Clinical Development

lutetium (^{177}Lu) vipivotide tetraxetan

AAA617 ([^{177}Lu]Lu-PSMA-617)

2.7.2 Summary of Clinical Pharmacology Studies in patients with prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer

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Abbreviations

AUC	Area under the curve
BCRP	Breast Cancer Resistance Protein
BMI	Body mass index
BSC/BSoC	Best Supportive/Best Standard of Care
BSEP	Bile Salt Export Pump
CL	Clearance
CLcr	Creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
DOTA	1,4,7,10-Tetraazacyclododecane-tetraacetic acid
EBRT	External Beam Radiation Therapy
EOI	End of injection/infusion
GBq	Gigabecquerel
Gy	Gray
hERG	Human Ether-a-go-go Related Gene
HPLC	High performance liquid chromatography
IV	Intravenous
MATE	Multidrug and toxin extrusion
mCRPC	Metastatic castration-resistant prostate cancer
NAAD	Novel androgen axis drugs
NADPH	Nicotinamide adenine dinucleotide phosphate
NCA	Non-Compartmental Analysis
OAT1	Organic anion transporters
OATP	Organic anion transporting polypeptides
OCT	Organic cation transporters
OLINDA	Organ Level INternal Dose Assessment
PC	Prostate cancer
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetics
PSMA	Prostate-Specific Membrane Antigen
RLT	Radioligand therapy
SPECT-CT	Single-photon emission computerized tomography- Computed Tomography
Tmax	Time to peak whole blood concentrations
WT_{BL}	Baseline weight

1 Background and Overview

1.1 General Overview

[^{177}Lu]Lu-PSMA-617 is a prostate-specific membrane antigen (PSMA) - targeted radioligand therapy (RLT) that is being developed to treat metastatic castration-resistant prostate cancer (mCRPC). The recommended dose of lutetium (^{177}Lu) vipivotide tetraxetan (or ([^{177}Lu]Lu-PSMA-617) is 7.4 GBq dose every 6 weeks (Q6W) for a total of 6 doses, and a total cumulative dose of 44.4 GBq. The therapeutic agent lutetium (^{177}Lu) vipivotide tetraxetan or [^{177}Lu]Lu-PSMA-617 (company research code: AAA617), is referred to as ^{177}Lu-PSMA-617 henceforth for the purpose of this document.

The tumor target, PSMA, is a type II transmembrane protein, also known as folate hydrolase I or glutamate carboxypeptidase II, and has been confirmed as a biological target for diagnostic imaging and therapy in prostate cancer (Silver et al 1997, O'Keefe et al 2018). PSMA is highly expressed in nearly all prostate cancers, including adenocarcinoma, but has restricted and several hundred-fold lower expression in some normal tissues such as the duodenal mucosa, renal proximal tubules, and salivary glands (Bostwick et al 1998, Sokoloff et al 2000, Chang 2004, Ghosh and Heston 2004). Additionally, PSMA overexpression is correlated with advanced, high-grade, metastatic, castration-resistant prostate cancer (Wright et al 1995, Silver et al 1997, Bostwick et al 1998, Murphy et al 1998, Sweat et al 1998, Ross et al 2003, Chang 2004, Queisser et al 2015). The differential expression of PSMA from tumor to non-tumor tissue supports targeted strategies in prostate cancer involving both disease localization using radioactive imaging as well as treatment with radioligand therapeutic intervention

The PSMA-617 precursor molecule consists of 3 components: the PSMA-targeting pharmacophore glutamate-urea-lysine, the chelator DOTA, and a linker connecting these 2 entities (Benešová et al 2015). Lu-177 is the radionuclide incorporated into the DOTA chelator of the PSMA-617 molecule, and it is the radioactive nature of this metal which is responsible for the therapeutic activity of ^{177}Lu-PSMA-617. The mechanism of action of ^{177}Lu-PSMA-617 is to deliver therapeutic radiation to cancer cells via its binding to PSMA. By design, PSMA-617 exhibits high PSMA binding affinity and internalization, prolonged tumor retention, and rapid kidney clearance (Benešová et al 2015).

While PSMA-617 has the capacity to chelate other radionuclides, Lu-177 is the radionuclide of choice for this application, based on its favorable radiochemical characteristics, including half-life and the path length of the β-particles (Sgouros et al 2020). The high affinity binding of the PSMA-targeting pharmacophore in ^{177}Lu-PSMA-617, leads to internalization through endocytosis and a sustained retention of the ligand, including its bound radioactive cargo, within the targeted cancer cell (Rajasekaran et al 2003, Eder et al 2012, Benešová et al 2015). The physical half-life of 6.647 days for Lu-177 allows for the continued irradiation of the lesion to maximize the benefit of this prolonged retention of the radioactive agent. Additionally, the emission of medium-energy β-particles from the radioactive Lu-177 atom decay results in a maximal tissue penetration of approximately 2 mm (Dash et al 2015, Deepa et al 2011). This path length reduces exposure to neighboring normal tissues, while maintaining crossfire effects within the tumor lesion to address potential target heterogeneity (Emmett et al 2017). The therapeutic effect of Lu-177 and subsequent cell death is the result of both direct effects of radiation on the molecular structure of the cell's DNA, as well as indirect DNA-damaging

effects from reactive species induced from molecules in the DNA environment (e.g., water, salts, proteins, and oxygen molecules). Therapeutic benefit from targeted Lu-177 exposure is well documented, and this radionuclide is incorporated into the approved product Lutathera (Sgouros et al 2020, Lutathera USPI 2020).

Numerous publications in the literature summarize the evaluation of the investigational ^{177}Lu-PSMA-617 PSMA-targeted radioligand therapy in mCRPC patients from patient populations with differing prior therapies and concomitant medications. These publications represent data from retrospective and prospective Phase 1, Phase 2 and dosimetry trials under country's local regulations using multiple sources of the PSMA-617 precursor and Lu-177 with different preparation processes for ^{177}Lu-PSMA-617. Despite these varying conditions, the literature suggests low toxicity and encouraging biochemical and radiographic response rates, overall survival and reduced pain using ^{177}Lu-PSMA-617 RLT in patients with mCRPC (Rahbar et al 2017, Hofman et al 2018, Kim et al 2018, von Eyben et al 2018, Yadav et al 2019, Violet et al 2020, Hofman et al 2021, Sadaghiani et al 2021).

A prospective, open-label, multicenter, randomized Phase 3 study (PSMA-617-01 (VISION)) has been conducted in patients with PSMA-positive mCRPC, comparing ^{177}Lu-PSMA-617 in addition to best supportive care (BSC)/best standard of care (BSoC) versus BSC/BSoC alone (referred to as main study in this document). Within this Phase 3 study a dosimetry (pharmacokinetics (PK) and electrocardiogram sub-study also has been conducted in a non-randomized cohort of ^{177}Lu-PSMA-617 plus BSC/ BSoC of 30 patients (dosimetry: 29 patients; one patient was able to undergo only a single planar image, therefore a complete dosimetry analysis was not available).

The summary of the Phase 3 clinical sub-study along with the summaries of the published literature supporting the clinical pharmacology assessments of ^{177}Lu-PSMA-617 in patients with prostate cancer are described in detail, in Section 2.

All PK data are expressed in mass units/volume (e.g. ng/mL) or radioactivity/volume (e.g. kBq/mL). The molecular weight of the unlabeled PSMA-617 precursor molecule, the non-radioactive form ^{175}Lu-PSMA-617 (as a surrogate for ^{177}Lu-PSMA-617) and ^{177}Lu-PSMA-617 are 1042.1 g/mol, 1214.1 g/mol and 1216.1 g/mol, respectively. To convert from ng/mL to µmol/L, divide by the molecular weight.

1.2 Summary of overall conclusions

1.2.1 Pharmacokinetics of ^{177}Lu-PSMA-617

Based on the results of in vitro studies conducted either with unlabeled PSMA-617 or ^{175}Lu-PSMA-617 (or a mix), results are considered to be fully translatable to ^{177}Lu-PSMA-617 for the purpose of drawing pharmacokinetic conclusions.

1.2.1.1 Blood-radioactivity single dose PK

Following an IV injection/infusion of ^{177}Lu-PSMA-617, time to peak whole blood concentrations (Tmax) ranged from 0.0167 to 1.68 hours, generally occurring within approximately 20 minutes after administration, with median Tmax value of 0.375 hours. Afterwards, whole blood concentrations followed a bi-exponential decline, which resulted in a

geometric mean terminal half-life of approximately 41.6 (geometric mean %CV 68.8%) hours. The geometric mean total systemic clearance (CL) was 2.04 L/hr (31.5%) in line with CL estimated by a population PK approach. Given the determined protein binding and information about excretion (and lack of transporter interaction), total clearance can be assumed to be equal to passive renal clearance. Geometric mean apparent volume of distribution (Vz) was 123 L (78.1%).

The effective half-live accounting for the decay of Lu-177 radioactivity was ~33 hours (Section 3.1.1).

1.2.1.2 Absorption, distribution, metabolism, excretion

As ^{177}Lu-PSMA-617 is administered intravenously, bioavailability is 100% (Section 3.1.2). ^{177}Lu-PSMA-617 displays moderate protein binding with a fraction bound of ~60-70% and does not distribute to erythrocytes (Section 3.1.3). ^{177}Lu-PSMA-617 is metabolically stable both in vitro and in vivo (Section 3.1.4) and primarily excreted passively via the kidney (Section 3.1.5).

1.2.1.3 Effects of intrinsic factors on PK and dosimetry

Demographic factors - gender, body weight, ethnicity, and age

The PK and dosimetry of ^{177}Lu-PSMA-617 has been limited to investigations in prostate cancer, exclusive to males, therefore there is no information regarding the impact of gender on PK or biodistribution (Section 3.4.2).

Population PK and dosimetry analyses showed that ^{177}Lu-PSMA-617 exposure and biodistribution are not affected by body weight, supporting the use of fixed dosing (Section 3.4.3).

No information is currently available about the effects of ethnicity or race on biodistribution and PK of ^{177}Lu-PSMA-617. Since ^{177}Lu-PSMA-617 is not metabolized by the liver and is eliminated passively through renal excretion, PK is unlikely to be affected by ethnic factors (Section 3.4.4).

Age in the range of 52 to 80 years (median 67 years) was shown not to have an effect on the exposure of ^{177}Lu-PSMA-617 in the PSMA-617-01 sub-study. While older subjects were associated with higher radiation absorbed dose levels in the kidneys and bone marrow, this correlation may be confounded by the negative correlation between age and renal clearance (Section 3.4.5).

Hepatic impairment

As ^{177}Lu-PSMA-617 is not metabolized by, or primarily eliminated through, the liver, PK and biodistribution are not affected by hepatic impairment (Section 3.4.8). Hence, no dose adjustment is needed in patients with hepatic impairment.

Renal impairment

No dedicated renal impairment study for ^{177}Lu-PSMA-617 has been conducted.

As the main route of excretion for ^{177}Lu-PSMA-617 is renal, renal function was assessed in the population PK analysis. Simulations were performed to explore the effect of renal impairment (at baseline) on ^{177}Lu-PSMA-617 PK exposure (Section 3.4.7). Simulations showed a 42% and 20% increase in median of simulated AUCinf for moderate and mild renal impairment respectively vs. for normal renal function. There was no significant effect on Cmax in patients with mild or moderate renal impairment. These findings should be interpreted with caution since the population included only one patient with moderate renal impairment (baseline creatinine clearance (CLcr) of 54 mL/min).

Correlation between kidney dosimetry at Cycle 1 and renal impairment showed a trend toward higher kidney dosimetry values in patients with mild or moderate renal impairment compared to those with normal renal function. However, as the single value of the kidney dosimetry in the moderate renal impaired patient was within the distribution observed for mild renal impairment group, this is likely of no concern, especially since no major renal toxicity was observed (as discussed in Section 3.3.2). Based on this population PK analysis, no dose adjustment is recommended in patients with mild (CLcr 60 to 89 mL/min) or moderate (CLcr 30 to 59 mL/min) renal impairment at baseline.

The pharmacokinetic profile and safety of ^{177}Lu-PSMA-617 have not been studied in patients with severe renal impairment or end-stage renal disease, therefore no information is available in such patients.

1.2.1.4 Effects of extrinsic factors on PK and dosimetry

Food Effect

As ^{177}Lu-PSMA-617 is administered intravenously, no food effect is expected.

Co-administration with other medications

As ^{177}Lu-PSMA-617 is metabolically stable both in vitro and in vivo, passively cleared via the kidney and not a substrate of any of the investigated uptake or efflux transporters (multidrug and toxin extrusion (MATE1), MATE2-K, organic anion transporters (OAT1, OAT3), organic cation transporter (OCT2), P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP)) based on in vitro assessments using a non-radioactive formulation containing unlabeled PSMA-617 and ^{175}Lu-PSMA-617, it is unlikely to become subject to any metabolic- or transporter-mediated drug interactions in vivo.

Androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor antagonists, have been reported to modulate PSMA expression in some nonclinical prostate cancer models, and in some clinical studies. However, a definitive effect of these therapies on the PK or biodistribution of ^{177}Lu-PSMA-617, particularly in normal tissues, has not been established. Additionally, the dosimetry results acquired from patients in the PSMA-617-01 sub-study, which allowed concomitant administration of novel androgen axis drugs (NAADs), showed good concordance with literature. Considering the general consistency in the reported biodistribution, ADTs appear unlikely to have an effect on the biodistribution and PK of ^{177}Lu-PSMA-617 that extends beyond the normal range of variability. Co-administration of ADT or other androgen pathway targeting therapies does not warrant dose

adjustments of ^{177}Lu-PSMA-617 as supported by the safety profile and efficacy of ^{177}Lu-PSMA-617 in PSMA-617-01 (Section 3.5.1).

1.2.1.5 Effect of ^{177}Lu-PSMA-617 on concomitant medications

Based on the risk assessment of in vitro data described in Section 3.5.2 using a non-radioactive formulation containing unlabeled PSMA-617 and ^{175}Lu-PSMA-617, ^{177}Lu-PSMA-617 is not an inducer of CYP1A2, 2B6 and 3A4 and was also not an inhibitor of all common CYPs (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5) and investigated efflux and uptake transporters (BCRP, Bile Salt Export Pump (BSEP), P-gp, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2) at ^{177}Lu-PSMA-617 and total peptide concentrations achieved with a clinical 7.4 GBq (± 10%) dose.

Therefore, ^{177}Lu-PSMA-617 is not expected to cause any CYP- or transport-mediated drug interactions in vivo.

1.2.2 Biodistribution and dosimetry

1.2.2.1 Rationale for Proposed Dose and Regimen

In general, the determination of the optimal dose regimen was guided by efficacy and safety considerations, with an accounting for the life-threatening nature of the disease. The selected dose was intended to maximize the probability of efficacy, while maintaining safety parameters which are appropriate for the patient population. A detailed assessment of the data that led to the selection of the 7.4 GBq (± 10%) dose every 6 weeks (Q6W) for a maximum of 6 cycles and a maximum cumulative dose of 44.4 GBq in the pivotal Phase 3 study PSMA-617-01 is described in Section 3.3.1.

At the time of protocol development in 2017-2018 there were 4 publications of interest reporting the efficacy and safety of ^{177}Lu-PSMA-617 (Rahbar et al 2017, Demirci et al 2017, Rahbar 2018, Hofman et al 2018), however this list now contains additional publications summarizing the investigational use of ^{177}Lu-PSMA-617 in mCRPC patient populations with differing prior therapies and concomitant medications (Kim et al 2018, von Eyben et al 2018, Yadav et al 2019, Violet et al 2020, Hofman et al 2021, Sadaghiani et al 2021). In these publications, several doses and regimens have been utilized, demonstrating that a fixed, non-adjusted (with dose reduction steps) or non-individualized 7.4 GBq dose should maximize the probability of efficacy, while maintaining safety parameters which are appropriate for the patient population.

- Doses typically ranged from 1.1-12.0 GBq/cycle ^{177}Lu-PSMA-617, with the schedule varying from once every 4 to 12 weeks, for between 1-9 cycles (Yadav et al 2020, Kulkarni et al 2018b, Grubmüller et al 2019, Sarnelli et al 2019).
- The efficacy and safety data from a Phase 2 study suggested that dosing of 4.0-8.9 (mean 7.5) GBq every 6 weeks for 4 cycles was well tolerated and efficacious (Hofman et al 2018), primarily influencing the choice of the 7.4 GBq Q6W dose. These data were further supplemented with final data and long-term follow-up from this study as reported by Violet et al (2020).
- Clinical studies also conveyed that more than 4 cycles of ^{177}Lu-PSMA-617 could be administered safely so as to maximize the benefit to the patient at the time of protocol development, and has since been confirmed in publications from studies concurrent with

the PSMA-617-01 study (Bräuer et al 2017, Yordanova et al 2017, Kulkarni et al 2018a, Kulkarni et al 2018b, Kulkarni et al 2018c, Rahbar et al 2018, Van Kalmthout et al 2019, Maffey-Steffan et al 2020, Yadav et al 2020). Hence, the PSMA-617-01 study protocol integrated language that patients after receiving 4 cycles of treatment were required to meet additional criteria (including evidence of response, signs of residual disease, and good tolerance of ^{177}Lu-PSMA-617) and agree to continue treatment with ^{177}Lu-PSMA-617 before the Investigator could administer 2 additional cycles, for a maximum of 6 cycles [Study PSMA-617-01-Section 9.1].

- Dosimetry studies in the literature with ^{177}Lu-PSMA-617 have identified the salivary glands, lacrimal glands, kidneys and bone marrow as the organs considered at risk from radiation due to their exposure levels, or radiosensitivity. However, the mean cumulative exposure to these tissues from 6 cycles of 7.4 GBq using literature estimates were below, or only marginally higher than, the reported thresholds in these tissues based on External Beam Radiation Therapy (EBRT) thresholds or ^{131}I in these tissues. Lacrimal glands have not routinely been utilized to limit ^{177}Lu-PSMA-617 dosing regimens, perhaps due to some of the challenges around accurate radioactivity quantification to this tissue, as well as a lack of reported adverse events. When considering the application of these thresholds it was also considered that the EBRT thresholds may be too conservative, particularly in this patient population and for RLT in general (Section 3.3.1.2).
- Clinical safety data for the approved ^{177}Lu-radioligand therapeutic, Lutathera showed that no patients in the NETTER-1 study following a dose of 7.4 GBq every 8 weeks, for a total of 4 cycles (29.6 GBq cumulative activity, for a calculated cumulative absorbed dose of 19.4 ± 8.7 Gy in the kidneys), developed Grade 3/4 renal toxicity, or had a marked reduction in CLcr based on assessments every 6 months in the 5 year follow-up period of the study. A similar profile was expected with ^{177}Lu-PSMA-617, as both the compounds are ^{177}Lu-radioligand therapeutics, with the same route of excretion, and with similar renal absorbed dose levels (Section 3.3.1.3).

In addition, dosimetry data from 29 patients from the PSMA-617-01 sub-study are available which support the use of the selected dose of 7.4 GBq every 6 weeks for a maximum of 6 cycles from a radiation exposure perspective (Section 1.2.2.2 and Section 2.3). This is in addition to the PSMA-617-01 main-study confirming efficacy and tolerability and a positive risk-benefit with the selected 7.4 GBq dose and regimen of 6 cycles of administration, as described in Section 3.3.1, [SCE] and [SCS].

1.2.2.2 Dosimetry in PSMA-617-01 Sub-study

Dosimetry estimates for ^{177}Lu-PSMA-617 were determined based on bio-distribution found using whole body conjugate planar image data, single-photon emission computerized tomography- computed tomography (SPECT-CT) image data, blood assay data, and urinary excretion data collected in 29 of the 30 enrolled patients in the PSMA-617-01 sub-study. One patient was able to undergo only a single planar image, therefore a complete dosimetry analysis was not available for that particular patient (Section 2.3).

Dosimetry data are summarized as absorbed dose per unit activity (Gy/GBq) and absorbed dose (Gy) calculated for a single 7.4 GBq dose as well as cumulative absorbed dose (Gy) calculated for a total of 6 doses of 7.4 GBq each (44.4 GBq cumulative activity) in Table 1-1.

Table 1-1 Estimated Radiation Absorbed Dose in PSMA-617-01 Sub-study (All patients)

	Absorbed dose per unit activity (Gy/GBq) [#] (N=29)		Calculated absorbed dose for the first cycle of 7.4 GBq dose (Gy) [#]		Calculated absorbed dose for 6 x 7.4 GBq (44.4 GBq cumulative activity) (Gy) [#]	
Organ	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Adrenals	0.033	0.025	0.24	0.19	1.5	1.1
Brain	0.007	0.005	0.049	0.035	0.3	0.22
Esophagus	0.025	0.026	0.18	0.19	1.1	1.1
Eyes	0.022	0.024	0.16	0.18	0.99	1.1
Gallbladder Wall	0.028	0.026	0.20	0.19	1.2	1.1
Left colon	0.580	0.140	4.1	1.00	26	6.0
Small Intestine	0.071	0.031	0.50	0.23	3.1	1.4
Stomach Wall	0.025	0.026	0.18	0.19	1.1	1.1
Right colon	0.320	0.078	2.3	0.58	14	3.4
Rectum	0.560	0.140	4.0	1.1	25	6.2
Heart Wall	0.170	0.120	1.2	0.83	7.8	5.2
Kidneys	0.430	0.160	3.1	1.2	19	7.3
Lacrimal Glands	2.100	0.470	15.0	3.4	92	21
Liver	0.090	0.044	0.64	0.32	4.0	2.0
Lungs	0.110	0.110	0.76	0.81	4.7	4.9
Pancreas	0.027	0.026	0.19	0.19	1.2	1.1
Prostate	0.027	0.026	0.19	0.19	1.2	1.1
Salivary Glands	0.630	0.360	4.5	2.6	28	16
Red Marrow	0.035	0.020	0.25	0.15	1.5	0.90
Osteogenic Cells	0.036	0.028	0.26	0.21	1.6	1.3
Spleen	0.067	0.027	0.48	0.20	3.0	1.2
Testes	0.023	0.025	0.16	0.18	1.0	1.1
Thymus	0.025	0.026	0.18	0.19	1.1	1.1
Thyroid	0.260	0.370	1.8	2.7	11	16
Urinary Bladder Wall	0.320	0.025	2.3	0.19	14	1.1
Total Body	0.037	0.027	0.27	0.20	1.6	1.2

Source: adapted from [Study PSMA-617-01-Appendix 16.2.9.4-Table 3], [Study PSMA-617-01-Appendix 16.2.9.4-Table 4] and [Study PSMA-617-01-Appendix 16.2.9.4-Table 5]

[#] Values have been calculated based on dosimetry estimates at full precision and rounded to relevant digits.

Radiation exposures from the PSMA-617-01 sub-study, especially for the organs considered at risk from radiation due to their exposure levels such as salivary glands, lacrimal glands, kidneys and bone marrow, were consistent with the ranges published in literature (Table 3-1). Overall,

the dosimetry data indicates minimal risk for patients based on the theoretical calculated radiation exposure after 6 cycles of 7.4 GBq. The dosimetry data is in line with clinical findings that indicate adverse events related with these organs are generally of a low-to-moderate severity, tolerable and of a reversible nature [SCS]. Comparison with literature values and detailed comparison with the observed safety profile in PSMA-617-01 main-study per organ at risk are discussed in more detail in Section 3.3.2.

1.2.3 Pharmacodynamics

^{177}Lu-PSMA-617 is a PSMA-targeted radioligand therapeutic that delivers radiation to cancer cells via binding to the PSMA cell-surface target. In vitro experiments showed high PSMA binding affinity in both cellular and enzyme activity assays. Additionally, PSMA-dependent uptake and internalization of ^{177}Lu-PSMA-617 was confirmed in cellular assays, and retention demonstrated in cancer PSMA-expressing tumor xenografts in mice. Hence, ^{177}Lu-PSMA-617 displays ideal pharmacological properties to deliver therapeutic radiation to sites of disease. In addition, no relevant pharmacodynamic effects related to the ligand itself are expected given the administration of a low micro-dose and infrequent administration every 6 weeks, as well as the lack of pharmacologic activity of a non-radioactive formulation in safety pharmacology and toxicology studies (Section 3.6).

1.2.4 Exposure-Response

1.2.4.1 PK/QT Analysis

Concentration-QTc effect analysis based on ECGs and time-matched PK that were collected in the PSMA-617-01 sub-study showed that ^{177}Lu-PSMA-617 had no clinically relevant effects on QTc or other ECG parameters at the time points where ECG measurements were made. Together with preclinical cardiac safety studies that indicated a negligible risk of an electrophysiological effect by ^{175}Lu-PSMA-617, a low uptake in the heart, and the absence of clinical findings related to QT prolongation in PSMA-617-01 sub-study, the data confirms that ^{177}Lu-PSMA-617 administration does not pose a cardiac risk (Section 3.7.1).

1.2.4.2 Exposure/Dosimetry-Acute toxicity

Effects of exposure and organ dosimetry on acute toxicity at Cycle 1 related to the organs at risk (i.e. kidney, bone marrow, salivary glands and lacrimal glands) were explored in the PSMA-617-01 sub-study (Section 3.7.2).

Longitudinal laboratory profiles showed a decrease in leukocytes, neutrophils and platelets starting from 8 days after treatment administration. However, only 20% of the sub-study patients experienced a worsening from baseline of at least one hematological adverse events of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 2 during Cycle 1.

Higher injected activity and higher kidney dosimetry tend to be associated with larger decrease from baseline in CLcr. However, none of the sub-study patients had any renal adverse event of CTCAE grade ≥ 2 during Cycle 1.

In addition, none of them experienced any lacrimal gland toxicity, and only 2 patients had a salivary gland adverse event during Cycle 1, limited to Grade 1.

No consistent trend was detected in the relationships between platelet count decrease, occurrence of hematological adverse events of CTCAE grade ≥ 2 and salivary gland toxicities with exposure metrics.

Exposure/Dosimetry-Acute Toxicity analyses are limited by the small sample size (N=30 for exposure and N=29 for dosimetry) and the small number of adverse events. In addition, these analyses could only explore Cycle 1 data.

1.2.4.3 Exposure-Dosimetry

^{177}Lu-PSMA-617 PK exposure effect on the dosimetry results for the organs at risk (i.e. kidney, bone marrow, salivary glands and lacrimal glands) during the first cycle of treatment in PSMA-617-01 sub-study patients was explored (Section 3.7.3). Linear regression was performed for each exposure-dosimetry relationship, and suggested that only AUCinf in blood was a statistically significant predictor of the radiation absorbed dose in the kidneys (p=0.005), with increasing AUCinf leading to an increase in the kidney absorbed radiation dose. However, the relationship between AUCinf and kidney dosimetry may not be a causal relationship as it is confounded by CLcr. Indeed, CLcr has a strong effect on AUCinf, and is also highly negatively correlated with kidney dosimetry.

2 Summary of Results of Individual Clinical Pharmacology Studies

This section details the individual clinical pharmacology study results, which include information from in vitro studies using human biomaterials (Section 2.1), clinical studies and published data. Details of a sub-study, which was part of the pivotal clinical Phase 3 study (Study PSMA-617-01) and which provided organ dosimetry, PK and supportive metabolite data of ^{177}Lu-PSMA-617 is provided in Section 2.3. Published patient literature supporting the submission is provided in Section 2.4.

2.1 In vitro studies using human biomaterials

Preclinical studies, such as in vitro stability and protein binding were conducted using the unlabeled PSMA-617 precursor molecule as well as a non-radioactive labeled form of PSMA-617 (^{175}Lu-PSMA-617) as a surrogate for ^{177}Lu-PSMA-617. For the purpose of drawing conclusions, results from unlabeled PSMA-617 or non-radioactive (Lu-175) isotope-labeled PSMA-617 can be fully transferred to the radioactive form ^{177}Lu-PSMA-617 [Nonclinical Overview].

2.1.1 Receptor binding and internalization

The PSMA-617 precursor molecule is designed to bind with high affinity to PSMA expressed on cancer cells. Cell binding assays determined ^{177}Lu-PSMA-617 to have nanomolar affinity for PSMA on PSMA-expressing LNCaP (prostate cancer) cells, with a Kd of 4.7 ± 1.1 nM [ULM-AAA-01-17], similar to what was has been reported in literature (Ki = 2.34 ± 2.94 nM, Benešová et al 2015) in the same cell line. Further, biochemical studies revealed the inhibition potency for ^{nat}Ga- and ^{nat}Lu-labeled PSMA-617 of 6.4 ± 1.02 nM and 6.91 ± 1.32 nM, respectively (Benešová et al 2015). Additionally, the in vitro uptake of ^{177}Lu-PSMA-617 into

PSMA[+] PC-3 PIP tumor cells was approximately 55% to 70%, while the internalized fraction was about 10% to 15% of total added radioactivity. The uptake dropped to < 0.5% when PSMA[-] PC-3 flu tumor cells were used, demonstrating PSMA-dependent uptake (Umbricht et al 2017).

2.1.2 Plasma Protein Binding

^{175}Lu-PSMA-617 and unlabeled PSMA-617 were both found to be moderately bound to plasma proteins when incubated at concentrations of either 1 µg/mL or 5 µg/mL at 37°C in human plasma. A concentration lower than 1 µg/mL could not be investigated due to the limit of detection. The plasma protein binding (% fraction bound) of ^{175}Lu-PSMA-617 was 70% and 62% at 1 µg/mL and 5 µg/mL, while the plasma protein binding of unlabeled PSMA-617 was 70% and 58% at 1 µg/mL and 5 µg/mL [Report 0597].

2.1.3 Blood-to-plasma ratios

^{175}Lu-PSMA-617 and unlabeled PSMA-617 were evaluated in human whole blood and plasma samples to characterize the blood-to-plasma ratios of each analyte [Report Q20_046]. The mean blood-to-plasma ratio for ^{175}Lu-PSMA-617 was 0.49, while the mean blood-to-plasma ratios for unlabeled PSMA-617 was 0.28. As these blood-to-plasma ratios were lower than 1, they support a lack of partitioning of either analyte into human erythrocytes.

2.1.4 Metabolism

^{175}Lu-PSMA-617 and unlabeled PSMA-617 were found to be metabolically stable in human liver and kidney S9 fractions at a concentration of 1 µM (1.21 and 1.04 µg/mL, respectively). The negative control incubations without enzyme cofactors and without S9 also showed no loss of analytes [Report 0590], [Report 0591]. Additionally, ^{175}Lu-PSMA-617 and unlabeled PSMA-617 at a concentration of 1 µM were both stable in human plasma for up to 2 hours at 37°C [Report 0594].

2.1.5 CYP Induction and Inhibition

Based on the results from in vitro CYP450 induction and inhibition studies showed that ^{177}Lu-PSMA-617 is neither an inducer nor an inhibitor of the investigated CYP450 enzymes [Report E0496] and [Report E0497] at the investigated range of concentrations, respectively.

The potential induction of a ^{175}Lu-PSMA-617 test solution (a mixture of ^{175}Lu-labeled PSMA-617 and unlabeled PSMA-617) towards three different cytochrome P450 isoforms (CYP 1A2, 2B6 and 3A4) was evaluated at 500 µg/mL (selected as the highest non-cytotoxic concentration level) and at the lower concentrations of 200, 70, 20, 7, 2, 0.7 and 0.0 µg/mL. The relevant metabolites of CYP specific substrates were quantified after an incubation period of approximately 48 hours of the test item with isolated human hepatocytes (one batch of cryoplateable human hepatocytes from 10 mixed-gender donors). A set of positive controls (reference inducer specific for each CYP isoform) and negative controls (NC, untreated cultures) were included in each experiment showing the validity of the assay results. Since the induction potency over the positive controls was largely under 20% across range of concentrations, no relevant induction effect of the ^{175}Lu-PSMA-617 test solution towards CYP 1A2, 2B6 and 3A4 in vitro was observed [Report E0496].

The competitive and time-dependent inhibition effect of the ^{175}Lu- PSMA-617 test solution on 7 different cytochrome P450 enzyme isoforms (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5) was evaluated. This was obtained by quantifying the relevant metabolites produced during the incubation of CYP specific substrates with Human Liver Microsomes (HLM) at the concentration of 0.1 mg prot/mL in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) (1 mM) and in the presence of the ^{175}Lu-PSMA-617 test solution at concentrations from 0.01 µg/mL to 10.0 µg/mL. The inhibition effect was evaluated estimating IC50 from the uninhibited fraction curves. Reference inhibitors specific for each CYP isoform were used as positive controls showing the validity of the experiment. Incubation in the presence of NADPH and substrate, but in the absence of any inhibitor, was used as negative control. After incubation with the ^{175}Lu-PSMA-617 test solution, no IC50 values could be determined for any CYP isoforms since the uninhibited fraction results did not meet the requirements for IC50 acceptability criteria for evaluation. No time-dependent inhibition effect was observed for any CYP isoforms by the ^{175}Lu-PSMA-617 test solution, since there was no significant IC50 shift [Report E0497]. Hence, it can be concluded that the ^{175}Lu-PSMA-617 test solution is neither a competitive nor a time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5 in vitro at concentrations up to 10.0 µg/mL.

2.1.6 Transporters

2.1.6.1 Transporter Inhibition assays

The in vitro inhibition potential of the ^{175}Lu-PSMA-617 test solution (a mixture of ^{175}Lu-labeled PSMA-617 and unlabeled PSMA-617) with the human BCRP, BSEP and P-gp (also called MDR-1) efflux (ATP-binding cassette (ABC)) transporters (vesicular transport inhibition assays) and with the human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 uptake transporters (uptake transporter inhibition assays) was tested at seven concentration points (at 0.0056, 0.0168, 0.0504, 0.151, 0.453, 1.36 and 4.082 µM; range 0.0058 to 4.25 µg/mL, considering only the ligand component).

The ^{175}Lu-PSMA-617 test solution did not inhibit any of the above mentioned efflux or uptake transporters, as evidence by the lack of effect on transporter-mediated probe substrate accumulation [Report Adacap-04-20Nov2019].

2.1.6.2 Transporter substrate assays

The in vitro transport of the ^{175}Lu-PSMA-617 test solution (a mixture of ^{175}Lu-labeled PSMA-617 and unlabeled PSMA-617) via human MATE1, MATE2-K, OAT1, OAT3 and OCT2 transporters at final concentrations of 0.408 and 4.082 µM (0.425 and 4.25 µg/mL, considering only the ligand component) in the presence and absence of respective reference inhibitors in the uptake transporter substrate assays was tested.

Accumulation of the ^{175}Lu-PSMA-617 test solution in transporter-expressing cells was low and comparable to that in control cells, suggesting no active transport of the ^{175}Lu-PSMA-617 test solution under the in vitro conditions examined in this assay.

In addition, the ^{175}Lu-PSMA-617 test solution is likely not an in vitro substrate of BCRP and P-gp efflux (ATP-binding cassette (ABC)) transporters. The test solution was shown to have

very low permeability therefore the BCRP or P-gp substrate testing could not be assessed in the bidirectional permeability assay [Report Adacap-04-20Nov2019].

2.2 Studies in healthy volunteers

^{177}Lu-PSMA-617 is a radioligand therapeutic targeting oncology patients and has therefore not been studied in healthy volunteers.

2.3 Studies in patients

An efficacy and safety Phase 3 study (Study PSMA-617-01) was conducted in patients with progressive PSMA-positive mCRPC. As part of this study, a sub-study was conducted in 30 non-randomized patients to evaluate dosimetry, PK, urinary metabolites, and ECG. Twenty-nine patients were included in the dosimetry analysis as one patient completed only a single imaging session. The clinical pharmacological data from the sub-study is presented below.

Both the Phase 3 study and sub-study are ongoing at the time of authoring of this document.

2.3.1 Study PSMA-617-01 - Sub-study

The purpose of this sub-study was to calculate whole body and organ radiation dosimetry of ^{177}Lu-PSMA-617 to evaluate the dose to critical organs (e.g., kidney and bone marrow). This sub-study also evaluated the PK profile, ECGs, safety and tolerability, and urinary metabolic stability of ^{177}Lu-PSMA-617.

The sub-study was conducted in a non-randomized cohort (^{177}Lu-PSMA-617+ (BSC/BSoC)) of 30 patients. BSC/BSoC was determined by the investigator, but excluded investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radioisotopes and hemi-body radiotherapy. The collection of dosimetry, pharmacokinetic, ECG, and urinary data occurred following the first dose of 7.4 GBq (±10%) ^{177}Lu-PSMA-617, although enrolled patients continued in the sub-study as per the PSMA-617-01 protocol (^{177}Lu-PSMA-617 dose every 6 (±1) weeks for a maximum of 6 cycles). Patients underwent full body (planar) and 3D SPECT/CT imaging, blood PK sampling and ECGs, during Cycle 1 of treatment. Urine was collected for High performance liquid chromatography (HPLC) analysis with in-line radiodetection (radio-HPLC). Baseline images were used to determine volumes in regions of interest (ROI/VOI) in selected major source organs such as the liver, spleen and kidneys. 3D SPECT/CT scans were also performed in the upper abdomen (comprising kidneys, liver and spleen) [Study PSMA-617-01-Appendix 16.1.1 Study Protocol Version 4.1].

2.3.1.1 Organ dosimetry and biodistribution

Dosimetry estimates for ^{177}Lu-PSMA-617 were determined based on bio-distribution found using whole body conjugate planar image data, SPECT-CT image data, blood assay data, and urinary excretion data collected in 29 of the 30 enrolled patients [Study PSMA-617-01 Appendix 16.2.9.4].

Whole body conjugate planar image data, and abdominal SPECT/CT images for the 29 patients who received ^{177}Lu-PSMA-617 were obtained at approximately 1-2 h, 18-26 h, 36-48 h, and 156-168 h post injection/infusion. Regions of Interest / Volume of Interest (ROI/VOIs) were constructed on the SPECT images for kidneys, liver, and spleen. ROIs were constructed on the

whole body conjugate planar images for brain, GI, heart, kidneys, lacrimal glands, liver, lungs, salivary glands, image reference standard, thyroid, and whole body. Patient specific organ volumes for kidneys, liver, and spleen were measured from the Computed Tomography (CT) image. ROI count statistics were quantified to determine bio-kinetic (time-activity) data in the organs and tissues. Red marrow activity was estimated based on assay of blood samples. Kinetic data were modeled to determine normalized number of disintegrations. Normalized number of disintegrations were used with the RADAR/Medical Internal Radiation Dose (MIRD) method for internal dosimetry as implemented in the FDA cleared OLINDA (Organ Level INternal Dose Assessment) software to produce radiation exposure estimates. The human alimentary model, and urinary voiding bladder model (with a voiding interval of 3.5 h) as implemented in OLINDA were utilized. Since lacrimal gland dosimetry is not included in OLINDA, dosimetry estimates for lacrimal glands were based on S-values taken from spheres for self-dose only.

The results and summary statistics of the absorbed dose per organ and whole body after the first dose (Cycle 1) are shown in Table 2-1. On average, the organs receiving the largest absorbed doses were the lacrimal glands at 2.1 (SD=0.47) Gy/GBq followed by the salivary glands at 0.63 (SD=0.36) Gy/GBq.

For a full six cycle cumulative administration of 44.4 GBq, the calculated estimated absorbed dose for lacrimal glands and salivary glands were 92 (SD=21) Gy and 28 (SD=16) Gy, respectively [Study PSMA-617-01 Appendix 16.2.9.4-Table 4]. Red marrow received an absorbed dose of 0.035 (SD=0.020) Gy/GBq, with a full six cycle calculated estimated absorbed dose of 1.5 (SD=0.90) Gy. On average, the kidneys received 0.43 (SD=0.16) Gy/GBq, which for a full six cycle cumulative administration of 44.4 GBq, results in a calculated estimated absorbed dose to the kidneys of 19 (SD=7.3) Gy.

Table 2-1 Dose Estimates Summary Statistics (Gy/GBq) (n=29)

	Mean	Min	Max	SD	%SD
Adrenals	0.033	0.016	0.15	0.025	78%
Brain	0.007	0.002	0.025	0.0050	75%
Esophagus	0.025	0.010	0.15	0.026	104%
Eyes	0.022	0.009	0.14	0.024	111%
Gallbladder Wall	0.028	0.013	0.15	0.026	93%
Left colon	0.58	0.33	1.0	0.14	24%
Small Intestine	0.071	0.043	0.22	0.031	44%
Stomach Wall	0.025	0.011	0.15	0.026	103%
Right colon	0.32	0.18	0.60	0.078	25%
Rectum	0.56	0.32	1.1	0.14	26%
Heart Wall	0.17	0.032	0.52	0.12	68%
Kidneys	0.43	0.22	0.83	0.16	38%
Lacrimal Glands	2.1	1.2	3.2	0.47	23%
Liver	0.090	0.043	0.22	0.044	50%
Lungs	0.11	0.030	0.57	0.11	106%
Pancreas	0.027	0.012	0.15	0.026	97%

	Mean	Min	Max	SD	%SD
Prostate	0.027	0.013	0.15	0.026	96%
Salivary Glands	0.63	0.22	1.5	0.36	58%
Red Marrow	0.035	0.020	0.13	0.020	59%
Osteogenic Cells	0.036	0.020	0.17	0.028	80%
Spleen	0.067	0.031	0.14	0.027	41%
Testes	0.023	0.010	0.14	0.025	111%
Thymus	0.025	0.010	0.15	0.026	106%
Thyroid	0.26	0.085	1.69	0.37	145%
Urinary Bladder Wall	0.32	0.29	0.43	0.025	7.9%
Total Body	0.037	0.019	0.17	0.027	73%

Source: [Study PSMA-617-01 Appendix 16.2.9.4-Table 3]

2.3.1.2 Pharmacokinetics

Blood samples for PK were collected before start of intravenous administration, end of injection/infusion (EOI), then 20 min (± 5 min), 60 min (± 5 min), 2hr (± 30 min), 4hr (± 30 min), 24hr (± 2 hr), 48hr (± 2 hr), 72hr (± 2 hr) and Day 6 (144 hr post-dose) post end of administration.

Whole blood pharmacokinetic parameters were estimated using Phoenix® WinNonlin 6.4 software (Certara, United States) using a non-compartmental approach (NCA) consistent with the intravenous route of administration. Blood concentration values from the pre-dose collection were used for time 0. Original whole blood concentrations were measured using a gamma counter and were received in radioactive units of KBq/mL. These units were converted to ng/mL for PK evaluation by decay corrected activity and Specific Activity of ^{177}Lu-PSMA-617 at time of administration [Study PSMA-617-01 Appendix 16.2.9.1].

Following an IV injection/infusion of ^{177}Lu-PSMA-617, time to peak whole blood concentrations (Tmax) ranged from 0.0167 to 1.68 hours, generally occurring within approximately 20 minutes after EOI, with median Tmax value of 0.375 hours. Whole blood concentrations followed a bi-exponential decline with a fast phase within the first 24-48 hrs and a slower phase up to 144 hrs, which resulted in a geometric mean (geometric mean CV%) terminal half-life of approximately 41.6 hr (68.8%) hours (Table 2-2). The geometric mean total systemic clearance (CL) was 2.04 L/hr (31.5%) and geometric mean apparent volume of distribution (Vz) was 123 L (78.1%).

Table 2-2 Summary ^{177}Lu-PSMA-617 PK Parameters (NCA)

Nominal Dose 7.4 GBq	Cmax (ng/mL)	Tmax (hr)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	T1/2 (hr)	CL (L/hr)	Vz (L)
Mean	7.22	NA	52.1	54.8	51.5	2.13	156
SD	3.60	NA	17.9	18.5	44.4	0.586	128
CV%	49.9	NA	34.3	33.8	86.3	27.5	82.1
Median	6.39	0.375	50.8	52.4	37.8	2.08	112
Min	3.40	0.0167	25.0	28.2	8.39	0.976	31.0

Nominal Dose 7.4 GBq	Cmax (ng/mL)	Tmax (hr)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	T1/2 (hr)	CL (L/hr)	Vz (L)
Max	19.4	1.68	117	118	228	3.34	635
Geometric Mean	6.58	0.266	49.7	52.3	41.6	2.04	123
Geometric Mean CV%	43.5	180	31.6	31.4	68.8	31.5	78.1

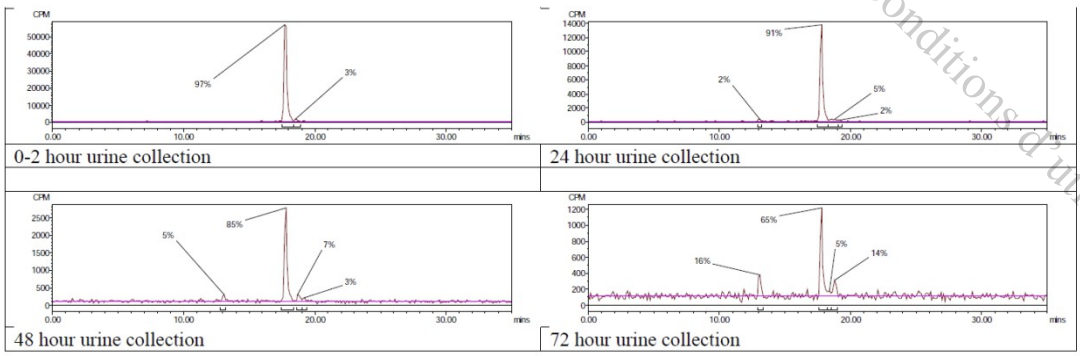
NCA: Non-Compartmental Analysis

Source: Modified based on [Study PSMA-617-01 Appendix 16.2.9.1-Table 1]

2.3.1.3 Assessment of urine metabolites

Cumulative whole urine samples were collected between the injection/infusion and the time of the first image (~2 hrs post-administration). Additional (non-cumulative) urine samples were collected from the patients at 24 hrs (± 2 hrs), 48 hrs (± 2hrs) and 72 hrs (± 2hrs). Samples were analyzed by radioHPLC using a validated method [SBP-Section 1.3], [Report 01360001] to qualitatively assess the presence or absence of excreted metabolites in urine. Because the urine collections were not cumulative, no assessment of ^{177}Lu-PSMA-617 concentration or recovery in urine was performed. Chromatograms for reference standard, blank matrix, and patient samples are located in [Study PSMA-617-01 Appendix 16.2.9.2-Figure 1 to Figure 32]. Radiochromatograms from all patients were generally similar in appearance, with sharp peaks and good resolution. Representative chromatograms of a single patient (Patient No. 293940-4656) are shown in Figure 2-1. Results were presented as a percentage of the total radioactivity in each sample, measured as the total counts of integrated peak areas in a sample. Increasing relative concentration over time did not indicate an increase in absolute urine concentration or recovery for each metabolite. The results for ^{177}Lu-PSMA-617 and potential metabolites in human urine samples are summarized in [Study PSMA-617-01 Appendix 16.2.9.2-Table 1]. Parent ^{177}Lu-PSMA-617 was detected in all samples containing radioactivity, the relative concentration in the 0 to 2 hours urine collection ranged from 91% to 100% of the radioactivity (with the exception of one patient). The relative concentration of radioactivity in each successive urine collection generally declined as the time post-dose increased. By 72 hours post-dose ^{177}Lu-PSMA-617 ranged between 49% and 100% of the total radioactivity.

Figure 2-1 Representative Urine Radiochromatograms



Source: [Study PSMA-617-01 Appendix 16.2.9.2-Figure 3]

A total of nine peaks (M1-M9) that may be associated with metabolites or chemical hydrolysis fragments were detected apart from parent, most of which only emerged at later time points. M1, M3, and M4 were the primary metabolites, and were detected in samples from all (M3) or most (M1, M4) patients. The retention time of M1 was significantly less (approximately 12 minutes) than the retention time of the ^{177}Lu-PSMA-617, indicating that M1 was more polar than the parent compound. The relative concentration of M1 generally increased at each successive time point, up to a maximum of 27% at 72 hours post-dose. M3 and M4 were part of a region of radioactivity eluting directly after the parent peak. M3 was present in the majority of the samples, comprising about 4% of the total radioactivity in the 0 to 2 hours collections, and up to 30% at 72 hours post-dose. M4 was generally below 10% of the total radioactivity, with a maximum contribution of 18% at 72 hours post-dose. Minor metabolites M5 and M8 were detected in 4 and 3 patients, respectively. M5 and M8 comprised ≤ 6% of the total radioactivity in any sample where they were detected. M2, M6, M7, and M9 were each detected in only a single patient (not the same individual). The structure of the metabolites have not been identified [Study PSMA-617-01 Appendix 16.2.9.2-Section 3].

Given that no metabolite was excreted in a significant amount in urine up to 48 hours, by which half of ^{177}Lu-PSMA-617 can be considered eliminated based on the determined geometric mean terminal elimination half-life of 41.6 hours (Section 2.3.1.2), it can be concluded that primarily unchanged parent is excreted in urine, and metabolites, which are renally excreted, exist in systemic circulation only in minor amounts that also don't accumulate over time. Metabolites emerging at 72 hr post-dose are likely metabolic or hydrolytic products that are present in such small amounts that they only emerge when the absolute radioactivity of the sample and parent become small. This is in line with the detected counts per minute of the primary metabolites, which remained in a similar range across time points [Study PSMA-617-01 Appendix 16.2.9.2-Table 2].

2.4 Published literature from pharmacokinetic, biodistribution and dosimetry studies in patients with prostate cancer

Various publications providing data related to the PK and biodistribution/dosimetry of ^{177}Lu-PSMA-617 in prostate cancer patients are available. Details of these publications are provided in Table 2-3 (overview), Table 5-1 (organ absorbed doses) and Table 3-1 (cumulative radiation exposure estimates after 6 cycles). The results are discussed in context with the dosimetry data of the Study PSMA-617-01 sub-study in Section 3.3.

The supportive pharmacokinetic and biodistribution/dosimetry information was collected from the available literature through June 2021, however the list of articles is not intended to be exhaustive or comprehensive, but is instead included to provide some background information which places the PSMA-617-01 sub-study results in context with historical values. The search for articles with potential supportive clinical pharmacology information regarding the use of ^{177}Lu-PSMA-617 were identified from the scientific literature database using PubMed. In the literature, ^{177}Lu-PSMA-617 may also be referred to as Lu-PSMA, ^{177}Lu-PSMA, ^{177}Lu-DKF-PSMA-617, ^{177}Lu-PSMA-DKFZ-617, Lu-177-DKFZ-PSMA-617, ^{177}Lu-labeled PSMA-617, [^{177}Lu]-PSMA-617, 177-Lu-DKFZ-617-PSMA, [^{177}Lu]-PSMA, and Lu-177-PSMA, therefore these names were used during the search. After screening based on study title and abstract, the

remaining articles were assessed based on full text review and excluded when appropriate. Only studies using ^{177}Lu-PSMA-617 were included.

In total, 7 articles evaluating the clinical pharmacology of ^{177}Lu-PSMA-617 in the setting of metastatic prostate cancer (PC) were suitable for inclusion as background information, as they contained relevant information on PK and biodistribution/dosimetry.

Specifically, two articles reported pharmacokinetic parameters based on radioactivity detection in blood when ^{177}Lu-PSMA-617 was administered in a total of 37 patients with PC (Kratochwil et al 2016, Kabasakal et al 2017). Biodistribution/dosimetry data is presented for 259 patients from 13 publications (Table 5-1).

Table 2-3 List of publications providing supportive pharmacokinetic and biodistribution/dosimetry data

Study/ Publication	Clinical pharmacology elements and patient population	No. of patients/Dose	Age (in years)	Results/Conclusion
Yadav et al (2017)	Assess the dosimetry of ^{177}Lu-PSMA-617 in mCRPC patients	26 / 1.11-5.50 GBq	38-81	Organs with the highest absorbed doses (mean ± SD) were the salivary glands, followed by the kidneys, receiving 1.24± 0.26 and 0.99 ± 0.31 mGy/MBq, respectively. The mean absorbed doses to the liver, urinary bladder and red marrow were 0.36 ±0.11, 0.234 ±0.09 and 0.048± 0.06 mGy/MBq, respectively. The mean whole-body dose was 0.016 ± 0.003 mGy/MBq.
Kratochwil et al (2016)	Assess the PK and dosimetry of ^{177}Lu-PSMA-617 in mCRPC patients	30 (4 patients for dosimetry)/ 3.7-6 GBq.	61-85	**PK:** The initial volume of distribution 1 hour after injection was 22 ±12 L, which approximates extracellular body water. Blood clearance could be fitted bi-exponentially with half-lives of 4 and 95 hours interpretable as fast clearance from extracellular body water and a slow clearance averaged from organs with specific uptake (including tumor tissue) assuming equilibrium between blood and the particular compartment, respectively. Approximately 50% of the injected activity was eliminated by urine during the first 48 h. Approximately 1%-5% of the injected dose was eliminated by fecal excretion. **Dosimetry:** The dosimetry analyses of 4 patients during their first and second treatment cycles revealed a mean (±SD) kidney dose of 0.75±0.19 Gy/GBq of ^{177}Lu-PSMA-617. The red marrow dose was 0.03 ±0.01, parotid 1.28±0.40, and submandibular gland 1.48±0.37 Gy/GBq. There was no relevant difference in dosimetry for the patients with low or high tumor load. In addition, there was no relevant difference in the kidney and red marrow dose between the first and second treatment cycle.
Kabasakal et al (2017)	Assess the in vivo and in vitro stability, PK, and dosimetry of ^{177}Lu-PSMA-617 in mCRPC patients	7 / 3.6-7.4 GBq	66-82	**PK:** Blood time activity curve showed a rapid bi-exponential clearance. Half-life of the distribution phase was calculated to be 0.16±0.09 hours and the half-life of elimination phase was calculated to be 10.8±2.5 hours. Mean total body residence time was 37.5±7.5 hours with wide inter-patient variability (23.1 hours to 44.0 hours). Almost half of the injected amount of radiopharmaceutical (56.5±8.8%, range 41.5% - 65.4%) was excreted within 24 hours. RP-HPLC analyses of the blood and urine samples showed a single radioactivity peak corresponding to ^{177}Lu-PSMA-617 even

Study/ Publication	Clinical pharmacology elements and patient population	No. of patients/Dose	Age (in years)	Results/Conclusion
				at 24 hours after injection. There was no other peak corresponding to metabolized ^{177}Lu-PSMA-617. **Dosimetry:** ^{177}Lu-PSMA-617 is a highly stable compound both in vitro and in vivo. The highest estimated radiation doses were calculated for the parotid glands (1.90±1.19 Gy/GBq) and kidneys (0.82±0.25 Gy/GBq). The calculated radiation dose to the bone marrow was 0.030±0.008 Gy/GBq
Delker et al (2016)	Assess the dosimetry of ^{177}Lu-PSMA-617 in mCRPC patients	5 / 3.4-3.9 GBq	54-81	The average (±SD) absorbed doses for the kidneys was 0.6 (±0.2) Gy/GBq), 1.4 (±0.5) Gy/GBq for the salivary glands, 0.1 (±0.06) Gy/GBq for the liver, 0.1 (±0.03) Gy/GBq for the spleen, and 0.012 (±0.005) Gy/GBq for the bone marrow. The organ absorbed doses did not differ significantly between cycles.
Scarpa et al (2017)	Assess the dosimetry of ^{177}Lu-PSMA-617 in mCRPC patients	10 / 5.4-6.5 GBq	56-82	^{177}Lu-PSMA-617 dosimetry indicated mean absorbed doses for the kidneys as 0.600 Gy/GBq, red bone marrow 0.042 Gy/GBq
Maffey-Steffan et al (2020)	Assess the dosimetry of ^{177}Lu-PSMA-617 in mCRPC patients	32 / 6 GBq	50-91	^{177}Lu-PSMA-617 dosimetry indicated mean absorbed doses for the kidneys as 0.771 Gy/GBq, red bone marrow 0.039 Gy/GBq.
Kamaldeep et al (2021)	Assess the dosimetry of indigenous 177Lu-PSMA-617 in mCRPC patients	30 / 4.44-5.55 GBq	49-79	The highest absorbed organ dose was observed in lacrimal glands and being a dose limiting organ, a cumulative activity up to 32.5 GBq (878 mCi) of ^{177}Lu-PSMA-617 in 4-5 therapy cycles appears safe and feasible to achieve full therapeutic window.
Hohberg et al (2016)	Assess the dosimetry of ^{177}Lu-PSMA-617 in metastatic prostate cancer patients	9 / 5.28 to 5.77 GBq	60-74	The mean absorbed doses were 2.82 Gy/GBq for the lacrimal glands, 0.72 Gy/GBq for the salivary glands, 0.53 Gy/GBq for the kidneys, and 0.42 Gy/GBq for the nasal mucous membrane. Based on routinely applied radiation thresholds, the lacrimal glands may represent the dose-limiting organs. Whole-body scintigraphy appears sufficient for dose estimation, but late measurements are mandatory, if accurate dose calculation is required.
Mix et al (2021)*	Assess the dosimetry of ^{177}Lu-PSMA-617 in prostate cancer patients	59 / 6 GBq (median dose)	NR	The average kidney dose per administered activity of all 176 cycles was 0.67 ± 0.24 Gy/GBq (range 0.21 - 1.60). Pretherapeutic renal function was not predictive for subsequent kidney dose during therapy. Extrapolation of individual data from dosimetry of the first cycle was highly predictive for the cumulative kidney dose at the end of treatment.

Study/ Publication	Clinical pharmacology elements and patient population	No. of patients/Dose	Age (in years)	Results/Conclusion
Violet et al (2019)	Assess the dosimetry of ^{177}Lu-PSMA-617 in mCRPC patients	30 / 5.7-8.7 GBq	67-75	Mean absorbed dose to kidneys, submandibular and parotid glands, liver, spleen, and bone marrow was 0.39, 0.44, 0.58, 0.1, 0.06, and 0.11 Gy/MBq, respectively. ^{177}Lu-PSMA-617 delivers high absorbed doses to tumor, with a significant correlation between whole-body tumor dose and PSA response. Patients receiving less than 10 Gy were unlikely to achieve a fall in PSA of at least 50%. Reduced salivary and kidney doses were observed in patients with a higher tumor burden. The parotid dose also reduced with increasing body mass and body surface area.
Rosar et al (2021)	Assess the dosimetry of ^{177}Lu-PSMA-617 in mCRPC patients	24 / 3-10.9 GBq	61-88	Mean absorbed doses estimated by SPECT 3D dosimetry were 0.54 ± 0.28 Gy/GBq for the kidneys, 0.10 ± 0.05 Gy/GBq for the liver, 0.81 ± 0.34 Gy/GBq for the parotid gland, 0.72 ± 0.39 Gy/GBq for the submandibular gland, and 1.68 ± 1.32 Gy/GBq for bone metastases. Absorbed doses of normal organs estimated by hybrid dosimetry showed small, non-significant differences (median up to 4.0%) to the results of 3D dosimetry. Using 2D dosimetry, in contrast, significant differences (median up to 10.9%) were observed.
Paganelli et al (2020)	Assess the dosimetry of ^{177}Lu-PSMA-617 in mCRPC patients	13 / 3.7-5.5 GBq	66-77	In advanced, heavily pre-treated mCRPC patients the median absorbed doses were 0.65 Gy/GBq (range 0.33-2.63) for parotid glands, 0.42 Gy/GBq (0.14-0.81) for kidneys, 0.036 Gy/GBq (0.023-0.067) for red marrow, and 0.038 Gy/GBq (0.018-0.135) for the whole body. 3.7 GBq/cycle of ^{177}Lu-PSMA-617 was safe and produced early biochemical and imaging responses at PSMA whole-body scan post injection. Dosimetry of salivary glands suggests that the coadministration of polyglutamate tablets may reduce salivary gland uptake.
Prive et al (2021)	Assess the dosimetry of ^{177}Lu-PSMA-617 in patients with metastatic hormone-sensitive prostate cancer	10 / 3-6 GBq	61-77	^{177}Lu-PSMA appeared to be a feasible and safe treatment modality in patients with metastatic hormone-sensitive prostate cancer.

*: Based on abstract only as full text was not available at the time of submission

3 Comparison and Analysis of Results Across Studies

3.1 Pharmacokinetics in Human

3.1.1 Single dose Blood-Radioactivity PK of ^{177}Lu-PSMA-617

The PK of ^{177}Lu-PSMA-617 has been characterized in the PSMA-617-01 sub-study (Section 2.3.1.2). Following an IV injection/infusion, whole blood concentrations followed a bi-exponential decline with a fast phase within the first 24-48 hrs and a slower phase up to 144 hrs, which resulted in a geometric mean (geometric mean %CV) terminal half-life of approximately 41.6 (68.8%) hours (Table 2-2). Time to peak whole blood concentrations ranged from 0.0167 to 1.68 hours (median 0.375 hr), due to high variability of the injection/infusion times. The geometric mean total systemic clearance (CL) was 2.04 L/hr (31.5%) and geometric mean apparent volume of distribution (Vz) was 123 L (78.1%).

Population PK analysis, that was conducted based on the blood-radioactivity PK, described the data best with a three-compartment model including a delayed zero-order absorption and linear elimination. CL in a typical subject (with normal CLcr and weight) was estimated to be 2.50 L/hr (CV%=22%), similar to NCA (Section 3.2). As ^{177}Lu-PSMA-617 is not metabolized (Section 3.1.4) and excreted primarily through the kidneys unchanged, blood radioactivity derived PK parameter reflect the PK of ^{177}Lu-PSMA-617. Since the estimated total mean pharmacokinetic clearance is in the range of a passive renal clearance of 1.6-2.16 L/hr (assuming a glomerular filtration rate of 90-120 ml/min and a fraction unbound of 0.3 based on protein binding results, Section 3.1.3), total and renal clearance are likely exchangeable.

Overall, PK results are in line with findings from literature describing the pharmacokinetic (PK) behavior of ^{177}Lu-PSMA-617 in blood (Kratochwil et al 2016, Kabasakal et al 2017). According to Kratochwil et al (2016), the PK of ^{177}Lu- PSMA-617 after intravenous (iv) infusion showed a bi-exponential behavior with half-lives of 4 hours and 95 hours, indicative of a fast clearance from extracellular body water and a slow clearance from organs with specific uptake (including tumor tissue). A rapid bi-exponential clearance with a $T1/2\alpha$ of 0.16 ± 0.09 hours and a $T1/2\ \beta$ of 10.8 ± 2.5 hours was observed by Kabasakal et al (2017).

Based on the terminal elimination half-life of 41.6 h determined in the PSMA-617-01 sub-study, and the physical half-life of Lu-177 of ~160 hours, the resulting effective half-life of ^{177}Lu-PSMA-617 is ~33 hours, calculated as per the following equation,

$$1/t_{eff} = 1/t_{elim} + 1/t_{decay}$$

where t_{eff} = effective half-life, t_{elim} = elimination half-life and t_{decay} = decay half-life.

3.1.2 Absorption

As the drug is administered intravenously, the bioavailability is 100% and no food effect would be anticipated. Hence, no biopharmaceutic studies have been carried out with 177Lu-PSMA-617 (see [SBP] for more details).

3.1.3 Distribution and protein binding

Unlabeled PSMA-617 and non-radioactive ^{175}Lu-PSMA-617 were moderately bound to human plasma proteins following incubation for 30 minutes at 37°C. The bound fraction observed in human plasma for both PSMA-617 and ^{175}Lu-PSMA-617 was 70% and ~60% at 1 and 5 µg/mL, respectively [Report 0597]. Additionally, the blood/plasma partitioning ratio of both PSMA-617 and ^{175}Lu-PSMA-617 in human blood was <1, indicating that ^{175}Lu-PSMA-617 was not distributed to human erythrocytes [Report Q20_046]. These results are translatable as well to 177Lu-PSMA-617 for the purpose of drawing conclusions.

3.1.4 Metabolism

Results from in vitro metabolism studies showed that both unlabeled PSMA-617 and non-radioactive ^{175}Lu-PSMA-617 were metabolically stable in human liver and kidney S9 fractions for up to 1 hour at 37°C [Report 0590], [Report 0591], and in human plasma at 37°C for up to 2 hours [Report 0594]. ^{177}Lu-PSMA-617 demonstrated metabolic stability in vivo, as analyses of blood and urine samples showed a single radioactivity peak even at 24 hours after injection/infusion (Kabasakal et al 2017), in line with findings from the PSMA-617-01 sub-study metabolite analysis in urine (Section 2.3.1.3) showing no major excretion of metabolites up to 48 hrs.

As only a very minor fraction of radioactivity is eliminated in feces according to literature (Section 3.1.5) it can be concluded that ^{177}Lu-PSMA-617 is not metabolized in vivo in systemic circulation, in the liver or in the kidneys.

3.1.5 Excretion

The excretion of ^{177}Lu-PSMA-617 occurs primarily through kidneys, and it is eliminated in the urine as an intact molecule (Kabasakal et al 2017, Section 2.3.1.2). Approximately half of the injected amount of ^{177}Lu-PSMA-617 was excreted within 24-48 hours (Kratochwil et al 2016, Kabasakal et al 2017), in line with derived geometric mean terminal elimination half-life of 41.6 hrs. According to Kratochwil et al (2016) only an estimated 1%–5% of the injected dose was eliminated by fecal excretion.

3.2 Population PK analysis

A population PK (popPK) model has been developed applying the non-linear mixed effects (NLME) modeling approach implemented in MonolixSuite2020R1 (Lixoft, Paris, France) [^{177}Lu-PSMA-617 Modeling Report-Section 7.1]. A three-compartment model with a delayed zero-order absorption and linear elimination adequately described the radioactivity-blood PK of decay-corrected ^{177}Lu-PSMA-617. All parameters were estimated with reasonable precision, and the diagnostic plots suggested a good description and prediction of the data.

Baseline $CLcr_{BL}$ had a statistically significant impact on clearance (CL), with a decrease of $CLcr_{BL}$ by 40%, such as a decrease from 101.5 mL/min to 60.9 mL/min, leading to an average decrease of CL by 21%.

Baseline weight (WT_{BL}) also had a statistically significant impact on the central volume of distribution (V_1), with a decrease of WT_{BL} by 23%, such as a decrease from 88.5 kg to 68.1 kg, leading to an average decrease of V_1 by 18%.

For a typical subject (with $CLcr_{BL}$=101.5 mL/min and WT_{BL}=88.5 kg), CL was estimated to be 2.50 L.h^{-1}. Volume of distribution from the three compartments, V_1, V_2 and V_3, were estimated at 11.53 L, 29.34 L and 11.51 L, respectively. The inter-compartmental clearance, Q_2 and Q_3, were estimated at 0.52 L.h^{-1} and 12.00 L.h^{-1}, respectively. Variabilities on Cl and V_1 were moderate (CV% = 22% and 42% respectively), while variabilities on Q_2 and V_2 were estimated at relatively high values (CV% = 80% and 93% respectively). An artificial delayed absorption was introduced in the structural model to reproduce the infusion. The delay (Tlag) and the duration of the artificial absorption (Tk0) were estimated at 0.01 h and 0.06 h with high variability (CV% = 291% and 264% respectively). The residual proportional error of the model was estimated at a low value (13.96%).

3.3 Dosimetry and Biodistribution

The dose utilized in the pivotal study, Study PSMA-617-01, was 7.4 GBq ^{177}Lu-PSMA-617 administered once every 6 weeks (Q6W) for a maximum of 6 cycles, with a maximum cumulative dose of 44.4 GBq. The dose was not adjusted based on body weight or body surface area, as for a targeted radioligand therapeutic that is specifically sequestered by tumor tissues overexpressing the target, a standard "dose/body weight" approach could potentially lead to under treatment in those patients that are in the low body weight range but have high tumor burden.

3.3.1 Rationale for the proposed dose and schedule

Prior to the conduct of PSMA-617-01 including the sub-study, where dosimetry data was collected in 29 of the enrolled 30 patients, the selection of the ^{177}Lu-PSMA-617 dose and administration schedule was based on published clinical studies characterizing the safety and efficacy experience with ^{177}Lu-PSMA-617. Further, published radiation dosimetry studies, and a consideration of EBRT dose thresholds in organs at risk, provided some general guidance applied to cumulative radiation exposures. Lastly, experience with the approved ^{177}Lu-radioligand therapeutic Lutathera® has provided class-based information.

The determination of the dose regimen was guided by efficacy and safety considerations, with an accounting for the life-threatening nature of the disease. The selected dose of 7.4 GBq Q6W was intended to maximize the probability of efficacy, while maintaining safety parameters which are appropriate for the patient population.

The efficacy and safety of ^{177}Lu-PSMA-617+BSC/BSoC are described in the [SCE] and [SCS] respectively. Sub-group efficacy analysis favored 5-6 cycles compared to 4 cycles only [SCE-Section 4.2]. In addition, individual patient safety and tolerability was well-tolerated and manageable after 6 cycles [SCS-Section 7]. The positive benefit-risk ratio in Study PSMA-617-01 confirmed the appropriateness of this 7.4 GBq dose and schedule, up to a cumulative dose of 44.4 GBq in this advanced cancer population of patients with mCRPC.

The body of evidence supporting the selected dose and regimen are summarized in detail below.

3.3.1.1 Evaluation of dose and schedule range from published clinical experience

The dose selection for ^{177}Lu-PSMA-617 in Study PSMA-617-01 was supported by the published clinical experience with this agent, documented in 24 publications from over 500 patients. Across these publications, doses ranged from 2.0-9.3 GBq/cycle, and schedules typically followed an administration schedule of once every 4 to 12 weeks, for 1-8 cycles. Although the German Society of Nuclear Medicine recommended a 6.0 GBq dose every 8 weeks for a maximum of 3 cycles (von Eyben et al 2018), the majority of these publications have used a regimen of 4 cycles of 6 GBq every 8 weeks. The efficacy and safety information from the prospective Phase II (LuPSMA) study suggested that dosing of 6-8 GBq every 6 weeks for 4 cycles was well tolerated and efficacious, and this data was a core consideration during the protocol design for PSMA-617-01 (Hofman et al 2017). However, there were also reports of more than 4 cycles of ^{177}Lu-PSMA-617 being administered safely as a means to maximize the benefit to the patient (Rahbar et al 2018), therefore the 2 additional cycles were incorporated into the protocol when confirmation of benefit and tolerability was made following the 4th cycle.

At the time of protocol development in 2017-2018 there were 4 publications of interest reporting the efficacy and safety of ^{177}Lu-PSMA-617 (Rahbar et al 2017, Demirci et al 2017, Rahbar 2018, Hofman et al 2018), however this list now contains additional publications summarizing the investigational use of ^{177}Lu-PSMA-617 in mCRPC patient populations with differing prior therapies and concomitant medications (Kim et al 2018, von Eyben et al 2018, Yadav et al 2019, Violet et al 2020, Hofman et al 2021, Sadaghiani et al 2021). These publications represent data from retrospective and prospective Phase 1, Phase 2 and dosimetry trials under country's local regulations using multiple sources of the PSMA-617 precursor and Lu-177 with different preparation processes for ^{177}Lu-PSMA-617. Despite these varying conditions, the literature suggests low toxicity and encouraging biochemical and radiographic response rates, overall survival and reduced pain using ^{177}Lu-PSMA-617 RLT in patients with mCRPC (Rahbar et al 2017, Hofman et al 2018, Kim et al 2018, von Eyben et al 2018, Yadav et al 2019, Violet et al 2020, Hofman et al 2021, Sadaghiani et al 2021). Across these publications, doses have ranged from 1.1-12.0 GBq/cycle, administered once every 4 to 12 weeks, for between 1-9 cycles (Yadav et al 2020, Kulkarni et al 2018b, Grubmüller et al 2019, Sarnelli et al 2019). Clinical studies also showed that more than 4 cycles of ^{177}Lu-PSMA-617 could be administered safely as a means to maximize the benefit to the patient at the time of protocol development, and has since been confirmed in publications from studies concurrent with the PSMA-617-01 study (Bräuer et al 2017, Yordanova et al 2017, Kulkarni et al 2018a, Kulkarni et al 2018b, Kulkarni et al 2018c, Rahbar et al 2018, Van Kalmthout et al 2019, Crumbaker et al 2020, Maffey-Steffan et al 2020, Paganelli et al 2020, Yadav et al 2020, Ahmadzadehfar et al 2021, Hofman et al 2021). In the TheraP (ANZUP1603) study in 200 Australian patients, that compared ^{177}Lu-PSMA-617 against cabazitaxel, the starting dose was 8.5 GBq ^{177}Lu-PSMA-617 and reduced by 0.5 GBq per cycle, i.e. 8.5, 8, 7.5, 7, 6.5, and 6. Importantly, the final efficacy and safety information from this randomized Phase 2 study demonstrated that this dosing of 6 cycles, for a total cumulative dose of up to 43.5 GBq, was well tolerated and efficacious (Hofman et al 2021).

3.3.1.2 Dosimetry and radiation safety considerations

Characterizing the multi-organ radiation exposure profile is a hallmark of RLT development in that it allows for a qualitative and quantitative estimation of the potential for normal tissue toxicities. This can be especially important in the early phase of development where little safety information is available, and where multi-cycle extrapolations can be helpful in guiding dose levels, timing, and cycle number selection. The reason dose estimate extrapolations have received attention is related to the potential timing of radiologic toxicities, which are not all acutely observed and may be delayed. Thus, unlike other treatment modalities where quantitative tissue distribution is unknown, the absorbed radiation dose estimates (dosimetry) for an RLT can provide tissue-level information which can be helpful when predicting safety and tolerability beyond a single cycle.

At present, the absorbed radiation dose thresholds for different organ systems have not been completely defined for RLTs, as existing thresholds are historically based on EBRT. The radiation dose administered during EBRT is frequently limited by the risk of long-term toxicities to adjacent organs as a consequence of treatment with high dose rate radiation, and these limits for EBRT have been estimated and published in the literature (Emami et al 1991, Dawson et al 2010, Marks et al 2010, Emami 2013). However, the application of these EBRT limits to RLT is likely too conservative due to the intrinsic differences between external and systemic radiotherapy. This includes different dose rates and fractionation schemes, an inhomogeneous absorbed dose distribution and potentially different radiobiological mechanisms of cytotoxicity resulting in varying biological effect (Wessels et al 2008, Bergsma et al 2016a). With this in mind, the application of these EBRT radiation thresholds serves mainly as a guide for RLT dose selection, as opposed to being restrictive limits, due to the differences between the radiation treatment modalities. Furthermore, the impact of predictive extrapolations relative to late developing toxicities has been considered within the context of the advanced nature of mCRPC in patients with few treatment options.

At the time of protocol development, 11 dosimetry studies in over 100 patients had been conducted and published. The results were consistent across the studies, and demonstrated exposure that correlated well with the expected rapid clearance of a small molecule, and the limited distribution pattern of a PSMA-targeted RLT. As summarized in Table 5-1, the primary sites of non-tumor uptake were the salivary glands, lacrimal glands, and kidneys, with excretory mechanisms, and PSMA expression in the proximal tubules, contributing to exposure in the kidneys. Approximately 50% of the injected dose was shown to be excreted into the urine within the first 48 hours. Normal bone marrow, although PSMA-negative, can be exposed transiently to ^{177}Lu-PSMA-617 while in circulation, or through proximal exposure from the uptake in neighboring PSMA-positive PC bone lesions, a common site of metastasis.

When determining the proposed dose in Study PSMA-617-01, a more specific consideration of cumulative radiation exposure in these tissues was considered as it related to multi-cycle treatment with ^{177}Lu-PSMA-617.

Kidneys

Kidneys represent the classic organ of interest with regard to dose-limiting radiation exposure for many radioligand therapies, including ^{177}Lu-PSMA-617, where a range of mean radiation

absorbed doses between 0.39 ± 0.15 Gy/GBq and 0.991 ± 0.312 Gy/GBq were observed in different studies (Table 5-1). One reason for the interest in renal radiation exposure is that the kidneys are the main route of excretion for ^{177}Lu-PSMA-617, and PSMA is expressed in the proximal tubule so renal exposure is expected. The second reason is that the onset of the toxic response to radiation exposure in the kidneys may not present in the acute setting, but appear as a delayed response. The reported EBRT threshold for bilateral whole-kidney external-beam irradiation is 23 Gy, when the radiation was delivered over 5 weeks (Emami et al 1991, Emami 2013). This 23 Gy limit is postulated as yielding symptoms of radiation nephritis in 5% of the population within 5 years (TD5/5). The TD5/5 was reduced to just 10 Gy if all radiation was delivered within 2 h, demonstrating that dose rate is a critical factor. This is one of many distinctions when comparing RLT with external beam radiotherapy, as RLT with 177Lu-PSMA-617 is an example of extreme fractionation with a 6 week recovery period between doses. It has been suggested that the EBRT limits are too conservative for RLT due to this fractionated nature of RLT treatment (Wessels et al 2008, Bergsma et al 2016a). This was a consideration made during the implementation of a 6 cycle regimen with a 6 week recovery period between cycles, as patients with kidney radiation exposures within the range reported in the literature could potentially exceed this 23 Gy EBRT threshold cumulatively with a 7.4 GBq dose of 177Lu-PSMA-617 over the 6 cycles. Additionally, the 23 Gy TD5/5 was considered somewhat overly conservative of a threshold for a mCRPC patient population at high risk of death from their disease, and with limited overall survival, where a 5% chance of developing symptoms of radiation nephritis within 5 years would be placed into a different benefit-risk context. Importantly, the development of Lutathera involved similar discussions regarding dose and number of cycles relative to kidney exposure due to its similar distribution profile to this organ system. In the NETTER-1 Phase 3 study, a kidney absorbed radiation dose of 19.4 ±8.7 Gy (after 4 cycles of 7.4 GBq Q8W with 29.6 GBq cumulative activity) was found to be tolerable from a renal toxicity standpoint (Lutathera USPI 2020, Lutathera® SmPC 2021).

Salivary Glands

With regard to the salivary glands, the recommended cumulative thresholds that are used for ERBT for exposure to the parotid and submandibular glands are 24-26 Gy and 39 Gy, respectively (Grundmann et al 2009). These thresholds are supported by acute and long-term safety data for this external beam treatment modality, however the threshold for RLT, including ^{177}Lu-PSMA-617, has not been determined. The range of mean radiation absorbed doses in salivary glands, also reported as either submandibular or parotid glands in different studies, were between 0.39 ± 0.17 Gy/GBq and 1.90 ± 1.19 Gy/GBq (Table 5-1), indicating a high variability of the data. Based on this reported range, 6 cycles of 7.4 GBq, Q6W would potentially result in salivary gland exposure which would exceed the EBRT threshold, and therefore dry mouth was monitored in the PSMA-617-01 trial.

Red Marrow

Range of mean radiation absorbed doses in red marrow reported from different studies were between 0.012 ± 0.00524 Gy/GBq and 0.11 ± 0.10 Gy/GBq (Table 5-1). The radiation absorbed dose limit that is commonly referred to for red marrow is 2 Gy which has been defined based on radioactive iodine therapy (I-131) for thyroid carcinoma (Howard et al 2017). As with the

EBRT-defined radiation absorbed dose thresholds for kidney and salivary glands, this red marrow radiation exposure limit is also considered somewhat conservative in the context of RLT (Bergsma et al 2016b) (Table 3-1). As reported by Bergsma et al 2016b, the clinical experience with Lutathera indicates that a higher bone marrow radiation absorbed dose limit could be appropriate for RLT. The authors reported that clinical risk factors were found to be the most important parameters for prediction of clinical hematological toxicity. Patients with impaired renal function at baseline, low WBC count, extensive tumour mass, and/or those of advanced age were found to be more likely to develop grade 3 or 4 haematological toxicity. The risk of hematological toxicity in patients with mCRPC is greatest in those who have been heavily pre-treated and/or have extensive red marrow involvement with their disease. The hematological toxicities were therefore closely monitored in Study PSMA-617-01.

While both salivary glands and bone marrow were considered as dose-limiting and accounted for in the dose selection rationale for Study PSMA-617-01, they were considered secondary to the kidney with regard to extrapolation of the cumulative radiation exposure. The more acute nature of the possible adverse effects in these tissues (salivary glands and red marrow) allows for an assessment to be done between the treatment cycles and a dose modifying toxicity scheme may be applied during the treatment, if needed.

Lacrimal Glands

Radiation exposure of ^{177}Lu-PSMA-617 to the lacrimal glands has only been reported in some studies in the literature, with a wide range of values and high uncertainties in determining absolute radiation exposures as described in Section 3.3.2. However, lacrimal gland radiation exposure limits have not routinely been considered in the literature when applying dosing parameters to treatment with ^{177}Lu-PSMA-617, and while not considered a dose-limiting organ with regard to dose selection, this tissue was monitored closely during the conduct of Study PSMA-617-01 to assess the risk of toxicities.

3.3.1.3 Class-based evidence (Lutathera)

Lutathera was the first approved peptide-based ^{177}Lu-radioligand therapeutic, and utilizes a dose of 7.4 GBq every 8 weeks for a total of 4 cycles, although other doses and schedules have been evaluated in the literature. The published experience with Lutathera informed much of the early development work that has been done with ^{177}Lu-PSMA-617. Considering Lutathera as a comparator is particularly relevant, as the kidney dosimetry profile for both agents is similar, due to the renal clearance of both agents, as well as their target expression on the renal proximal tubules. In the pivotal Phase 3 NETTER-1 study, in which patients with advanced progressive midgut neuroendocrine tumors were treated with Lutathera, no Grade 3/4 renal toxicity with a 19.4 ± 8.7 Gy cumulative kidney absorbed radiation dose was observed (Lutathera® USPI 2020, Lutathera® SmPC 2021). A small number of patients received kidney doses greater than 28 Gy and none developed Grade 3/4 renal toxicity or had annual reduction in CLcr greater than 10%. Based on the extensive clinical experience with ^{177}Lu-radioligand therapeutic Lutathera, the kidney absorbed radiation dose thresholds in RLT were suggested to be higher than the EBRT threshold for kidneys suggested by several authors (Bergsma et al 2016a, Wessels et al 2008).

3.3.1.4 Summary

Based on these data, and with the intention of delivering the highest possible dose to the tumor for an effective antitumor effect in the selected patient population, a dose of 7.4 GBq ^{177}Lu-PSMA-617 administered once every 6 weeks for a maximum of 6 cycles was selected for Study PSMA-617-01, for a maximum cumulative dose of 44.4 GBq. After 4 cycles of treatment, patients were required to meet additional criteria (including evidence of response, signs of residual disease, and good tolerance of ^{177}Lu-PSMA-617) and agree to continue treatment with ^{177}Lu-PSMA-617 before the Investigator could administer 2 additional cycles [Study PSMA-617-01-Section 9.1].

The 7.4 GBq ± 10% dose range is set as a result of technical steps and practical consideration for the purpose of supplying the patients with a predefined, ready-to-use radioactive dose at administration time. A 5% range is applied to the volumetric activity of the solution at calibration time (1000 MBq/mL ± 5%) in accordance with the requirements of the Guideline of Radiopharmaceuticals (EMA 2008). In consideration of the variability associated with the vial filling step and the start time of treatment at the hospital including transportation time, a ±10% variability in the dose range for each individual dose is determined to account for the precision on volumetric adjustment and time of administration of the finished product [Module 3.2.P.1-Description and Composition of the Drug Product].

Dosimetry data from 29 patients from the PSMA-617-01 sub-study is available (and discussed in Section 3.3.2) and supports the use of the selected dose of 7.4 GBq Q6W over 6 cycles from a radiation exposure perspective, in addition to the PSMA-617-01 main study confirming efficacy and tolerability of the selected 7.4 GBq Q6W dose and schedule for a total of 6 doses.

3.3.2 Dosimetry in PSMA-617-01 - Sub-study

Dosimetry estimates for ^{177}Lu-PSMA-617 were determined based on bio-distribution found using whole body conjugate planar image data, SPECT-CT image data, blood assay data, and urinary excret-ion data collected in 29 of the 30 enrolled patients (Section 2.3.1.1). The results for all tissues and organs are shown in Table 2-1.

Results of the image quantification and dosimetry were reasonably consistent across the patient population, showing varying degrees of variability depending on the organ. The radiation absorbed dose in the kidneys, salivary glands, lacrimal glands and red marrow were of particular interest as organs known for their PSMA-expression (such as the renal proximal tubules, lacrimal and salivary glands (Bostwick et al 1998, Ghosh and Heston 2004, Mannweiler et al 2009), as the major organ of elimination for ^{177}Lu-PSMA-617 (the kidneys, Section 3.1) or as tissues particularly at risk for radiation-related toxicities (e.g. myelosuppression).

Kidneys

In the kidneys, the mean radiation absorbed dose was 0.43 ± 0.16 Gy/GBq (Table 3-1). This is close but even lower than the lower end of the range of mean kidney radiation absorbed doses reported in the literature (0.39 - 0.991 Gy/GBq) (Table 5-1). Based on the dosimetry estimates determined from the first cycle data, for a cumulative activity administration of 44.4 GBq (6 cycles of 7.4 GBq Q6W), the calculated estimated mean kidney radiation absorbed dose is ~19 Gy ± 7.3 Gy. Based on these first cycle estimates, 21 of the 29 patients (72.4%) have cumulative

kidney radiation absorbed doses less than or approximately equal to 23 Gy assuming 6 cycles of treatment (and assuming no intra-subject variability) [Study PSMA-617-01- Appendix 16.2.9.4-Appendix C]. As discussed in Section 3.3.1.2, the 23 Gy radiation exposure threshold based on ERBT is likely overly conservative for the mCRPC patient population at high risk of death from their disease, and with limited overall survival, and potentially, overly conservative for RLTs in general.

In the PSMA-617-01 main-study, despite the broad search for renal effects (Standardized MedDRA Queries (SMQ) Acute Renal Failure), the search retrieved relevant renal events in only 8.7% of patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 5.9% in the BSC/BSoC only arm. The frequency of grade 3 renal AEs were similar between arms (3.4% vs. 2.9%) in the 177Lu-PSMA-617+BSC/BSoC arm and BSC/BSoC only arm, respectively, and there were no grade 4 or 5 renal events in either arm. The most frequent event terms in this renal category were Blood Creatinine Increased and Acute Kidney Injury, the latter appearing sometimes to be a synonym for increased creatinine [SCS-Section 2.1.5.1]. There was only one event of Renal Failure, occurring in the ^{177}Lu-PSMA-617+BSC/BSoC arm [Study PSMA-617-01-Table 12-21]. Hence, despite higher radiation exposures that may occur in the kidneys of patients treated with 177Lu-PSMA-617, renal toxicity was not an important safety concern in Study PSMA-617-01, predominantly low grade with the majority of creatinine increases that were reversible. Serious renal events were infrequent and less common in ^{177}Lu-PSMA-617+BSC/BSoC than in BSC/BSoC only arm (1.7% and 3.4%, respectively).

Table 3-1 Dose estimates for ^{177}Lu-PSMA-617 in selected normal tissues

PSMA-617-01 sub-study (All patients)	Mean ± SD absorbed dose (Gy/GBq) N=29	Mean ± SD calculated cumulative exposure (Gy) estimate after 6 cycles of 7.4 GBq	Reported radiation exposure threshold (Gy)
Kidneys	0.43 ± 0.16	19 ± 7.3	23[a]
Salivary glands	0.63 ± 0.36	28 ± 16	24-39[b]
Red marrow	0.035 ± 0.020	1.5 ± 0.90	2[c]
Lacrimal glands	2.1 ± 0.47	92 ± 21	40[d]

Source: [Study PSMA-617-01-Appendix 16.2.9.4 - Table 3]; [Study PSMA-617-01-Appendix 16.2.9.4-Table 4]

[a] Threshold based on EBRT (Emami et al 1991, Emami 2013, ICRP 2012).

[b] Threshold based on EBRT with the range listed for parotid and submandibular glands (Grundmann et al 2009)

[c] Threshold based on radioactive iodine therapy (I-131) for thyroid carcinoma (Howard et al 2017).

[d] Threshold based on EBRT Letschert et al (1991)

Salivary Glands

The mean radiation absorbed dose for ^{177}Lu-PSMA-617 in salivary glands was 0.63 ± 0.36 Gy/GBq, within the wide range of mean values (0.39 - 1.90 Gy/GBq) reported in the literature (Table 5-1). As can be seen in Table 3-1, the calculated estimated mean salivary gland radiation exposure following 6 cycles of 7.4 GBq Q6W is 28 ± 16 Gy, which is within the range of the ERBT threshold (24-39 Gy). It has been suggested that a ^{177}Lu-PSMA-617 total cumulative dose of as much as 50 GBq could be administered without long-term salivary gland toxicity, based on an absorbed dose range of 0.5–1.0 Gy/GBq (Virgolini et al 2018).

Safety-wise, treatment with ^{177}Lu-PSMA-617 has been associated with a frequent but relatively low severity of salivary gland toxicity (dry mouth / xerostomia) as reported in the literature (68% reversible grade 1/2 dry mouth in Hofman et al (2019). In concordance with this finding, incidence of dry mouth was 38.8% in the 177Lu-PSMA-617+BSC/BSoC arm (vs. 0.5% in the BSC/BSoC only arm) with no grade 3 or 4 adverse events and only one discontinuation of ^{177}Lu-PSMA-617 due to the toxicity in the PSMA-617-01 main-study [Study PSMA-617-01 -Table 14.3.2.13.2], [Study PSMA-617-01-Table 12-10].

Red Marrow

The mean absorbed radiation dose for ^{177}Lu-PSMA-617 was 0.035 ± 0.020 Gy/GBq, which equates to a calculated estimated mean radiation exposure of 1.5 ± 0.90 Gy for 6 cycles of 7.4 GBq Q6W. This cumulative radiation exposure estimate therefore is not in excess of the established radiation dose limit for ^{131}I of 2 Gy (Table 3-1). However, it is recognized that with the variability in red marrow uptake reported in the dosimetry literature, and as shown in the PSMA-617-01 sub-study, this radiation dose limit may be approached or exceeded in some cases.

While myelosuppression (including anemia, thrombocytopenia, lymphopenia, leukopenia) was more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm than in the BSC/BSoC only arm (47.4% vs. 17.6%) and led to withdrawal of ^{177}Lu-PSMA-617 in some patients (7.0%) [Study PSMA-617-01-Table 12-18], effects were usually transient or manageable, allowing continuation of treatment with supportive care and with only few delays in treatment cycles. The nature, rate and severity of theses hematological AEs in the long-term follow-up were similar to the background experience seen in the BSC/BSoC only arm during randomized treatment.

Lacrimal Glands

Radiation exposure to the lacrimal glands was notable in the PSMA-617-01 sub-study with a mean radiation absorbed dose of 2.1 ± 0.47 Gy/GBq (Table 3-1), but within the range (0.85 - 2.82 Gy/GBq) reported in literature, which was quite variable (Table 5-1). Cumulative estimated radiation exposure is calculated to be 92 ± 21 Gy, about 2-fold higher than the theoretical threshold associated with lacrimal gland toxicities following external beam radiotherapy (Letschert et al 1991). However, lacrimal gland radiation exposure limits have not routinely been considered when applying dosing parameters to treatment with ^{177}Lu-PSMA-617. Also, dosimetric assessments of lacrimal gland uptake can be challenging as described in [Study PSMA-617-01-Appendix 16.2.9.4-Section 4] due to the size of the organ, proximity to the body surface, and difficulties with the methodology, resulting in a high degree of uncertainty in estimating lacrimal dosimetry in particular (Hohberg et al 2016). However, despite the high apparent radiation exposure, incidences of the AE of dry eye, were infrequent in the PSMA-617-01 main-study (3% vs. 1% in comparator arm, all grade 1/2; no Grade 3/4) [Study PSMA-617-01-Table 14.3.2.13.2].

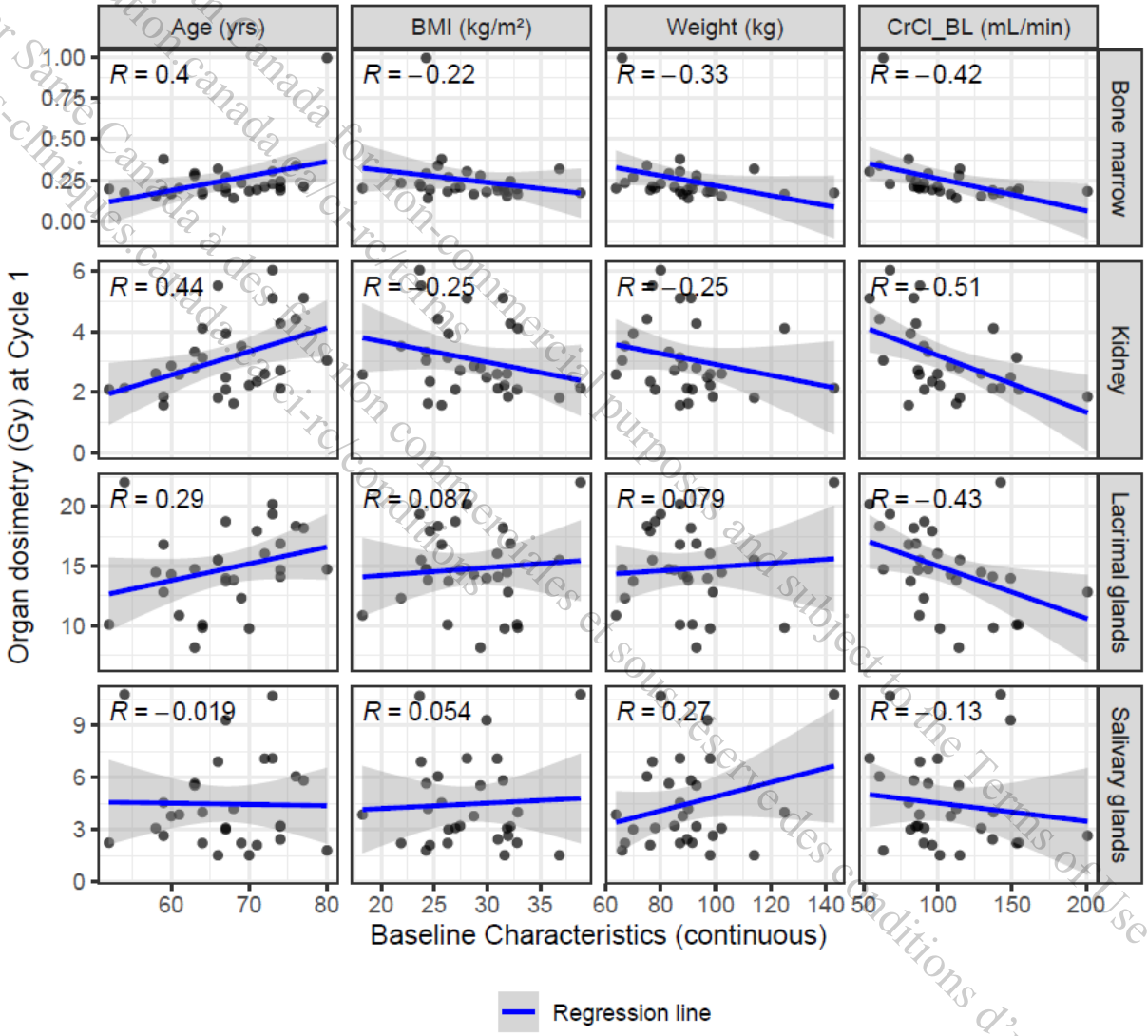
3.3.3 Correlation between baseline characteristics and organ dosimetry

Physiological characteristics, demographics and baseline factors tend to be correlated with organ dosimetry [^{177}Lu-PSMA-617 Modeling Report-Section 7.2.1]. As illustrated in Figure

3-1, higher baseline $CLcr_{BL}$ was associated with lower values of absorbed radiation dose in kidneys, bone marrow and lacrimal glands. Older subjects had higher absorbed radiation dose levels in the kidneys and bone marrow. Of note, this may be confounded by the negative correlation between age and $CLcr_{BL}$.

No strong correlation was observed between organ absorbed radiation dose and body mass index (BMI) or weight.

Figure 3-1 Correlations between organ dosimetry and continuous baseline characteristics (N=29)



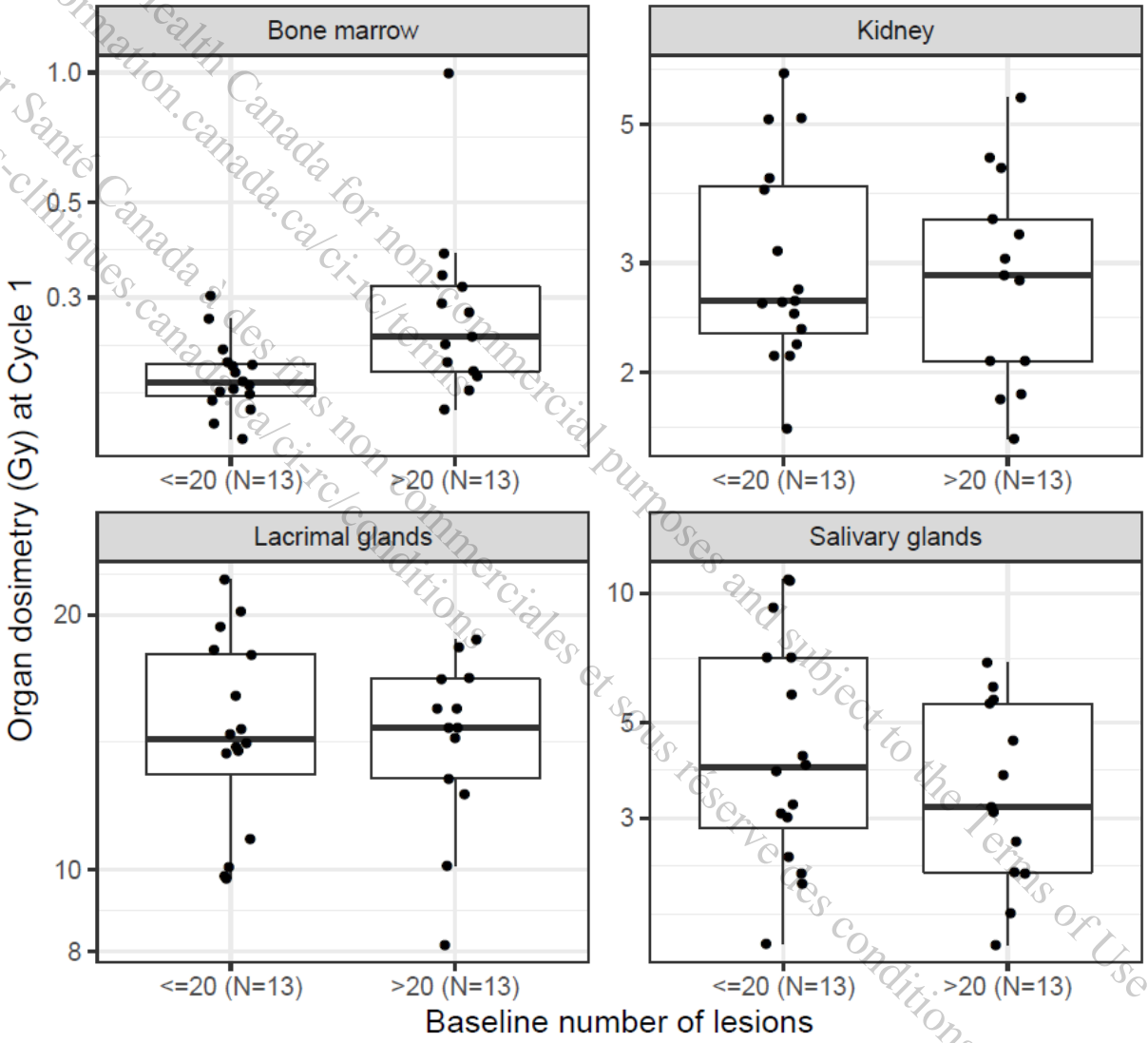
CAAA000A1/pk/pk_1/pgm/pkpd/Task01−PK−Dosimetry.R
−> CAAA000A1/pk/pk_1/reports/pkpd/Task01−Dosimetry.vs.Baseline.Cont.pdf

The blue lines are the regression lines with the 95% confidence intervals in grey.

Source: [^{177}Lu-PSMA-617 Modeling Report-Figure 7-20]

Correlations between organ dosimetry and the number of bone lesions at baseline were also explored as shown in Figure 3-2. There is a trend toward higher absorbed radiation dose values in bone marrow for patients with a large number of bone lesions (> 20 lesions). It may be explained by the presence of extensive bone metastases in the mCRPC population. However, number of bone lesions was only available as an ordinal variable.

Figure 3-2 Correlations between organ dosimetry and baseline number of bone lesions (N=26)



CAAA000A1/pk/pk_1/pgm/pkpd/Task01-PK-Dosimetry.R
-> CAAA000A1/pk/pk_1/reports/pkpd/Task01-Dosimetry.vs.Baseline.Cat.pdf

3 patients with missing number of bone lesions at baseline have been excluded from the plot. The y-axis is in log-scale. For each box plot, the top horizontal line is the 3rd quartile, the middle line is the median and the bottom line if the 1st quartile.
Source: [^{177}Lu-PSMA-617 Modeling Report-Figure 7-21]

3.4 Pharmacokinetics and dosimetry in sub-populations

3.4.1 Patients vs healthy subjects

^{177}Lu-PSMA-617 has not been studied in healthy subjects. Data in patients with mCRPC have been discussed in respective sections of this document.

3.4.2 Gender

As the treatment is targeted to males with prostate cancer, this is not applicable.

3.4.3 Body weight

For a radioligand therapeutic that is specifically binding (and internalized) by tumor tissues overexpressing the target, body-weight adjusted dosing may lead to potential under-dosing in those patients that are in the low body weight range but have high tumor burden. Therefore, the proposed dose for ^{177}Lu-PSMA-617 is expressed as a fix dose and it is not meant to be adjusted based on body weight or body surface area.

Baseline weight (WT_{BL}) was retained as a statistically significant covariate on the central volume of distribution (V_1) in the final ^{177}Lu-PSMA-617 population PK model [^{177}Lu-PSMA-617 Modeling Report-Section 7.1.5]. The population PK dataset included 30 subjects with WT_{BL} ranging from 63.8 kg to 143.0 kg (median 88.8 kg). Increasing WT_{BL} was associated with higher V_1. However, WT_{BL} was not clinically relevant, as there is no significant impact on ^{177}Lu-PSMA-617 PK exposure (i.e. Cmax), and hence does not warrant any weight-based dose adjustment.

As shown in Section 3.3.3 there was no strong correlation observed between organ dosimetry and BMI or weight, hence biodistribution is not influenced by weight or BMI.

3.4.4 Ethnic origin

No information is currently available about the effects of race or ethnicity on biodistribution and PK of ^{177}Lu-PSMA-617 as all patients enrolled in the PSMA-617-01 sub-study were White, and only one patient was Hispanic or Latino [^{177}Lu-PSMA-617 Modeling Report-Section 7.1.1]. Since ^{177}Lu-PSMA-617 is not metabolized by the liver and is eliminated passively through renal excretion, PK is unlikely to be affected by ethnic factors.

3.4.5 Elderly patient population

The available data from published literature is in elderly patients (Table 2-3).

Age, in the range of 52 to 80 years (median 67 years) in the PSMA-617-01 sub-study, was not found as a statistically significant covariate in the ^{177}Lu-PSMA-617 population PK model [^{177}Lu-PSMA-617 Modeling Report-Section 7.1.4], [^{177}Lu-PSMA-617 Modeling Report – Section 7.1.1]. Hence, PK is not affected by age.

3.4.6 Children (less than 18 years old)

Prostate cancer is a disease which occurs in an older, adult population, therefore the use of ^{177}Lu-PSMA-617 in the pediatric population would not be relevant and hence was not studied.

3.4.7 Impaired renal function

No dedicated renal impairment study for ^{177}Lu-PSMA-617 has been conducted.

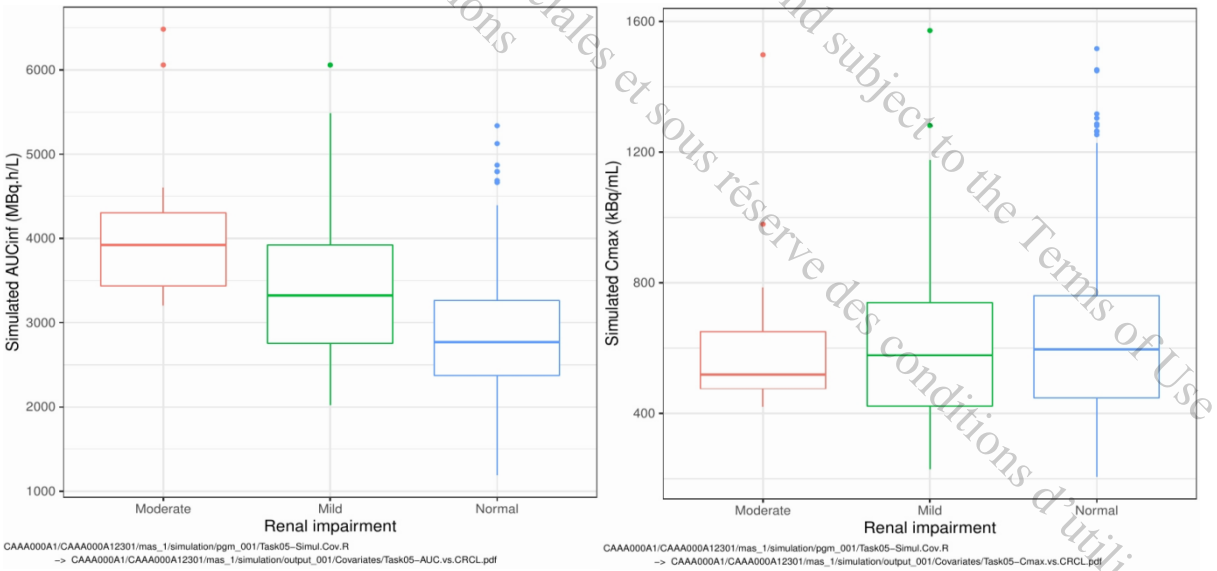
As the main route of excretion for ^{177}Lu-PSMA-617 is renal, sufficient renal function (CLcr ≥ 50 mL/min), encompassing normal to moderately decreased renal function (as defined by renal impairment guidances (EMA 2016, FDA 2020a), in patients was considered as an eligibility criteria for treatment in Study PSMA-617-01 including the sub-study.

Renal function was therefore assessed in the population PK analysis. $CLcr_{BL}$ was retained as a statistically significant covariate on CL in the final ^{177}Lu-PSMA-617 population PK model [^{177}Lu-PSMA-617 Modeling Report-Section 7.1.5]. Increasing $CLcr_{BL}$ was associated with higher CL. The population PK dataset included subjects with sufficient renal function with a median $CLcr_{BL}$ of 98 mL/min, and values ranges from 54 mL/min to 201 mL/min. A decrease of $CLcr_{BL}$ by 40%, such as a decrease from 101.5 mL/min to 60.9 mL/min, will lead to an average decrease of CL by 21%.

Simulations were performed to explore the effect of renal impairment on ^{177}Lu-PSMA-617 PK exposure. Among the 30 sub-study patients, one (3.3%) and 10 (33.3%) patients had moderate and mild renal impairment, respectively, while 19 (63.3%) patients had normal kidney function. [^{177}Lu-PSMA-617 Modeling Report – Section 7.1.8].

As illustrated in Figure 3-3, simulations showed a 42% and 20% increase in median of simulated AUCinf for moderate and mild renal impairment respectively vs. for normal renal function. It should be noted that simulations of moderate renal impairment were based only on one observed value ($CLcr_{BL}$=54 mL/min). Renal impairment did not show any significant effect on Cmax.

Figure 3-3 Box plot of simulated AUCinf and Cmax by renal impairment category



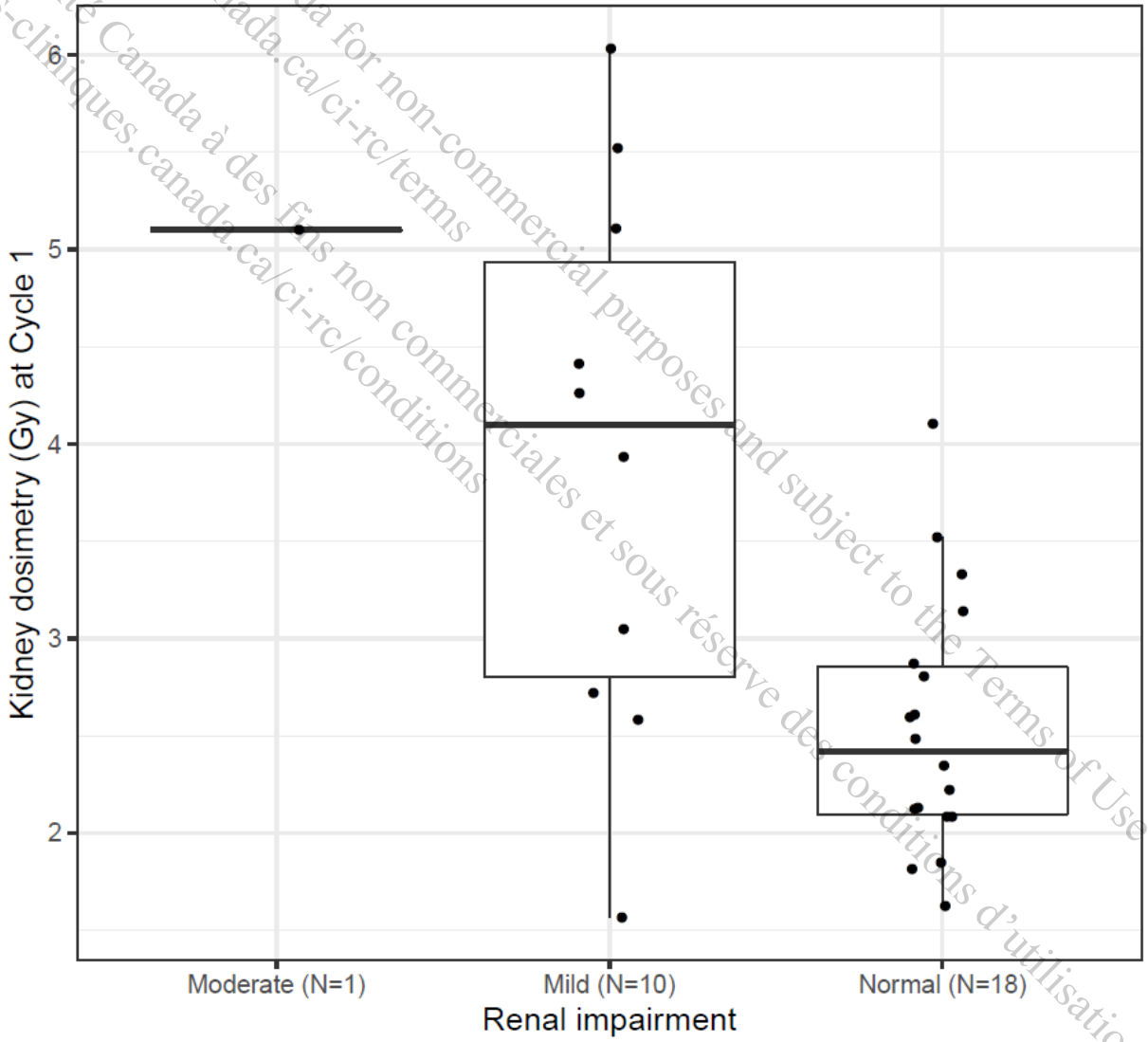
Simulations of 500 individuals were performed with covariates randomly sampled with replacement from the observed values. Only one individual had a moderate renal impairment ($CLcr_{BL}$=54mL/min). For each box plot, the top horizontal line is the 3rd quartile, the middle line is the median and the bottom line is the 1st quartile.

Source: [^{177}Lu-PSMA-617 Modeling Report-Figure 7-14]

Effects of severe renal impairment or end-stage renal disease could not be evaluated due to lack of relevant information.

Dosimetry data included one (3.4%) and 10 (34.5%) patients with moderate and mild renal impairment respectively, and 18 (62.1%) patients with normal renal function [^{177}Lu-PSMA-617 Modeling Report-Section 7.2.1.2]. Correlation between kidney dosimetry at Cycle 1 and renal impairment are represented in Figure 3-4. A trend toward higher kidney dosimetry values in patients with mild renal impairment (median 4.10 Gy) compared to those with normal renal function (median 2.42 Gy) was observed. The patient with moderate renal impairment had a kidney dosimetry equal to 5.10 Gy [^{177}Lu-PSMA-617 Modeling Report–Section 7.2.1.2].

Figure 3-4 Correlation between observed kidney dosimetry at Cycle 1 and renal impairment (N=29)



CAAA000A1/pk/pk_1/pgm/pkpd/Task01-PK-Dosimetry.R
-> CAAA000A1/pk/pk_1/reports/pkpd/Task01-Kidney.dosim.Renal.imp.pdf

The top horizontal line is the 3rd quartile, the middle line is the median and the bottom line is the 1st quartile.
Source: [^{177}Lu-PSMA-617 Modeling Report-Figure 7-22]

Mild to moderate renal impairment seems to affect kidney absorbed dose. However, the clinical relevance of this finding is difficult to interpret as there is no clear relationship established between kidney dosimetry and clinical safety. As the value of kidney absorbed dose in the moderate renal impaired patient was, however, within the distribution observed for mild impairment and since no clinically significant renal toxicity was observed in Study PSMA-617-01 (as discussed in Section 3.3.2), mild and moderate renal impairment are unlikely to warrant any dose adjustments. No information is available for severe renal impairment or end-stage renal disease.

3.4.8 Impaired hepatic function

Preclinical and clinical experience with ^{177}Lu-PSMA-617 showed that liver metabolism of the compound is negligible (Section 3.1.4), and the liver is not the primary organ responsible for clearance and excretion (Kratochwil et al 2016, Section 3.1.5). Hence, hepatic impairment is unlikely to significantly alter the PK of ^{177}Lu-PSMA-617. In accordance with hepatic impairment guidances (i.e. hepatic metabolism and/or excretion < 20% of the absorbed drug, no narrow therapeutic index) a dedicated study in patients with liver impairment is not considered necessary and thus not conducted (FDA 2003, EMA 2005).

No dose adjustment is therefore needed for any degree of hepatic impairment.

3.5 Drug interactions in vivo

3.5.1 Effect of concomitant medication on ^{177}Lu-PSMA-617

Since ^{177}Lu-PSMA-617 is metabolically stable both in in vitro and in vivo (Section 3.1.3), is passively cleared renally, and is not a substrate of any of the investigated uptake or efflux transporters (i.e. MATE1, MATE2-K, OAT1, OAT3, OCT2, P-gp and BCRP) based on in vitro assessments (Section 2.1.6.2), it is unlikely to become subject to any metabolic- or transporter-mediated drug interactions in vivo.

Androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor antagonists, have been reported to modulate PSMA expression in some nonclinical prostate cancer models, and in some clinical studies (Afshar-Oromieh et al 2018, Emmett et al 2019, Vaz et al 2020, Mathy et al 2021). However, a definitive effect of these therapies on the PK or biodistribution of ^{177}Lu-PSMA-617, particularly in normal tissues, has not been established. Importantly, the dosimetry results acquired from patients in the PSMA-617-01 sub-study, which allowed concomitant administration of NAADs, showed good concordance with literature across a population with varied ADT treatments, doses, and administration times relative to the ^{177}Lu-PSMA-617 administration. Considering the general consistency in the reported biodistribution across these multiple clinical scenarios, ADTs appear unlikely to have an effect on the biodistribution and PK of ^{177}Lu-PSMA-617 that extends beyond the normal range of variability.

Based on sub-group analysis by NAAD treatment at baseline or concurrent use, differences in incidences of TEAEs overall, by type and severity were minor in the presence or absence of NAAD [SCS – Section 5.2.2].

Efficacy subgroup analyses carried out for NAAD either as a stratification factor, i.e. NAAD as part of BSC/BSoC at start of study [Study PSMA-617-01-Section 11.1.4], or concurrent use of NAAD as part of BSC/BSoC at any time during study treatment [SCE-Section 3.3] showed that these results were consistent with the overall efficacy results.

These analyses as well as the lack of definitive effects of these therapies on the normal tissue distribution of ^{177}Lu-PSMA-617 supports the conclusion that co-administration of ADT or other androgen pathway targeting therapies has no impact on the outcome or safety of ^{177}Lu-PSMA-617 and thus does not warrant dose adjustments.

3.5.2 Effect of ^{177}Lu-PSMA-617 on concomitant medications

As recommended in FDA and EMA guidelines, the highest concentration tested in the assays determining the inhibition potential of a drug should be approximately 50-fold higher than the theoretical Cmax at the clinically relevant dose (EMA 2012, FDA 2020b). While blood-radioactivity PK reflects ^{177}Lu-PSMA-617 due to the lack of metabolism and absence of metabolites as discussed in Section 3.1.1, the geometric mean of 6.58 ng/ml (Table 2-2), measured by radioactivity of ^{177}Lu-PSMA-617 in the blood, does not reflect the total peptide mass, comprised of Lu-177 (“hot”), Lu-175 (“cold") and unlabeled peptide that is injected into a patient when a dose is administered. This may increase, depending on what day the drug product is administered to adjust to an activity of 7.4 GBq (± 10%) as the drug product is manufactured and supplied for the treatment of an individual patient at a specific date and time. Due to this, the dose volume can range between 7.5 and 12.5 mL [Module 3.2.P.1-Description and Composition of the Drug Product] corresponding to a peptide mass range usually between 112.5 and 187.5 µg. Only at the limit of the specifications for the precursor content an higher amount of up to 275 µg could be anticipated (most conservative scenario).

Hence, for the conduct of the in vitro inhibition assays, the anticipated Cmax (total, not unbound) was calculated as the maximum theoretical concentration of PSMA-617 achieved at time zero after injection/infusion of an average 7.4 GBq dose (including an average ~200 µg of total peptide), assuming a plasma volume of 2.5 L and the molecular weight of PSMA-617 of 1042.14 g/mol, translating to a theoretical maximum peptide “Cmax” of 0.080 µg/ml (76.7 nM). However, to cover a greater than 50-fold margin, concentrations up 500 µg/ml (CYP induction), 10 µg/ml (CYP inhibition) and 4.25 µg/ml (transport inhibition) were used (Section 2.1.5 and Section 2.1.6). Even under the most conservative scenario of 275 µg of total peptide translating to a theoretical maximum peptide "Cmax" of 0.11 µg/ml (106 nM), a ~39-fold margin would be retained in the transport inhibition study.

Thus, under clinical concentrations (and accounting for the total peptide mass injected with a dose) ^{177}Lu-PSMA-617 is not an inducer of CYP1A2, 2B6 and 3A4 in vitro and was also not an inhibitor of all common CYPs (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5) and investigated efflux and uptake transporters (BCRP, BSEP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2).

Therefore, ^{177}Lu-PSMA-617 is not expected to cause CYP- or transport-mediated drug interactions in vivo.

3.6 Pharmacodynamics

^{177}Lu-PSMA-617 is a PSMA-targeted radioligand therapeutic that delivers radiation to cancer cells via binding to the PSMA cell-surface target. Specifically, this agent has been designed to bind with high affinity to PSMA expressed on the surface of prostate cancer cells in order to target therapeutic radiation to sites of disease. The targeting and binding of the agent to PSMA occurs through the glutamate-urea-lysine pharmacophore portion of the molecule (Benešová et al 2015). In vitro experiments showed PSMA binding affinity to be high with nanomolar affinity reported in cellular assays (Section 2.1.1). PSMA-dependent uptake and internalization of ^{177}Lu-PSMA-617, were also confirmed in cellular assays that lead to prolonged retention in the targeted cancer cell. The resulting radiation exposure causes DNA damage in these targeted cancer cells, as well as in neighboring cells due to bystander and cross-fire effects, from the release of medium-energy β-particles emitted from Lu-177.

Importantly, no relevant pharmacodynamic effects related to the ligand itself are expected, as the total peptide mass of PSMA-617 ligand that is injected is low (with a potential maximum of 275 µg of total peptide as discussed in Section 3.5), it is administered infrequently (every 6 weeks), and nonclinical studies demonstrated a lack of direct pharmacological and toxicological effects across in vitro and in vivo assays at much higher exposures [Nonclinical Overview-Section 2.3].

3.7 Exposure-Response

Traditional PK/PD or exposure-response analysis describe the relationship of standard exposure-related PK parameters such as Cmax and AUC with either safety or efficacy. For radioligand therapies, however, where the mechanism of action is the delivery of therapeutic radiation to cancer cells via binding to a cell-surface target, dosimetric analysis provides a quantification of radiation exposure in the various tissues, which may be more relevant for safety and efficacy evaluations of an RLT molecule than systemic blood exposure.

Since Study PSMA-617-01 (main study) did not include PK or dosimetry, no exposure-response analysis with either efficacy or safety could be carried out. For the 30 patients in the PSMA-617-01 sub-study, where PK parameters were derived by either (non-)compartmental or populations methods and organ (but not tumor) dosimetry was acquired, both exposure metrics were used to explore the relationship between PK or organ radiation absorbed dose and acute toxicities related to the organ at risk as well on QT prolongation. Since the sub-study is still ongoing by the time of submission, only acute safety after the first dose of ^{177}Lu-PSMA-617 was assessed.

In addition and as correlation analysis between blood-radioactivity PK and dosimetry have rarely been carried out systematically in the past, the relationship between systemic exposure and absorbed dose in PSMA-expressing key organs were investigated (Section 3.7.3).

3.7.1 PK/QT analysis

Preclinical cardiac safety studies, conducted in vitro and in vivo, indicate a negligible risk of an electrophysiological effect by ^{177}Lu-PSMA-617. In the in vitro human ether-a-go-go related gene (hERG) assay, ^{175}Lu-PSMA-617 test solution did not show effects on the hERG tail current at concentrations between 1 µM and 100 µM, far greater than the anticipated maximum total peptide Cmax of 77 nM (80 ng/mL as calculated in Section 3.5.2). No significant effects were observed on cardiac electrophysiological function or hemodynamics as measured by telemetry in conscious minipigs [Nonclinical Overview-Section 2.3].

For clinical cardiodynamic evaluation compliant with ICH E14, ECGs and time-matched PK were collected in the sub-study for PSMA-617-01. ECGs and PK samples were collected prior to administration and at 1, 4, and 24 hours post-dose. The primary objective was to evaluate the effect of ^{177}Lu-PSMA-617 on the QTc interval using the Fridericia method (QTcF) using a by-timepoint analysis as the primary analysis and concentration-QTc effect analysis as a secondary analysis. Details of the results, statistical methodology and the PK-QT analysis set used for the analyses are described in the ^{177}Lu-PSMA-617 Cardiac Safety Report [Study PSMA-617-01-Appendix 16.2.9.3].

In the by-timepoint analysis (N=30), ^{177}Lu-PSMA-617 had no clinically relevant effect on QTcF, with the QTcF change-from-baseline ranging from -5.2 ms to 2.1 ms. The concentration-QTc analysis was confirmatory, with a model predicted QT change from baseline (ΔQTcF) of 3.1 ms (2-sided 90% upper confidence bound 5.5 ms) at geometric mean Cmax 3.8 ng/mL. Based on the concentration-QTc analysis, an effect on ΔQTcF exceeding 20 ms can be excluded within the full observed range of ^{177}Lu-PSMA-617 plasma concentrations and up to ~6 ng/mL. The concentration-QTc model predicted a peak QTcF increase of about 8.7 ms (90% upper CI 13.6 ms) at the Cmax of 6.58 ng/mL [Study PSMA-617-01-Appendix 16.2.9.3 – Table 1.10]. However, this prediction is outside the observed concentration range and should be interpreted with caution. ^{177}Lu-PSMA-617 also had no clinically relevant effect on heart rate, PR interval, or QRS duration. In summary, ^{177}Lu-PSMA-617 at the studied dose had no effects on QTc or other ECG parameters in this analysis at the time points where ECG measurements were made.

While no matched ECG/PK sample was collected at EOI where a higher geometric mean Cmax of ^{177}Lu-PSMA-617 was observed, and while the analysis cannot account for the theoretical total peptide mass injected with each dose, given the negative hERG assay across a large concentration range and a fast first elimination phase of ^{177}Lu-PSMA-617 [Study PSMA-617-01-Appendix 16.2.9.1], no effects on QTcF are anticipated even at greater concentrations. This is in line with the absence of clinical findings related to QT prolongation in Study PSMA-617-01 [SCS-Section 2.1.5.1.2].

In summary, the results of the PK/QT analysis together with the preclinical cardiac safety studies indicating a negligible risk of an electrophysiological effect by ^{175}Lu-PSMA-617, low uptake in the heart (Table 2-1) and the absence of clinical findings related to QT prolongation in PSMA-617-01 sub-study, confirms that ^{177}Lu-PSMA-617 administration does not pose a cardiac risk.

3.7.2 Exposure/Dosimetry-Acute Toxicity

Relationships between exposure/dosimetry and acute toxicity related to the organs at risk (i.e. kidney, bone marrow, salivary glands and lacrimal glands) during the first cycle of treatment in PSMA-617-01 sub-study patients were explored [^{177}Lu-PSMA-617 Modeling Report-Section 7.2.2]. For this descriptive analysis, exposure metrics included the injected activity, the predicted radioactivity-blood PK metrics (i.e. AUCinf and Cmax) derived from the population PK model, and the organ dosimetry.

Descriptive longitudinal analyses during Cycle 1 showed an impact of ^{177}Lu-PSMA-617 on hematological laboratory assessments, with a decrease in leukocytes, neutrophils and platelets starting from 8 days after treatment administration. Specifically, 86% of patients presented a decrease from baseline in platelet count. However, only 20% of the sub-study patients experienced a worsening from baseline of at least one hematological adverse event of CTCAE grade ≥ 2 during Cycle 1. In addition, those patients were the ones with low baseline hematological laboratory values. No hematological recovery can be observed during Cycle 1.

Longitudinal CLcr, reflecting kidney function, showed an initial peak observed from baseline to Day 8, before a slight decrease from baseline. 59% of sub-study patients presented a decrease from baseline in CLcr. However, none of them had any renal adverse event of CTCAE grade ≥ 2 during Cycle 1.

In addition, none of the sub-study patients experienced any lacrimal gland toxicity, and only 2 patients had a salivary gland adverse event during Cycle 1, limited to Grade 1.

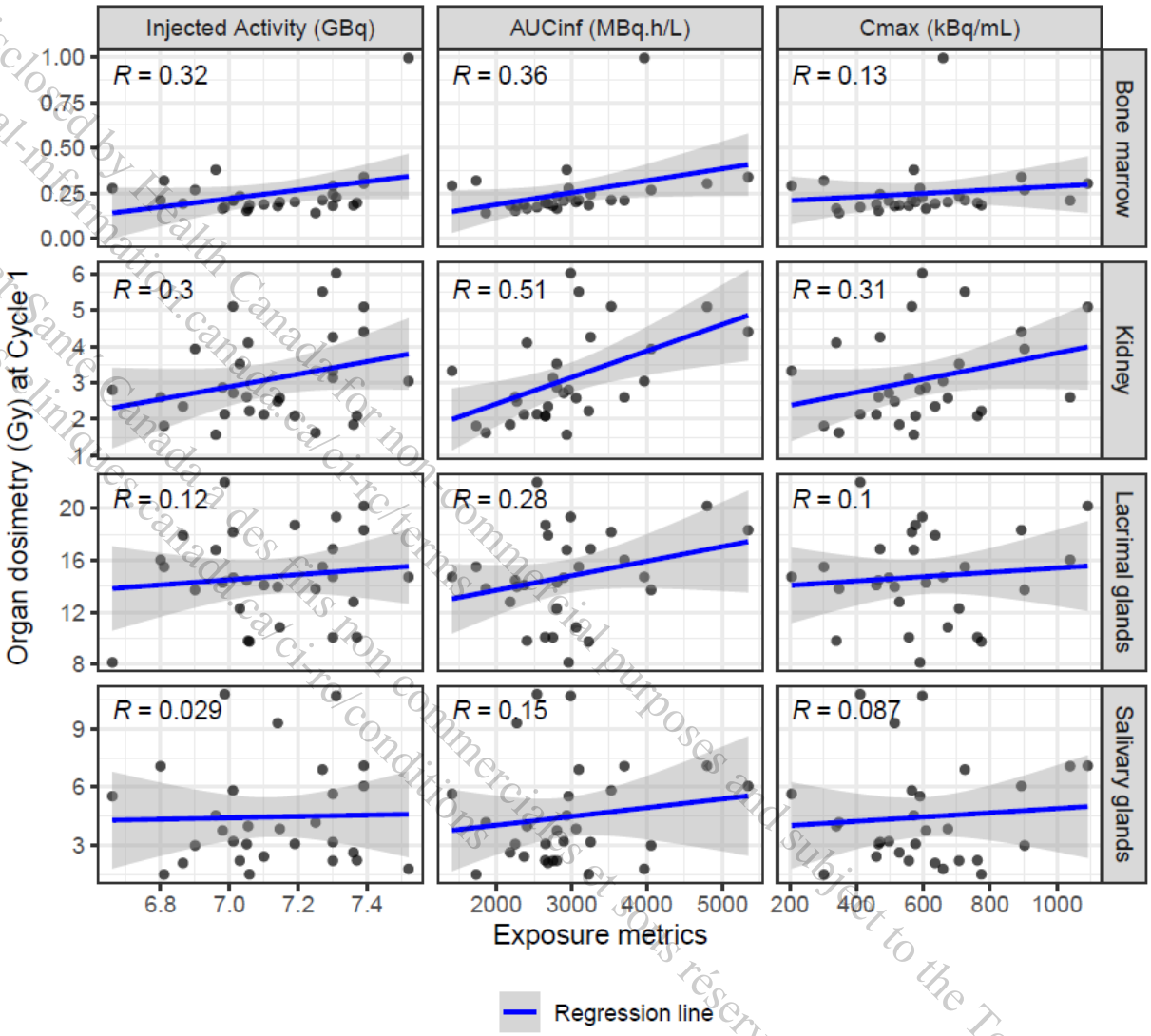
No clear and consistent trend was detected between worst platelet count decrease and exposure. Higher injected activity and higher kidney dosimetry tend to be associated with larger decrease from baseline in CLcr. No consistent trend was detected in the relationships between hematological adverse events of CTCAE grade ≥ 2 and salivary gland toxicities with exposure metrics.

Exposure/Dosimetry-Acute Toxicity analyses are limited by the small sample size (N=30 for exposure and N=29 for dosimetry) and the small number of adverse events. In addition, these analyses were only based on Cycle 1 data.

3.7.3 Exposure-Dosimetry

Exposure effect on dosimetry from the organs at risk (i.e. kidney, bone marrow, salivary glands and lacrimal glands) during the first cycle of treatment in PSMA-617-01 sub-study patients (N=29) was explored [^{177}Lu-PSMA-617 Modeling Report-Section 7.2.1]. Exposure metrics included the injected activity and the predicted radioactivity-blood PK metrics (i.e. AUCinf and Cmax) derived from the population PK model. Scatterplots of each exposure-dosimetry relationship along with Pearson correlation coefficient (R) are represented in Figure 3-4. The strongest correlation was observed between blood AUCinf and kidney dosimetry (R=0.51).

Figure 3-4 Relationships between exposure and organ dosimetry at Cycle 1 (N=29)



CAAA000A1/pk/pk_1/pgm/pkpd/Task01-PK-Dosimetry.R
-> CAAA000A1/pk/pk_1/reports/pkpd/Task01-Dosimetry.vs.Exposure.pdf

The blue lines are the regression lines with the 95% confidence intervals in grey.

Source: [^{177}Lu-PSMA-617 Modeling Report-Figure 7-19]

Linear regression was performed for each exposure-dosimetry relationship, and suggested that only AUCinf in blood was a statistically significant predictor of the absorbed radiation dose in the kidneys (p=0.005). Increase in AUCinf by 1000 MBq.h/L would lead to increase in kidney dosimetry by 0.7 Gy. However, as $CLcr_{BL}$ has a strong effect on AUCinf and is also highly negatively correlated with kidney dosimetry, the observed relationship between AUCinf and kidney dosimetry is therefore confounded [^{177}Lu-PSMA-617 Modeling Report – Section 7.2.1.2].

4 Special Studies

No special studies were performed.

5 Appendix

5.1 Tables

Table 5-1 Summary of human ^{177}Lu-PSMA-617 dosimetry studies: Radiation Absorbed Doses

Source/Study	No. of patients Dose per cycle	Imaging Modality	Kidneys (Gy/GBq) Mean±SD	Salivary glands (Gy/GBq) Mean±SD	Bone Marrow (Gy/GBq) Mean±SD	Liver (Gy/GBq) Mean±SD	Spleen (Gy/GBq) Mean±SD	Lacrimal glands (Gy/GBq) Mean±SD
Yadav et al (2017)	26 pts 1.11-5.50 GBq	Planar (SPECT/CT for salivary gland volume only)	0.991 ± 0.312	1.244 ± 0.268	0.048 ± 0.059	0.3615 ± 0.108	NR	NR
Kratochwil et al (2016)	4 pts 6 GBq	Planar (single-abdominal SPECT/CT not used for dosimetry)	0.75 ± 0.19	1.48 ± 0.37 (SM) 1.28 ± 0.40 (PG)	0.03±0.01	0.10 ± 0.03	0.19 ± 0.07	NR
Kabasakal et al (2017)	7 pts 3.6-7.4 GBq	SPECT/CT	0.82 ± 0.25	1.90 ± 1.19 (PG)	0.03±0.008	0.17 ± 0.09	NR	NR
Delker et al (2016)	5 pts 3.4-3.9 GBq	SPECT/CT	0.6 ± 0.19 (Left) 0.61 ± 0.16 (Right)	1.4 ± 0.53	0.012 ± 0.00524	0.11 ± 0.06	0.10 ± 0.03	NR
Scarpa et al (2017)	10 pts 5.4 to 6.5 GBq	Planar (single abdominal SPECT/CT)	0.60±0.36	0.498 ± 0.15 (SM) 0.56 ± 0.25 (PG)	0.04±0.028	0.12±0.06	0.12±0.09	1.01±0.69

Source/Study	No. of patients Dose per cycle	Imaging Modality	Kidneys (Gy/GBq) Mean±SD	Salivary glands (Gy/GBq) Mean±SD	Bone Marrow (Gy/GBq) Mean±SD	Liver (Gy/GBq) Mean±SD	Spleen (Gy/GBq) Mean±SD	Lacrimal glands (Gy/GBq) Mean±SD
Maffey-Steffan et al (2020)	32 pts 6GBq	Planar (single abdominal SPECT/CT)	0.77±0.56	0.46 ± 0.17 (SM) 0.53 ± 0.22 (PG)	0.04±0.028	0.13±0.079	0.13±0.16	0.85±0.51
Kamaldeep et al (2021)	30 pts 4.44–5.55 GBq	Planar (small ROI with no overlap to avoid overestimation errors)	0.52 ± 0.16	0.53 ± 0.30	0.04 ± 0.03	0.08 ± 0.05	0.17 ± 0.07	1.45 ± 0.85
Hohberg et al (2016)	9 pts 5.28–5.77 GBq	Planar (ROIs specifically drawn to avoid overlap)	0.525 ± 0.173	0.721 ± 0.142	NR	NR	NR	2.82 ± 0.76
Mix et al (2021)[1]	59 pts 6 GBq/cycle (Median dose)	SPECT/CT	0.67 ± 0.24	NR	NR	NR	NR	NR
Violet et al (2019)	30 pts 5.7–8.7 GBq	SPECT/CT	0.39 ± 0.15	0.44 ± 0.36 (SM) 0.58 ± 0.43 (PG)	0.11 ± 0.10	0.1 ± 0.05	0.08 ± 0.06	0.36 ± 0.18
Rosar et al (2021)[2]	24 pts 3–10.9 GBq	SPECT/CT	0.54 ± 0.28	0.72 ± 0.39 (SM) 0.81 ± 0.34 (PG)	NR	0.10 ± 0.05	NR	NR
Paganelli et al (2020)[3]	13 pts 3.7‑5.5 GBq	Planar (single abdominal SPECT/CT)	0.42 (0.14-0.81)	0.59 (0.23-1.51) (SM) 0.65 (0.33-2.63) (PG)	0.036 (0.023-0.067)	0.13 (0.05-0.53)	NR	2.26 (0.48- 3.59)

Source/Study	No. of patients Dose per cycle	Imaging Modality	Kidneys (Gy/GBq) Mean±SD	Salivary glands (Gy/GBq) Mean±SD	Bone Marrow (Gy/GBq) Mean±SD	Liver (Gy/GBq) Mean±SD	Spleen (Gy/GBq) Mean±SD	Lacrimal glands (Gy/GBq) Mean±SD
Prive et al (2021)[4]	10 pts 3 -6 GBq	SPECT/CT	0.49 ± 0.11	0.39 ± 0.17	0.02 ± 0.00	0.09 ± 0.01	NR	NR

SM = submandibular; PG = parotid gland; NR: Not Reported

[1] Based on the abstract only as full text was not available at the time of submission.

[2] Data using planar and single SPECT/CT not shown

[3] Dosimetry performed in 9 patients during cycle 1 and 4 patients during cycle 2; data represents the median values of the mean absorbed dose (range)

[4] Study conducted in hormone-sensitive, metastatic prostate cancer; Dosimetry was done for two cycles in each of the 10 patients, therefore the mean and SD are derived from 20 evaluations.

5.2 References

5.2.1 Published literature

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5.2.2 Health Authority guidance

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