor for the planar image. using the following equation:

$$C_p = \frac{I_p}{\frac{I_s}{C_s D} \left(\frac{1}{e^{-\lambda_p t}} \right) \left(\frac{1}{A_0} \right)}$$

Where:

C_p = Planar image calibration factor (counts/kBq)

I_p = Scatter corrected geometric mean counts in the planar image “SPECT FOV” ROI

I_s = Counts in the entire SPECT image FOV

C_s = SPECT calibration Factor (cps/kBq)

D = Image duration factor (s)

λ_p = Physical decay constant (h^{-1})

t = Time between planar image and SPECT image acquisitions (h)

A_0 = Injected activity (kBq)

Quantification of activity at 48 hours in the whole body planar images, for organs such as lungs and salivary glands, that are not in the field of view in the SPECT/CT images will then be determined using the planar image organ ROI counts obtained from the planar images and the calibration factor according to the following equation:

$$A_{org} = \frac{I_{org}}{C_p}$$

Where:

A_{org} = Activity in an organ (kBq)

I_{org} = Scatter corrected geometric mean counts in the planar image organ ROI

C_p = Planar image calibration factor (counts/kBq)

The whole body and organ activities determined using the above methodology, will be used with the bio-kinetic organ data determined during the cycle one treatment to create time-activity curves for the whole body and all of the standard organs. using the following equation.

$$A_{orgCX}(t_i) = A_{orgC1}(t_i) \frac{A_{orgCX}(48h)}{A_{orgC1}(48h)}$$

Where:

$A_{orgCX}(t_i)$ = Activity (kBq) in an organ in cycle X at timepoint i

$A_{orgC1}(t_i)$ = Activity (kBq) in an organ in cycle 1 at timepoint i

$A_{orgCX}(48h)$ = Activity (kBq) in an organ in cycle X at 48 hours

$A_{orgC1}(48h)$ = Activity (kBq) in an organ in cycle 1 at 48 hours

Blood pharmacokinetics, GI uptake and excretion, and urinary excretion will be assumed to behave in the same fashion as quantified in the first treatment cycle. Remainder activity will be determined via subtraction of all quantified organ and tissue activities from the whole body activity.

Once the activities in the whole body and organs/tissues have been determined, the time integrated activity coefficients (TIACs)—mathematically equivalent to the number of decays per unit injected activity ([Stabin MG et al., 2005](#))—will be calculated from multi-exponential fits to the time–activity curves will be modeled using sums of exponentials utilizing the same methodology for the main source organs and remainder of body. By way of example, a bi-exponential clearance pattern can be used to simulate the source organ time-activity data an organ as utilized during cycle one. follows:

$$A_{organ} = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t}$$

Parameter values A_1 , A_2 , λ_1 , and λ_2 , are determined via non-linear regression to complete the mathematical model.

Integration of these mathematical models results in the total number of radioactive decays (TIACs or normalized number of disintegrations or residence times) that occur in each of the organs, red marrow, and remainder tissues as follows:

$$\tilde{A}_{organ} = \frac{A_1}{\lambda_1 + \lambda_p} + \frac{A_2}{\lambda_2 + \lambda_p}, \text{ with } \lambda_p \text{ being the physical decay constant of } {}^{177}\text{Lu.}$$

The quotient of \tilde{A} and the injected activity (IA) will be calculated to yield the TIAC = \tilde{A}/IA .

Regions of interest will be constructed on the CT image to determine organ volumes for kidneys, liver, and spleen. Dosimetry estimates will then be created using OLINDA 2.2 with organ mass modifications in the same manner as was performed in cycle one.

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Protocol: PSMA-617-01

PSMA-617 Sub-study manual

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8. Appendices

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
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Appendix 1

A small icon representing Microsoft Excel, showing a grid of cells.

PSMA-617-01 Sub
Study Time Point Calc

PSMA-617-01 Sub
Study Time Point Calc

Appendix 2

Image Transmittal Forms**FORM IM 02**
Data Transmittal Form
Protocol PSMA-617-01

For each Form IM 02 Data Transmittal Form, please complete a corresponding Form IM 03 Data Transmittal Acquisition Parameters.

Site Name		
Subject Enrollment Number	_____ - _____	
Weight (kg) _____	Height (cm) _____	Injected Activity (GBq) _____
Date and time of administration: _____		_____ : _____
Treatment Cycle (check one): <input type="checkbox"/> C1 <input type="checkbox"/> C2 <input type="checkbox"/> C3 <input type="checkbox"/> C4 <input type="checkbox"/> C5 <input type="checkbox"/> C6		
Image Data Transmitted to Imaging Core Laboratory (ICL): check all in present in current image data transmission		
<input type="checkbox"/> ANT/ POST Whole Body Scan 1-2 h <input type="checkbox"/> ANT/POST Whole Body Scan 18-26 h		<input type="checkbox"/> ANT/POST Whole Body Scan 36-48 h <input type="checkbox"/> ANT/POST Whole Body Scan 156-168 h
<input type="checkbox"/> SPECT/CT 1-2 h; # bed positions _____ <input type="checkbox"/> SPECT/CT 18-26 h; # bed positions _____		<input type="checkbox"/> SPECT/CT 36-48 h; # bed positions _____ <input type="checkbox"/> SPECT/CT 156-168 h; # bed positions _____
<input type="checkbox"/> CT Scout <input type="checkbox"/> CT Axial ; No. of reconstructions _____		<input type="checkbox"/> Calibration Scans - No. of scans: _____ <input type="checkbox"/> Other _____
Date Uploaded via ShareFile:		Date (DD/MMM/YY)
Comments:		
Image Data Uploaded By: _____		Date (DD/MMM/YY)
Signature:		

FORM IM 03
Data Transmittal Acquisition Parameters
Protocol PSMA-617-01

Site Name				
Subject Enrollment Number		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/>		
Confirm applied settings used to acquire ^{177}Lu -PSMA-617 images by checking box next to each parameter below:				
Acquisition Parameters:	Whole Body	SPECT/CT	Other	
Primary Energy Peak	<input type="checkbox"/> 15% at 208 keV	<input type="checkbox"/> 15% at 208 keV		
Supplemental energy windows for scatter correction	<input type="checkbox"/> 15% at 170 keV <input type="checkbox"/> 10% at 240 keV	<input type="checkbox"/> 15% at 170 keV <input type="checkbox"/> 10% at 240 keV		
Collimator	<input type="checkbox"/> MEGP	<input type="checkbox"/> MEGP		
Velocity	<input type="checkbox"/> 10 cm/min	<input type="checkbox"/> 120 total frames (60 per head) <input type="checkbox"/> 20 s /frame		
Matrix	<input type="checkbox"/> 256 x 1024	<input type="checkbox"/> 128 x 128		
Contouring	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		
Zoom	<input type="checkbox"/> 1.0	<input type="checkbox"/> 1.0		
Imaging Standard	Activity <input type="text"/> <input type="text"/> <input type="text"/> MBq			
Activity Date / Time	<input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>			
Comments:				
I confirm that: <input type="checkbox"/> Images have been anonymized and labeled per instructions.				
Signature:		Date (DD/MMM/YY)		
Print Name:				

Appendix 3

Certus Data Resolution Form (example)
Data Resolution Form (DRF)
Protocol PSMA-617-01

Please respond to the issue(s) below. Have the form signed and dated and email back to CertusICL@certusintl.com. A copy of this form must be maintained as part of the subject's source documents.

Site Name	[REDACTED]
Subject Enrollment Number	[REDACTED]
DRF Number	01
DRF Date	12/MAY/2020
Data Clarification: <ol style="list-style-type: none"> 1. Please process and submit attenuation and scatter corrected SPECT reconstructions using the co-registered CT acquired at the first time point. One corrected time point was received; however, we are looking for corrected data for each subsequent SPECT time point (AC + SC) 2. When possible, multiple SPECT bed positions should be combined into one reconstruction. 	
Site Response: 	
The information provided above is true and correct to my knowledge.	
Signature	Date [REDACTED]/[REDACTED]/[REDACTED]
Print Name	

For ICL Use Only:DRF resolved: Yes No

Comments/Resolution:

Signature

Date [REDACTED]/[REDACTED]/[REDACTED]

Print Name

Appendix 4

eCRF completion checklist for dosimetry

Check	eCRF page to be completed	Time points <i>(All Time points are post dose until otherwise specified)</i>	All time points collected Yes/No	If No please enter reason
Imaging collection				
Cycle 1				
1a	Whole Body Planar Imaging	1 - 2 hrs 18 – 26 hrs 36 – 48 hrs 156 – 168 hrs		
2a	3D SEPCT/CT Imaging	1 - 2 hrs (SPECT) 1 - 2 hrs CT 18 – 26 hrs (SPECT) 36 – 48 hrs (SPECT) 156 – 168 hrs (SPECT)		
Cycle 2 through Cycle 6				
1b	Whole Body Planar Imaging	36 – 48 hrs		
2b	3D SEPCT/CT Imaging	36 – 48 hrs		
Blood Pressure and Triplicate ECG collection at Cycle 1 only				
3	Blood pressure (prior to ECG) Triplicate ECG	Pre-dose 1 hr 4 hrs 24 hrs		
4	Blood pressure & ECG collection at Cycle 2 Day 1 (if needed)	Select from drop down list		
Blood collection at Cycle 1 only				
5	PK blood sampling • Date and Time	Immediately before the infusion Just before the end of infusion 20 mins (+/- 5 mins) 60 mins (+/- 5 mins) 2 hrs (+/- 30 mins) 4 hrs (+/- 30 mins)		

		24 hrs (+/- 2 hrs)		
		48 hrs (+/- 2 hrs)		
		72 hrs (+/- 2 hrs)		
		Day 6 post end of infusion		
6	Activity measurements: <ul style="list-style-type: none">• Date and Time• Total volume of sample measured• Activity count (Not decay corrected)• Aliquot activity (KBq)	All time points above		
Urine collection at Cycle 1 only				
7	Urine sampling: <ul style="list-style-type: none">• Date and Time• Cumulative volume of urine collection• Volume of sample measured• Activity count (Not decay corrected)• Aliquot activity (KBq)	0-2 hrs post collection (up to first image)		
8	Urine sampling: <ul style="list-style-type: none">• Date and Time	24 hrs (+/- 2 hrs)		
		48 hrs (+/- 2 hrs)		
		72 hrs (+/- 2 hrs)		
Well Counter Calibration Factor at Cycle 1 only				
9	Reference source data: <ul style="list-style-type: none">• Date and Time• Well counter calibration factor• cpm/kBq• cps/kBq			
¹⁷⁷Lu-PSMA-617 Administration eCRF				
10	Dose formulation information: <ul style="list-style-type: none">• Subject ID• ¹⁷⁷Lu-PSMA-617 Peptide concentration (µg/mL)• Date and Time• Total Dose Administered (MBq)• Total Volume of Dosing Formulation Administered (mL)• Pre-¹⁷⁷Lu-PSMA-617 Injection Syringe Activity Measurement (MBq)• Post-¹⁷⁷Lu-PSMA-617 Injection Syringe Activity Measurement (MBq)			
Serum Creatinine (eGFR calculation) cycle 1 through cycle 6 (Pre-dose)				
11	<ul style="list-style-type: none">• Serum creatinine collection date	Collected at CxD1 from previous visit		

Protocol: PSMA-617-01

PSMA-617 Sub-study manual

	<ul style="list-style-type: none">• Serum creatinine:• Serum Creatinine units: <input type="checkbox"/> mg/dL <input type="checkbox"/> µmol/L• Age at time of Serum Creatinine collection:			
--	--	--	--	--

Appendix 5

50-mL Falcon tube**Study No.** PSMA-617-01**Patient no.** _____ - _____**Urine; date of Collection (dd/mmm/yyyy)** _____**time of Collection (hh:mm)** _____**Timepoints:**Sample 1: 0 – 2 h p.i.

MBq/mL

**RADIOACTIVE****Radioactivity measurements:** Sample 2: 24 h p.i.

MBq/mL

Radioactivity measurements: Sample 3: 48 h p.i.

MBq/mL

Radioactivity measurements: Sample 4: 72 h p.i.

MBq/mL

Radioactivity measurements:

MBq/mL

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Appendix 6

HPLC transmittal form**Study Number:** PSMA-617-01**General Information**

Site no.:
Name of Investigator:
Site Address:
Phone No.:

Sample identification

Patient no.: -
Gender: Male
Date and time of first administration: / / :

Sample Information

temperature excursions before delivery to Courier				
date:		°C from		to
date:		°C from		to
date:		°C from		to

to be completed at the site of sample collection			to be completed at CRL	
Timepoints	Date of collection	Time of collection	Check if sample included in the shipment and in good condition	Dry ice present?
Sample 1: 0-2 h p.i.	<u> </u> / <u> </u> / <u> </u>	<u> </u> : <u> </u>	<input type="checkbox"/>	<input type="checkbox"/>
Sample 2: 24 h p.i.	<u> </u> / <u> </u> / <u> </u>	<u> </u> : <u> </u>	<input type="checkbox"/>	<input type="checkbox"/>
Sample 3: 48 h p.i.	<u> </u> / <u> </u> / <u> </u>	<u> </u> : <u> </u>	<input type="checkbox"/>	<input type="checkbox"/>
Sample 4: 72 h p.i.	<u> </u> / <u> </u> / <u> </u>	<u> </u> : <u> </u>	<input type="checkbox"/>	<input type="checkbox"/>

Total radioactivity: /M_bq**Signature Delivery**

date of forwarding _____ Name, Signature (Investigator/Study Coordinator/Study Nurse)

Signature Recipient

date of receipt _____ Name, Signature Recipient

Notes:

Appendix 7

MARKEN BOOKING FORM

PROJECT DETAILS**ACCOUNT NUMBER:** US1372**SITE NUMBER:****PROTOCOL:** PSMA-617-01**SPONSOR:** Endocyte**LOCAL MARKEN CONTACT DETAILS****Marken Frankfurt**

Mönchhofallee 13

65451 Kelsterbach

Germany

Tel: +49 6142 301 820**Fax:** +49 6142 301 8210**Email:** marken.germany@marken.com**BOOKING PROCESS**

1. Please complete this Booking Form and email or fax it to your Local Marken Contact as per your latest call time (LCT) to schedule the collection as per your latest pick up time (LPT).
2. The packaging material will be provided to the site by the Marken driver during pick-up. If you have any special requirements, please specify these on this Booking Form.
3. Await arrival on site of the Marken Representative at the agreed collection time.

PICKUP ADDRESS – SHIPPER's ADDRESS

Site #

SHIPMENT TO

Charles River Laboratories

1407 George Rd,

Ashland, OH 44805

USA

Tel: +1 (419)-282-6862

Required SHIPMENT Declaration**UN3373 Biological Substance, Category B,****UN2910 Radioactive Material, Excepted Package - Limited Quantity of Material**

REQUESTED PICK UP DATE	REQUESTED PICK UP TIME
____/____/____ (dd/mm/yy)	____:____ hrs (24 hrs clock)

Date

Signature

Customs Invoice

Date: _____

SHIPPER:

Protocol: PSMA-617-01

Site Contact Details to be added

We are forwarding the enclosed package(s) for urgent delivery to:

Consignee:

Charles River Laboratories

1407 George Rd,

Ashland, OH 44805

USA

Tel: +1 (419)-282-6862

Contents:

UN3373 Biological Substance, Category B

Radioactive Material, Excepted Package - Limited Quantity of Material

Packed Frozen on Dry Ice

This shipment includes ____ package(s) containing ____ ml each (____ ml total)

Total Radioactivity: _____

USDA Statement(s):

USDA PERMIT IS NOT REQUIRED, EXEMPTED UNDER USDA GUIDELINE# 1101:

HUMAN MATERIAL CONTAINING NO ANIMAL MATERIAL AND NOT OF TISSUE CULTURE ORIGIN. HUMAN MATERIAL THAT WAS NEITHER EXPOSED TO OR INOCULATED WITH ANY EXOTIC LIVESTOCK OR AVIAN DISEASE AGENTS. NOT ORIGINATING AT ANY FACILITY THAT WORKS WITH ANY EXOTIC LIVESTOCK OR AVIAN DISEASE AGENTS. NOT EXPOSED TO INFECTIOUS AGENTS OF INFECTIOUS AGENTS OF AGRICULTURE CONCERNS, INCLUDING ZOONOTIC AGENTS. OBTAINED DIRECTLY FROM HUMANS, NOT RECOMBINANT NOT CULTURED.

CDC Statement:

CDC IMPORT PERMIT IS NOT REQUIRED FOR THIS SHIPMENT. THE MATERIAL IS NOT KNOWN TO CONTAIN ANY ETIOLOGICAL AGENT, HOST OR VECTOR OF HUMAN DISEASE AND/OR SHOWS NO INDICATION THAT IT CONTAINS AN INFECTIOUS AGENT.

For laboratory testing only.

This shipment has no commercial value. Value for customs purposes is \$____10____ (USD).

Pieces: _____

Weight: _____

Print Name: _____

Signature: _____

Title: _____

Protocol: PSMA-617-01

PSMA-617 Sub-study manual

Appendix 8

Urine HPLC Results (for use by Charles River - Ashland)**Study Number:** PSMA-617-01**General Information**

Site no.:

Name of Investigator:

Sample identification

Patient no.:

[REDACTED] - [REDACTED]

Gender:

Male

Results

Time interval	Compound A (¹⁷⁷ Lu-PSMA-617)				Compound B				Compound C				Compound D			
	RT (min)	Radioconcentration (MBq/mL)	Concentration (μ g/mL)	Relative Observed Intensity (%)	RT (min)	Radioconcentration (MBq/mL)	Concentration (μ g/mL)	Relative Observed Intensity (%)	RT (min)	Radioconcentration (MBq/mL)	Concentration (μ g/mL)	Relative Observed Intensity (%)	RT (min)	Radioconcentration (MBq/mL)	Concentration (μ g/mL)	Relative Observed Intensity (%)
Sample 1: 0-2 h p.i.																
Sample 2: 24 h p.i.																
Sample 3: 48 h p.i.																
Sample 4: 72 h p.i.																

Signature

Name, Signature

date of sample processing

Notes: _____

Appendix 9

Temperature Log (while keeping urine sample at the site)