Clinical Development

lutetium (^{177}Lu) vipivotide tetraxetan

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

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods in patients with prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer

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Abbreviations

AAA	Advanced Accelerator Applications
HPLC	High Performance Liquid Chromatography
MBq	megabecquerel
mCi	Millicurie
mCRPC	metastatic castration-resistant prostate cancer
PSMA	prostate specific membrane antigen
RLT	targeted radioligand therapy

1 Background and Overview

1.1 General overview

The therapeutic agent lutetium (^{177}Lu) vipivotide tetraxetan or [^{177}Lu]Lu-PSMA-617 (company research code: AAA617), referred to as ^{177}Lu-PSMA-617 henceforth for the purpose of this document, is a prostate-specific membrane antigen (PSMA) - targeted radioligand therapy (RLT) that is being developed to treat metastatic castration-resistant prostate cancer (mCRPC). PSMA is a transmembrane protein, also known as folate hydrolase 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, but has restricted and several hundred-fold lower expression in some other tissues such as normal prostate, salivary glands, renal tubular cells, and small intestine (Bostwick et al 1998, Ghosh and Heston 2004, Mannweiler et al 2009). Additionally, PSMA overexpression is correlated with advanced, high-grade, metastatic, androgen independent prostate cancer (Ross et al 2003).

The PSMA-617 precursor consists of three components: the PSMA-targeting pharmacophore glutamate-urea-lysine, the chelator DOTA, and a linker connecting these two entities (Benešová et al 2015). Lutetium-177 (Lu-177) is a 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. 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 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).

Lu-177 is a medium-energy β emitter (497 keV) with a maximal tissue penetration of approximately 2 mm. The shorter β-range of Lu-177 provides better irradiation of small tumors, in contrast to the longer β-range of ^{90}Y (Emmett et al 2017, Dash et al 2015). The shorter path length also acts to direct the energy within the tumor rather than into the surrounding normal tissues, while the path length is still sufficient to create bystander and crossfire effects within the tumor lesion. The radiation energy will cause single and/or double stranded DNA damage in the targeted cell as well as in surrounding cancer cells. Moreover, Lu-177 also has a physical half-life of 6.647 days that combines with the intratumoral retention of ^{177}Lu-PSMA-617 to maximize the benefit of PSMA-targeted radiation to prostate cancer cells (Deepa et al 2011).

In the literature, ^{177}Lu-PSMA-617 may also be referred to as LuPSMA, ^{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 [SCP-Section 2.4].

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).

Recently, a prospective, open-label, multicenter, randomized Phase III [Study PSMA-617-01] (VISION) has been conducted in patients with PSMA-positive mCRPC.

Study PSMA-617-01 used two formulations with minor differences from the proposed commercial formulation. These differences were assessed and no impact in the clinical performance of this product is expected [Module 3.2.P.2 Pharmaceutical development - Formulation development].

1.2 Drug substance and drug product

1.2.1 PSMA-617 Precursor

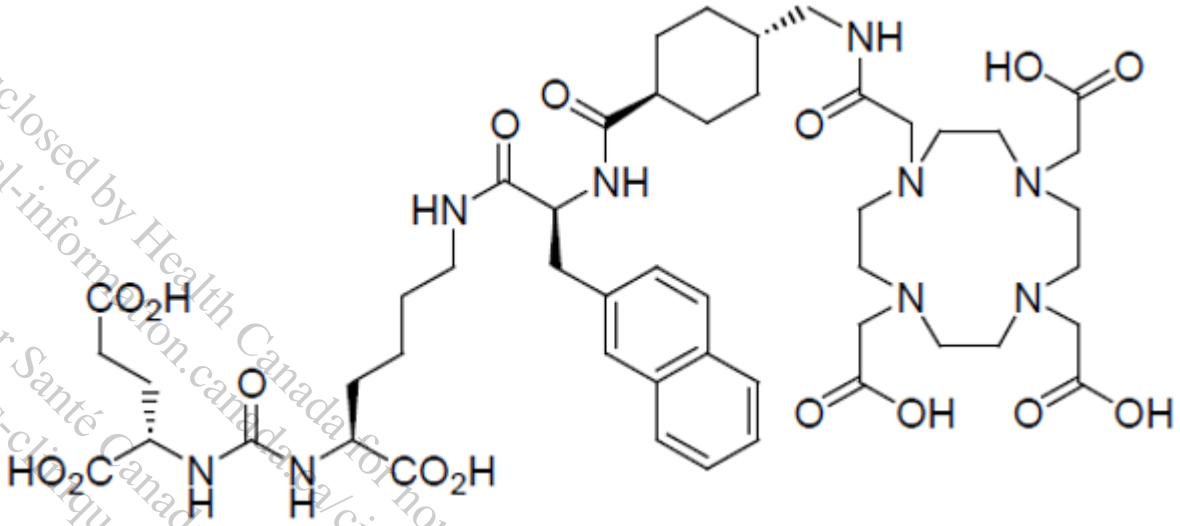
The chemical characteristics of the PSMA-617 precursor are outlined in Table 1-1 and the structural formula is shown in Figure 1-1.

Table 1-1 Chemical characteristics of the PSMA-617 precursor

Chemical name:	2-[3-(1-Carboxy-5-{3-naphthalen-2-yl-2-[(4-{[2-(4,7,10-tris-carboxymethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-acetylamino]-methyl}-cyclohexanecarbonyl)-amino]-propionylamino}-pentyl)-ureido]-pentanedioic acid
Molar mass:	1042.1 g/mol
Molecular formula:	$C_{49}H_{71}N_9O_{16}$
CAS Registry number:	1702967-37-0
Physical description:	white to off-white solid
Packaging:	Plastic vials
Storage:	– 20 ± 5 °C

Source: [Module 3.2.S.1.1 Nomenclature], [Module 3.2.S.1.2 Structure], [Module 3.2.S.1.3 General properties], [Module 3.2.S.6 Container closure system], [Module 3.2.S.7.1 Stability Summary and Conclusion]

Figure 1-1 Structural formula of the PSMA-617 precursor



Source: [Module 3.2.S.1.2 Structure]

1.2.2 Radioactive isotope ^{177}Lutetium

The chemical name of the radioactive starting material is lutetium (Lu-177) chloride corresponding to the molecular formula $^{177}LuCl_3$. $^{177}LuCl_3$ has a molecular mass of 283.3 g/mol. Two different sources of radionuclide starting material $^{177}LuCl_3$ (carrier added and no-carrier added) are used for the synthesis of the commercial radiopharmaceutical drug product ^{177}Lu-PSMA-617 solution for injection/infusion, and can be used interchangeably. Lu-177 decays by emission of medium-energy beta (β-) particles as well as low-energy gamma photons to the stable isotope Hafnium-177 (^{177}Hf), and has a half-life of 6.647 days.

Radionuclidic properties of Lu-177 are described in Table 1-2.

Table 1-2 Physical properties of Lu-177

Properties	Values
Half-life	6.647 days
Beta energy (%)	47.7 keV (11.6%)
	111.7 keV (9.1%)
	149.4 keV (79.3%)
Gamma energy (%)	112.9 keV (6.2%)
	208.4 keV (10.4%)
Decay product	Hafnium-177 (^{177}Hf)

Source: [Module 3.2.S.1.3 General properties] and (Council of Europe 2008)

-To be noted that the energies are expressed in MeV in the Ph. Eur instead of keV but the values are equivalent

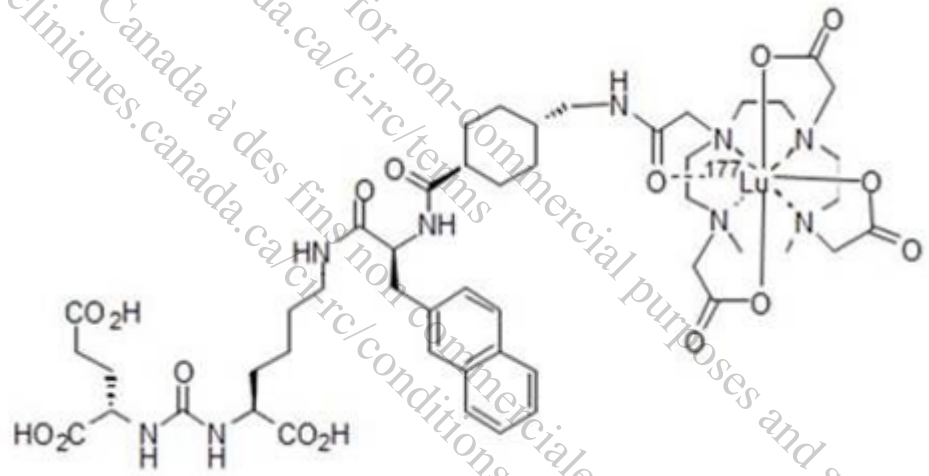
1.2.3 ^{177}Lu-PSMA-617 drug substance

The radioactive drug substance ^{177}Lu-PSMA-617 is produced as an aqueous concentrated solution (mother solution) manufactured by radiolabeling of vipivotide tetraxetan (PSMA-617) chemical precursor with Lu-177 chloride radioactive starting material. The drug substance results from the complexation of the radioisotope lutetium-177 (^{177}Lu) with the DOTA moiety of PSMA-617.

The drug substance ^{177}Lu-PSMA-617 is a clear, colorless to slightly yellow solution, with a molecular formula $C_{49}H_{68}{}^{177}LuN_9O_{16}$ and a relative molecular mass of 1216.06 g/mol [Module 3.2.S.1.3 General properties], [Module 3.2.S.1.2 Structure].

The chemical structure of ^{177}Lu-PSMA-617 drug substance is shown in Figure 1-2.

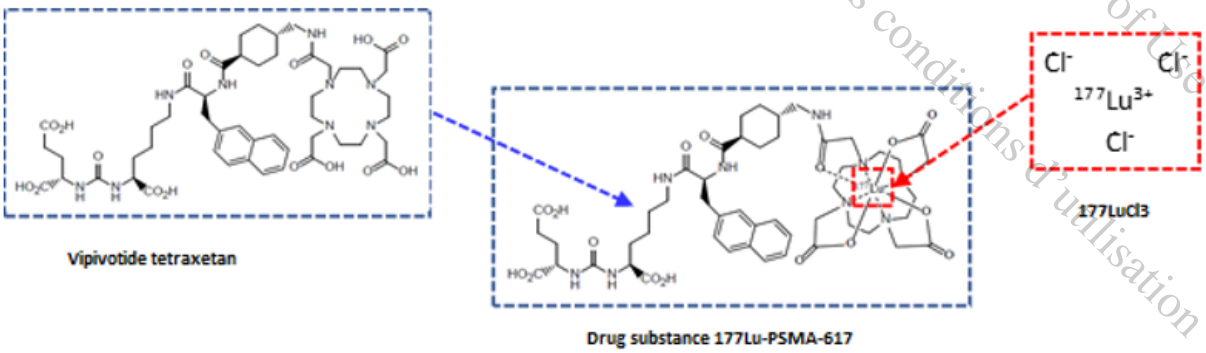
Figure 1-2 Structural formula of ^{177}Lu-PSMA-617 drug substance



Source: [Module 3.2.S.1.2 Structure]

Figure 1-3 illustrates the structures of the PSMA-617 precursor molecule and the Lu-177 chloride starting material and their basic contributions to the structure of the drug substance ^{177}Lu-PSMA-617.

Figure 1-3 Synthetic route of ^{177}Lu-PSMA-617 drug substance



Source: [Module 3.2.S.2.2 Description of Manufacturing Process and Process Controls]

The synthesis of ^{177}Lu-PSMA-617 drug substance and its formulation into the ^{177}Lu-PSMA-617 solution for injection/infusion drug product are part of an automated continuous process which does not allow for isolation and testing of the pure ^{177}Lu-PSMA-617 drug substance due to its radioactive decay.

1.2.4 Drug product - ^{177}Lu-PSMA-617 solution for injection/infusion

The radiopharmaceutical drug product ^{177}Lu-PSMA-617 1000 MBq/mL solution for injection/infusion (also referred as ^{177}Lu-PSMA-617 solution for injection/infusion) is a sterile ready-to-use solution containing the drug substance ^{177}Lu-PSMA-617 in sodium acetate/acetic acid buffer with the excipients gentisic acid, sodium ascorbate, pentetic acid (DTPA) and water for injections. The drug product has a volumetric activity of 1000 MBq/mL at date and time of calibration.

The Drug Product composition is provided in [Module 3.2.P.1 Description and composition of the drug product].

The drug substance ^{177}Lu-PSMA-617 results from the complexation of the radioisotope lutetium-177 (Lu-177) with the DOTA moiety of the PSMA-617 precursor molecule. ^{177}Lu-PSMA-617 solution for injection/infusion is a single-dose vial, containing a suitable volume of finished solution that allows delivery of 7.4 GBq (200 mCi) ± 10% of radioactivity at date and time of administration.

1.2.4.1 Differences in clinical trial formulation versus proposed commercial formulation

The Phase III clinical trial Study PSMA-617-01 used ^{177}Lu-PSMA-617 1000 MBq/mL solution for injection/infusion formulations with only minor differences in the quantities of excipients compared to the proposed commercial formulation. An adjustment in excipient quantity (i.e., the reduction of sodium acetate) along with the addition of acetic acid in the commercial formulation as opposed to its *in situ* formation in the Study PSMA-617-01 clinical trial formulation, is to establish robust buffering system, while maintaining the same quality of the final product.

The quantitative adjustment made to the excipients are considered minor (i.e., all excipient quantities are within the range of the clinical trial formulation amounts with the exception of the sodium acetate buffer, which has been reduced in quantity) and do not have an impact on the product quality. The quality results obtained on final formulation developed by AAA demonstrated that this minor qualitative composition adjustment of buffer excipients still ensures an optimal pH for the radiolabeling reaction, by using equimolar amounts of sodium acetate and its conjugated acid (acetic acid).

The other excipients sodium ascorbate and pentetic acid (DTPA) of the final formulation proposed by the Applicant are within the quantitative range of the PSMA-617-01 Phase III trial formulations. The amount of gentisic acid is at the upper range and is aligned with the quantity used in the formulation for the North American clinical sites (i.e., manufactured at Radiomedix Inc. and NCM-USA). The amount of gentisic acid affords better protection against the radiolysis associated with the higher radioactivity required in the scaled-up commercial process

and assures adequate stability for the radiopharmaceutical drug product throughout the radiopharmaceutical shelf-life.

The proposed commercial formulation and its differences are presented alongside the investigational medicinal product formulations in Table 1-3.

Table 1-3 Clinical and proposed commercial formulation of ^{177}Lu-PSMA-617 solution for injection/infusion

Ingredient	Function	Clinical unit formula		Commercial unit formula
		ABX, Germany	Radiomedix	
Active ingredient (per GBq)				
^{177}Lu-PSMA-617	Radiopharmaceutical active ingredient at reference date and time	1 GBq/mL	185 -1850 MBq/mL	1 GBq/mL
Other ingredients (mg/ mL)				
Acetic acid	pH adjuster	-	-	0.30
Sodium acetate	pH adjuster	0.9 – 2.0	3.0 – 3.6	0.41
Gentisic acid	Radiation Stability Enhancer	0.08 – 0.2	0.36 – 0.44	0.39
Sodium ascorbate	Radiation Stability Enhancer	45 – 55	54 – 66	50.0
Pentetic acid	Chelating agent	0.05 – 0.1	0.09 - 0.11 m	0.10

Based on the above, ^{177}Lu-PSMA-617 solution for injection/infusion developed by the Applicant has essentially the same qualitative and quantitative composition as the product used in Study PSMA-617-01 Phase III trial. The excipients selected are able to guarantee a correct pH at both the radiolabeling step and the finished product (acetic acid/sodium acetate buffering system), to prevent the degradation of the active ingredient (gentisic acid and sodium ascorbate) and to sequester the possible free $^{177}Lu^{3+}$ that might be present in the finished product.

Refer to [Module 3.2.P.1 Description and composition of the drug product] and [Module 3-Section 3.2.P.2 Pharmaceutical development - Formulation development] for the formulation composition, the development, and the justification of the selected formula for commercial use.

1.3 Analytical methods

A method was validated to characterize ^{177}Lu-PSMA-617 in human urine using high performance liquid chromatography (HPLC) with in-line radiodetection. The validation was successful and the chosen method suitable for use for determining concentrations of ^{177}Lu-PSMA-617 and derived radioactivity in human urine samples [Report 01360001]. The method was used for radio-HPLC analysis of urine samples in the PSMA-617-01 sub-study, presented in the [PSMA-617 SCP]. The summary of the validated method parameters is shown in Table 1-4.

Table 1-4 Validation Summary Table: ^{177}Lu-PSMA-617

Parameter	Result
Analyte	^{177}Lu-PSMA-617
Species / Matrix	Human Urine
Assay Volume	10 µL extract for HPLC
Lower Limit of Detection	0.21 µCi/mL
Calibration Curve Concentrations	0.21 to 6.75 µCi/mL
Quality Control Concentrations	0.42, 1.19, 5.4 µCi/mL
Quality Control Intra-Batch Precision Range (%RSD)	0.07%-6.76%
Quality Control Intra-Batch Accuracy Range (%RE)	-31.6% to -3.58%
Quality Control Inter-Batch Precision Range (%RSD)	4.2% to +10.3%
Quality Control Inter-Batch Accuracy Range (%RE)	-26% to +1.4%
Dilution Integrity	-11%
Stability in Stock Solutions Room Temperature Storage	Stable for up to 6 weeks
Stability in Human Urine Short Term Refrigerated (Approximately 4°C) Storage 1 and 2 Week Frozen Storage (Approximately -70°C) 3 Freeze-Thaw Cycles	 95%-98% 93% 92% (High Quality Control); 76% (Low Quality Control)
Matrix Effects	None
Source [Report 01360001-Table 1]	

2 Summary of Results of Individual Studies

No dedicated biopharmaceutic studies were conducted in humans, such as relative bioavailability, bioequivalence or food effect, as explained further in Section 3.

3 Comparison and Analysis of Results Across Studies

3.1 Bioavailability

^{177}Lu-PSMA-617 solution for injection/infusion is administered intravenously. Consequently, the absolute bioavailability is 100% [SCP-Section 1.2.1.2].

3.2 Effect of food

As the ^{177}Lu-PSMA-617 drug product is administered intravenously, no food effect studies are required and thus have not been conducted.

3.3 Comparability of Formulations

No bioequivalence studies were conducted for the ^{177}Lu-PSMA-617 drug product as the formulation used in Study PSMA-617-01 had only minor differences in composition compared to the proposed commercial formulation. A study to show bioequivalence is generally not

required if the test product is to be administered as an aqueous intravenous solution containing the same active substance unless any excipient interacts with the drug substance (e.g. complex formation), or otherwise affects the drug absorption or disposition of the drug substance (EMA 2010), (FDA 2019). Since the formulation differences only encompassed minor changes in composition with respect to excipients (Section 1.2.4.1), no impact is expected on the pharmacokinetics or biodistribution of ^{177}Lu-PSMA-617 and thus the clinical performance of the proposed commercial formulation.

3.4 Inter- and intra-subject variability

The inter- and intra-subject variability of PK and biodistribution related to the differences in the formulations was not assessed in patients in Study PSMA-617-01, but can be considered negligible given the minor change in composition (Section 1.2.4.1). PK and dosimetry assessments from different studies reported in literature indicate inter- and intra-patient variability, but in these studies there are several sources of variability (dose, imaging acquisition time, equipment, data collection, data analysis). Therefore, it is difficult to relate the inter- and intra-subject variability to the variability in the formulation composition. However, there is a general consistency in the range of absorbed radiation doses in the different organs/tissues between PSMA-617-01 sub-study and those reported in literature, see [SCP-Section 3.3] for more details.

3.5 *In vitro* / *in vivo* correlation

No in vitro and in vivo correlations were studied.

4 Summary of overall conclusions

Physicochemical data / formulations

The Phase III clinical trial Study PSMA-617-01 used a ^{177}Lu-PSMA-617 1000 MBq/mL solution for injection/infusion formulation with minor differences in the quantities of excipients compared to the proposed commercial formulation. An adjustment in excipient quantity with the purposeful addition of acetic acid in the commercial formula as opposed to its *in situ* formation in the Study PSMA-617-01 clinical trial formulation is to establish robust buffering system, while maintaining the same quality of the final drug product.

Drug substance

The drug substance results from the complexation of the radioisotope lutetium-177 (Lu-177) with the DOTA moiety of the PSMA-617 precursor molecule.

Drug product

^{177}Lu-PSMA-617 solution for injection/infusion is a single-dose vial, containing a suitable volume of finished solution that allows delivery of 7.4 GBq (200 mCi) ± 10% of radioactivity at the date and time of administration.

Analytical methods

A method was validated to characterize ^{177}Lu-PSMA-617 in human urine using HPLC with in-line radiodetection. The method was used for radio-HPLC analysis of urine samples in the Study PSMA-617-01 sub-study.

Bioavailability and intra subject variability

^{177}Lu-PSMA-617 drug product is administered intravenously, consequently the absolute bioavailability is 100%. No dedicated biopharmaceutic studies for ^{177}Lu-PSMA-617 drug product were conducted in humans, such as relative bioavailability, bioequivalence or food effect. The inter- and intra-subject variability possibly related to the minor differences in the clinical trial formulation compared to the proposed commercial formulation was not assessed.

5 Appendix

5.1 Literature references

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5.2 Health authority guidance

Available upon request.

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