29 January 2026
EMA/38034/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ilumira

International non-proprietary name: lutetium (177Lu) chloride

Procedure No. EMEA/H/C/006596/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

$^{176/177}$Yb	Ytterbium-176/177
^{177}Hf	Hafnium-177
^{177}Lu	Lutetium-177
$^{177}LuCl_3$	Lutetium (^{177}Lu) Chloride
^{18}F	Fluor-18
5-FU	5-fluorouracil
^{68}Ga	Gallium-68
^{90}Y	Yttrium-90
AA	Amino Acid
ADT	Androgen-deprivation therapy
AE	Adverse Event
AL	Acute Leukaemia
AML	Acute Myeloid Leukaemia
ALT	Alanine aminotransferase
AR	Androgen Receptor
ART	Activity reference time
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BED	Biological effective dose
BPI	Brief pain inventory
BSA	Bovine serum albumin
Ca-DTPA	Trisodium calcium diethylenetriaminepentaacetate
Ca-EDTA	Calcium disodium ehtylenediaminetetraacetate
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximum blood concentration
CR	Complete remission
CRPC	Castration resistant prostate cancer
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DNA	Deoxyribonucleic acid

DOTANOC	DOTA-(1-Nal)3-octreotide
DOTATAE	DOTA-oxodotreotide
DOTATE	DOTA-Octreotate
DOTATOC	DOTA-Edotreotide
DTPA	Diethylenetriaminepentaacetic Acicd
EB	Evans Blue
ECOG	Eastern cooperative oncology group
EDTMP	Ethylenediamine tetra(methylenephosphonic acid)
EMA	European Medicines Agency
ENETS	European neuroendocrine tumour society
EORTC	European organization for research and treatment of cancer
EORTC-QLQ30	European organization for the research and treatment of cancer Quality of Life Questionnaire
Er	Erbium
ESMO	European society for medical oncology
Eβ(max)	Maximum energy of beta particle
Eγ	Energy of gamma radiation
FAA/g	Administered activity per gram
FDA	Food and drug administration
FDG	Fludeoxyglucose
G-CSF	Granulocyte colony-stimulating factor
GEP-NET	Gastroenteropancreatic neuroendocrine tumours
GFR	Glomerular filtration rate
gNETS	Gastrointestinal neuroendocrine tumours
HPLC	High Performance Liquid Chromatography
HR	Hazard ratio
i.v.	Intravenous(ly)
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
ICP-OES	Inductively Coupled Plasma Optical Emission Spectrometry
ICRP	International Commission on Radiological Protection
IR	Infra Red Spectroscopy

KPS	Karnofski performance score
LAR	Long-acting release
Lu	Lutetium
Lu3+	Ionic lutetium
MA	Marketing authorisation
MAA	Marketing authorisation application
MIA	Manufacturing and Importation Authorisation
MDS	Myelodysplastic Syndrom
MIRD	Medical internal radiation dose
MR	Minimal response
MRI	Magnetic resonance imaging
n.c.a	Non carrier added
NET	Neuroendocrine tumours
ORR	Objective response rate
OS	Overall survival
PC	Prostate carcinoma
PD	Pharmacodynamics / / Progressive disease
PERCIST	PET response criteria in solid tumours
PET–CT	Positron emission tomography/Computed tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PL	Package leaflet
pNET	Pancreatic neuroendocrine tumour
PR	Partial remission
PRAC	Pharmacovigilance Risk Assessment Committee
PSA	Prostate-Specific Antigen
PSMA	Prostate-specific membrane antigen
QoL	Quality of life
RCT	Randomised clinical trial
RECIST	Response evaluation criteria in solid tumors
RLT	Radioligand therapy

SAEs	Serious adverse events
SD	Stable disease
SmPC	Summary of product characteristics
SSAs	Somatostatin analogues
SST	Somatostatin
SSTR	Somatostatin receptor
SUV	Standardized uptake value
SUVmax	Maximum standardized uptake value
TIAC	Time-integrated activity coefficient
TLS	Tumour lysis syndrome
TTP	Time to progression
UV - VIS	Ultra Violet Visible Spectroscopy
VAS	Visual analogue score
WHO	World health organisation

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	Ilumira
Active substance	Lutetium (^{177}Lu) chloride
INN or common name	Lutetium (^{177}Lu) chloride
Applicant	SHINE Europe B.V. Jan Salwaweg 1 E Verdieping 4 9641 LL Veendam NETHERLANDS
EMA Product Number	EMEA/H/C/006596
ATC code and Pharmacotherapeutic group	V10X L2: v10therapeutic radiopharmaceuticals, L3: v10xother therapeutic radiopharmaceuticals, L4: v10xxvarious therapeutic radiopharmaceuticals
Pharmaceutical form(s) and strength (s)	Radiopharmaceutical precursor, solution 37 GBq/ml
Packaging	vial (glass)
Package size(s)	2 mL vial: 1 2 , 3 and 4 vials 10 mL vial: 1 2 , 3 and 4 vials
Route of administration	Route of administration not applicable
Device or diagnostic	Not applicable
Orphan designation	N
Orphan indication status confirmed	Not applicable
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 10(a) of Directive 2001/83/EC
Final indication	Ilumira is a radiopharmaceutical precursor, and it is not intended for direct use in patients. It is to be used only for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with lutetium (^{177}Lu) chloride.
New active substance status	Not applied for

1.2. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.3. Eligibility to the centralised procedure

The applicant SHINE Europe B.V. submitted on 3 January 2025 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ilumira (Lutetium (^{177}Lu) chloride), through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 May 2024.

The applicant applied for the following indication: *'Ilumira is a radiopharmaceutical precursor, and it is not intended for direct use in patients. It is to be used only for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with lutetium (^{177}Lu) chloride.'*

1.4. Legal basis and dossier content

The legal basis for this application refers to:

Article 10a of Directive 2001/83/EC as amended – relating to applications relying on well-established medicinal use supported by bibliographic literature.

The well-established medicinal use application is supported by administrative information, complete quality data, non-clinical and clinical data based on bibliographic literature substituting all non-clinical tests and clinical studies.

1.5. Information on paediatrics

Not applicable.

1.6. Information on orphan market exclusivity

1.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:	Janet Koenig
Co-Rapporteur:	Antonio Gomez-Outes

The Rapporteur and Co-Rapporteur appointed by the PRAC were:

PRAC Rapporteur:	Adam Przybylkowski
PRAC Co-Rapporteur:	Martin Huber

The application was received by the EMA on	3 January 2025
The procedure started on	23 January 2025
The CHMP Rapporteur's first Assessment Report was received on	16 April 2025
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	16 April 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	30 April 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 May 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 August 2025
The following GMP inspection was requested by the CHMP and its outcome taken into consideration as part of the Quality assessment of the product: A GMP inspection at finished product manufacturing site SHINE Technologies LLC, 3380 Innovation Court, Janesville, WI 53546 USA between 25 and 29 August 2025. The outcome of the inspection carried out was issued on:	30 January 2025 12 November 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on	23 September 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	2 October 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	16 October 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 December 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	16 January 2026
The CHMP Rapporteur circulated the CHMP and PRAC updated Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	23 January 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ilumira on	29 January 2026

1.8. Final CHMP outcome

1.8.1. Final opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ilumira is favourable in the following indication(s):

Ilumira is a radiopharmaceutical precursor, and it is not intended for direct use in patients. It is to be used only for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with lutetium (^{177}Lu) chloride.

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

1.8.2. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.8.3. Other conditions and requirements of the marketing authorisation

1.8.3.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

1.8.4. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.8.4.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- at the request of the European Medicines Agency;
- whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

2. Introduction

2.1. Therapeutic Context

The applicant seeks a marketing authorisation for the medicinal product Ilumira with the following therapeutic indication

Ilumira is a radiopharmaceutical precursor, and it is not intended for direct use in patients. It is to be used only for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with lutetium (^{177}Lu) chloride.

Radionuclides have been used in medical applications such as diagnostic molecular imaging for decades, with the first radiopharmaceuticals commercialised in 1950. For example, tumours as well as metastases can be localised by radiopharmaceuticals targeting tumour-tissue, such as prostate-specific membrane-antigen (PSMA) or somatostatin-analogues (Sgouros G, 2020).

Apart from being used for diagnostic imaging, radiopharmaceuticals are also increasingly used in molecular radiotherapy or radioligand therapy (RLT).

2.2. Aspects of development

This application is based on Article 10a of Directive 2001/83/EC relating to applications relying on well-established medicinal use supported by bibliographic literature.

The data included in the present dossier is taken from publicly available information in the literature, mainly from the database of the National Center for Biotechnology Information PubMed. References to SmPCs of other authorised medicinal products have however been deleted from the dossier. An additional search was conducted using terms related to independent ^{177}Lu-labelled radiopharmaceuticals evaluated in the clinical context (e.g. DOTATATE, DOTATOC, PSMA).

The applicant justified the well-established use (WEU) following the criteria established for such applications:

- Duration of use: Evidence of regular clinical use in the EU over time, beyond clinical trials (e.g. real-world exposure, marketing experience, pharmacovigilance data, PSURs).
- Extent of use: Quantitative data on clinical practice in the EU, including prescription volumes, patient numbers, and geographical distribution.
- Scientific interest: Volume and quality of publications in peer-reviewed literature, excluding reliance on other MA dossiers or EPARs.
- Consistency of scientific assessments: Alignment of conclusions across independent publications and clinical guidelines.

It bears noting that, as applicable for all applications for marketing authorisation, the Applicant declared that the data submitted are not subject to regulatory data exclusivity in the Union.

To determine if the application fulfils the requirements of Article 10a with regard to well-established medicinal use of Ilumira (lutetium (^{177}Lu) chloride), a radiopharmaceutical precursor not intended for direct use in patients, the CHMP took into account the following factors:

- ***Time over which the substance has been used:***

Lutetium-labelled radiopharmaceuticals have been used for the treatment of patients in the EU since early 2000s, however the first reports indicating the use of $^{177}LuCl_3$ worldwide is dating from 1960

(Anderson et al., 1960). Due to its favourable radiochemical characteristics lutetium-177 is widely established in clinical practice when used for radiolabelling of molecular tracers. Several products containing $^{177}LuCl_3$ have been authorised in the EU, as well as in other countries outside the EU, for the radiolabelling of radiopharmaceuticals.

- ***Quantitative aspects of use of the substance:***

Based on literature search executed for the purpose of this Marketing Authorization Application, at least over 1300 patients have been treated in the EU with ^{177}Lu-labelled tracers in the course of published clinical trials so far (see Table 1 in 5.1.2. 5.1.2.). On those 1166 patients, 1044 have received 177-Lu tracers in clinical studies enrolling patients with NETS, 155 in clinical studies enrolling European patients with mCRPC and 125 in clinical studies enrolling European patients with other cancers (and treated with ^{177}Lu- therapy). The applicant declared that this number excludes publications concerning studies under data protection in the EU. Much higher number of patients treated with ^{177}Lu-labelled tracers is assumed given the following:

- several medicinal products containing $^{177}LuCl_3$ precursor have been authorised via the centralised procedures (EndolucinBeta approved in 2016, Lumark approved in 2020; Lutetium (^{177}Lu) chloride Billev approved in 2022; Theralugand approved in 2024),

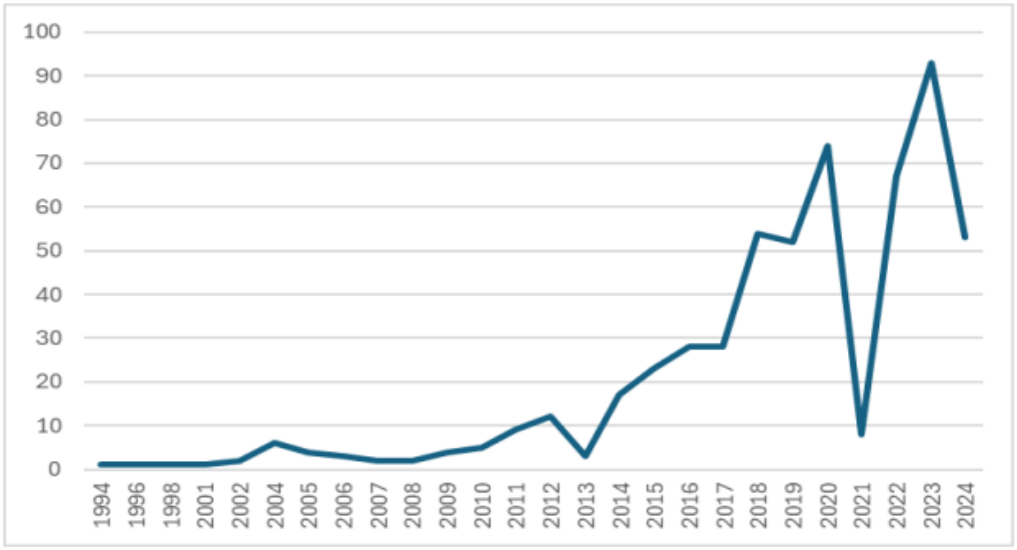
- $^{177}LuCl_3$ is used as starting material in the production of commercial radiopharmaceuticals,

- many patients in the EU are treated with ^{177}Lu -labelled radiopharmaceuticals on a named- patient or compassionate use basis,

- the use of ^{177}Lu-labelled compounds is widely distributed throughout the EU.

- ***Degree of scientific interest in the use of the substance (reflected in the published scientific literature):***

There is continued scientific interest in lutetium, with continuous publications in the EU for about 20 years. After evaluation of all public sources mentioned previously, 122 references were chosen to be included in the clinical overview, and 51 references were chosen to support the non-clinical overview to be presented by the applicant. The first clinical use of ^{177}Lu-labelled tracers in the EU was described for ^{177}Lu-DOTATATE in 2011 and ^{177}Lu-DOTATOC in 2005, respectively (in publications that do not fall under data protection in the EU). Since then, numerous publications have followed. The increasing total number of publications focussing on ^{177}Lu and ^{177}Lu-labelled radiopharmaceuticals are listed in PubMed. Those include clinical trials, meta-analyses and reviews. During the last two decades in total 553 publications have been reported, with the number of publications per year growing exponentially (see Figure 1).



* Using the terms "lutetium" OR "lutetium-177" OR "177Lu".

*Figure 1. Number of scientific publications per year**

Additional search of clinical trials conducted in EU (using the terms "lutetium" OR "177Lu) in clinicaltrials.gov confirms a constant, high level of scientific interest in the use of the substances containing ^{177}Lu. Up to date, over 40 positions have been listed.

- ***Coherence of scientific assessments:***

As per Annex 1, Part III, point 2.2 of Directive 2001/83/EC as amended in Directive 2003/63/EC, Annex I:

"Clinical information generated from clinical studies using the precursor itself is not considered to be relevant in the specific case of a radiopharmaceutical precursor intended solely for radiolabelling purposes. However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented".

The clinical utility of ^{177}Lu is demonstrated through the comprehensive evaluation of efficacy and safety data from published clinical trials, which have been conducted with ^{177}Lu-labelled tracer molecules, focussing mainly on the most established carriers used for radionuclide therapy targeting neuroendocrine tumours (NETs) or prostate cancer (PCa). The evidence accumulated consistently demonstrates a favourable benefit-risk ratio of the molecules studied, providing a clinically meaningful efficacy profile and an acceptable level of safety across the diseases studied.

The CHMP considers that the bibliographic literature provided by the applicant supports the well-established use and that the requirements of Article 10a of Directive 2001/83/EC are met.

2.3. Description of the product

Ilumira 37 GBq/mL is a sterile radiopharmaceutical precursor solution with an activity concentration of 37 GBq/ml at the calibration date and time, consisting of lutetium (^{177}Lu) chloride dissolved in diluted hydrochloric acid.

The medicinal product Ilumira (lutetium (^{177}Lu) chloride) is a radiopharmaceutical precursor solution, containing as active substance, lutetium (^{177}Lu) solution for radiolabelling as radionuclide precursor. According to article 1 no. 9 in "*Definitions*" of directive 2001/83/EC a radionuclide precursor is, citation: "*Any other radionuclide produced for the radiolabelling of another substance prior to administration*."

That means that the lutetium (^{177}Lu) solution for radiolabelling is not dedicated for direct patient use but to radiolabel another substance to obtain a radioactive labelled drug substance which has its own pharmacokinetic. That means the radiolabelled clinically relevant active substance consists of two main components. The component radionuclide lutetium-177 which provides as beta emitter the therapeutic radiation for cancer treatment and the second component which provide as tracer component the necessary pharmacokinetic (biodistribution) to transport the lutetium-177 to the tumour so that the β-radiation can reach the tumour cells.

The radionuclide lutetium-177 is used as oncologic therapeutic radionuclide because of its radioactive decay properties providing by its radioactive decay with a physical half-life of 6.7 days β-radiation with a maximum β-energy of 497 keV (78,6 %), 384 keV (9,1 %) and 176 keV (12,2 %).

The radionuclide precursor lutetium (^{177}Lu) solution for radiolabelling is described in Ph. Eur. monograph no. 2798.

Name:	[^{177}Lu]Lutetium chloride
Dosage form and strength:	Radionuclide precursor solution 37 GBq / mL calibration
Procedure:	Centralized marketing authorization procedure
Therapeutic class or indication:	Radionuclide precursor for radiolabeling in oncology
Proposed dosage range:	Not for direct patient use

2.4. Inspection issues

2.4.1. GMP inspection(s)

For the active substance manufacturer, a declaration of the QP of the importer MIAS Pharma Limited, Ireland, based on an audit of the active substance manufacturing site, confirms that the active substance manufacturing process is in compliance with good manufacturing practice of active substances.

For the manufacture of the finished product, initially only the registration of the manufacturing site for the business operations analysis, API manufacture, label, sterilize was declared by the applicant.

For the manufacturer of the finished product, the CHMP adopted a request for a routine GMP inspection. The GMP status was confirmed after inspection by the Irish Health Product Authority and a GMP certificate, dated 12th November 2025 covering the manufacturing of terminally sterilised small volume liquids of the type radiopharmaceuticals has been issued in EUDRA-GMDP. Importation and market release into the EU / EEA market is done by the importer MIAS Pharma Limited, Suite 1 First Floor, Stafford Hours, Strand Road, Portmarnock, D13 WC83, Ireland, which possesses a current valid Irish Manufacturer / Importer Authorisation, registration No. M12166/00001.

Conclusion:

For the manufacturing of the medicinal product ILUMIRA and its importation to the EU – market current valid GMP – certification exist.

2.4.2. GLP inspection(s)

No inspection required.

2.4.3. GCP inspection(s)

Not applicable.

This application is based Article 10a of the Directive 2001/83/EC relating to well-established use applications for medicinal products for human use, as amended, on the basis of the well- established use of ^{177}LuCl3 for the radiolabelling of radiopharmaceuticals, performed in the EU market for more than 10 years. No clinical studies are required and thus, no inspection is required.

3. Quality aspects

3.1. Introduction

The finished product is not intended for direct administration to patients, but it is to be used as starting material in the production of radioligand therapy products.

The finished product is presented as solution of radiopharmaceutical precursor 1 mL solution contains 37 GBq lutetium (^{177}Lu) chloride at calibration time (CAL) corresponding to maximum 9 micrograms of lutetium (^{177}Lu) (as chloride) as active substance.

Each 2 mL vial contains a volume varying from 0.05 mL to 1.2 mL corresponding to an activity ranging from 1.8 to 44.4 GBq at CAL.

Each 10 mL vial contains a volume varying from 0.05 mL to 6.6 mL corresponding to an activity ranging from 1.8 to 244.2 GBq at CAL.

CAL is defined as Tuesday following end of synthesis at 19:00 Central European Time (CET). The minimal specific activity is 3000 GBq/mg at CAL.

The activity at the date and time ordered by the customer, indicated as ART (activity reference time) is determined by the time elapsed from the CAL and the half-life of lutetium (^{177}Lu).

The other ingredient is diluted hydrochloric acid.

The product is available in clear type I glass 2 mL or 10 mL vial, with a fluorpolymer coated bromobutyl rubber stopper, closed with an aluminium cap as described in section 6.5 of the SmPC.

3.2. Active substance

General information

The chemical name of the active substance is (^{177}Lu) Lutetium trichloride corresponding to the molecular formula $^{177}LuCl_3$. It has molecular weight of 283.3 g/mol.

Lutetium chloride is presented as white monoclinic crystals and alternatively a hexahydrate $LuCl_3 \cdot 6H_2O$. The anhydrous lutetium (III) chloride has an $LuCl_3$ layer structure with octahedral lutetium ions. Detailed discussion of the crystal structures of (^{177}Lu) Lutetium chloride as a salt was not considered necessary because of the very low amount of radioactive Lutetium-177, and that the active substance will eventually be in solution in the finished product.

Regarding the radio physical properties, the active substance is a β-emitter with a maximum energy of 497 keV (78.6%). The average beta energy is approximately 130 keV. Lu-177 also emits low-energy γ-rays at 208 keV (11%) and 113 keV (6.4%).

The decay properties of the radioactive [^{177}Lu]Lutetium (half-life of 6.7 days) mean that the radionuclide will be completely decayed after less than 10 weeks, thus facilitating the nuclear waste management in the clinic.

Manufacture, characterisation, and process controls

The active substance is manufactured at one manufacturing site. Satisfactory GMP documentation has been provided.

The active substance is synthesised in 2 main steps.

In the initial application the manufacturing process was described as a single process including both active substance and finished product steps. During the procedure a major objection (MO) was raised requesting a separate process validation and / or evaluation of the active substance manufacturing process In response, the applicant provided the requested process validation data and a clear borderline between the active substance part and the finished product part of the manufacturing process was defined. This was considered satisfactory and the MO was resolved.

The active substance lutetium (^{177}Lu) chloride is produced by neutron bombarding of target followed by chemical and chromatographic purification.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance, dried lutetium (177Lu) chloride, is processed to the finished product without considerable storage times. Therefore, no container closure system is used.

Specification / Control of Drug Substance

There is no active substance specification.

For fast decaying radionuclides it is established that they are not isolated as an active substance but directly transferred to finished product manufacturing process to save time. This is typical for diagnostic radionuclides.

The quality of the (^{177}Lu) lutetium chloride active substance is confirmed by testing as per the finished product specification.

Considering that the only difference between the active substance and the finished product is that as active substance lutetium (^{177}Lu) chloride is a dried substance and is in the finished product solved in hydrochloric acid, this is considered acceptable.

Stability

For the same reasons as above, stability is described in the finished product section.

3.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is presented as clear colourless solution.

The goal of the finished product development was to create a lutetium (^{177}Lu) chloride solution for radiolabelling that complies with the Ph. Eur. monograph 2798, suitable for radiolabelling of carrier

molecules. The product is not intended for direct administration to patients, but it is to be used as starting material in the production of radioligand therapy products.

The active substance is an inorganic substance, well soluble in water and in diluted hydrochloric acid. ^{177}Lu in the active substance is a non-carrier-added radionuclide.

In line with Ph. Eur. monograph 2798 Lutetium (^{177}Lu) solution for radiolabelling, diluted hydrochloric acid is used as solvent. Hydrochloric acid is a simple inorganic acid with low potential for unintended side reactions with carrier molecules to be radiolabelled or their buffer components.

Diluted hydrochloric acid is a well known pharmaceutical ingredient, and its quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The CHMP requested as MO that the hydrochloric acid (concentrated) and the water for injection which form the excipient, diluted hydrochloric acid, should be described in the dossier. Following the CHMP feedback, as requested, hydrochloric acid (concentrated) and water for injection have been described in the dossier, excipient specifications for the diluted hydrochloric acid have also been established, including concentration and metal ion impurities. This was considered acceptable and the MO fulfilled.

The finished product manufacturing process development was described, including how the process parameters for the reconstitution, dispensing and sterilisation steps were defined and verified.

Extractable and leachable samples were analysed for inorganic elements by ICP-MS analysis did not detect any elements above the reporting thresholds, when compared to corresponding control. All elemental concentrations were below the ICH Q3D control limits for parenteral finished products.

The primary packaging is a clear type I glass vial, with a fluoropolymer coated bromobutyl rubber stopper, closed with an aluminium cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

During the procedure, a MO was raised as the manufacturer of the active substance and finished product lacked a suitable proof of GMP compliance. An inspection was performed at the site and satisfactory GMP documentation was provided. Therefore, the MO was considered solved.

The manufacturing process of the finished product consists in 3 main steps: reconstitution, dispensing, and sterilisation. The manufacturing process is considered non-standard.

Adequate in-process controls are applied during the manufacturing process. The specifications and control methods of intermediates and reagents have been presented. Sterilisation is performed by autoclave.
Active substance and finished product are produced in a continuous process. Therefore, the same impurities profile applies to both.

Major steps of the manufacturing process have been validated in 3 consecutive batches by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form: appearance (visual), radionuclidic identity (Gamma spectrometry), chloride identity (ICP-MS), pH, radioactivity content (dose calibrator or HPGe), specific activity (ICP-MS and HPGe), radionuclidic purity (gamma spectrometry), radiochemical purity (HPLC), chemical purity (ICP-MS), bacterial endotoxin (chromogenic kinetic method) and sterility (direct inoculation).

Lutetium (^{177}Lu) chloride solution is described in Ph. Eur. monograph no. 2798 with relevant characterised potential impurities which are considered in the specification.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. During the procedure a MO was raised requesting that the calibration of the radioactivity detectors used for the determination for the radioactive content should be done with [^{177}Lu] Lutetium solutions. Satisfactory information regarding the reference standards used for testing was presented and the MO was solved.

Batch analysis results are provided for a number of batches confirming the consistency of the manufacturing process and its ability to manufacture the intended product specification.

Stability of the product

The real time stability study of the finished product has been conducted on ten commercial scale batches stored at room temperature over a period of up to 14 days in inverted vial orientation (2 mL and 10 mL). The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Accelerated stability studies are not required since the available stability data covers the whole proposed shelf life (10 days). Photostability studies are not required due to the fact that the product is stored in lead shielding containers and does not have contact with light.

Samples were tested for appearance, radionuiclidic identity, chloride identity, pH, radioactivity content, specific activity, radionuclidic purity, radiochemical purity, chemical purity, sum of chemical impurities, bacterial endotoxin, and sterility. The analytical procedures used are stability indicating.

The results of the stability studies performed are within the acceptance criteria for all batches tested throughout the testing period, as per applied testing schedule.

Based on available stability data, the proposed shelf-life of 10 days and without special storage conditions as stated in the SmPC (section 6.3) are acceptable. After first opening, from a microbiological point of view, unless the method of withdrawal from the vial or any insertion into the vial precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Adventitious agents

No excipients derived from animal or human origin have been used.

3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

Four MOs were raised during the procedure; to provide a separate process validation and / or evaluation of the active substance manufacturing process to describe hydrochloric acid (concentrated) and water for injection, which form the excipient diluted hydrochloric acid, in the dossier, to provide proof of GMP compliance for the manufacturer of the active substance and finished product, and to request calibration of the radioactivity detectors used for the determination for the radioactive content with [^{177}Lu] Lutetium solutions. The responses provided were all deemed satisfactory and the MOs were considered fulfilled. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

3.6. Recommendation(s) for future quality development

Not applicable

4. Non-clinical aspects

4.1. Introduction

The present application is submitted under Article 10(a) of Directive 2001/83/EC as amended, relating to applications relying on well-established medicinal use supported by bibliographic literature and where the nonclinical part of the registration dossier consists of an up-to-date review of published data identified in the scientific literature.

Ilumira (lutetium (^{177}Lu) chloride) is not intended to be administered directly to the patient. As a precursor it should only be used for *in vitro* labelling of appropriate carrier molecules for targeted radiotherapy. Accordingly, it has no primary pharmacodynamic function and only very few data are available on the general pharmacodynamics.

4.2. Analytical methods

Not applicable.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

The proposed indication for $^{177}LuCl_3$ does not envisage any direct administration to patients. The active substance is intended to be used for *in vitro* radiolabelling of carrier molecules specifically designed for this purpose and further clinical use of the labelled carrier. The primary pharmacodynamic (PD) effect is thus a stable and efficient labelling.

Studies evaluating the stability of lutetium (^{177}Lu) complexes with various ligands have shown high stability suggesting a low risk of lutetium (^{177}Lu) release after administration (Stimmel et al., 1998; Li et al., 2001; Breeman et al., 2003; Brouwers et al., 2004).

Two ^{177}Lu-containing radiotherapeutics with a carrier currently approved in the European Union, ^{177}Lu-DOTATATE (Lutathera) and ^{177}Lu-PSMA-617 (Pluvicto), showed minimal metal release and high complex stability in PBS and human serum (Pawlak et al. 2007, Benesova et al. 2015).

4.3.1.2. Secondary pharmacodynamics

Lutetium was shown to displace calcium from various binding sites, e.g. from dog bone osteocalcin (Pilgaard Elements. Lanthanides and calcium binding interactions). Lutetium is known to interfere with γ-aminobutyric acid (GABA) neurotransmission increasing GABA currents in rat neurons (Kumamoto et al., 1996, Ma et al., 1993). Lutetium demonstrated a concentration-dependent inhibition of human mitochondrial nicotinamide adenine dinucleotide (NAD)-dependent malic enzyme (m-NAD-ME) (Kuo et al., 2004).

These effects are caused by free (not complexed) lutetium ions, which are not expected to form during radioligand therapy.

4.3.1.3. Safety pharmacology

Lutetium (^{177}Lu) was reported to inhibit smooth muscle contraction induced by norepinephrine, high potassium and histamine (Weiss et al., 1975). In the isolated ileum of the rabbit, lutetium (^{177}Lu) chloride

produced a concentration dependent relaxant effect. It was demonstrated to block circular and longitudinal muscular contractions in guinea pig enteric ganglia (Haley et al., 1964). These effects are manifestations of calcium blockade by lutetium as calcium entry is essential for contractions.

$LuCl_3$ administered intravenously to dogs led to a transient increase in blood pressure and heart rate but did not affect respiratory rates (Graca et al., 1964). In cats, no effects on respiration or on the cardiovascular system were observed following IV dosing of up to 10 mg/kg lutetium (^{177}Lu) chloride. However, administration of 20 mg/kg to cats induced a complete CV collapse coupled with respiratory paralysis (Haley et al., 1964). Similar effects on cardiovascular effects were noted after IV administration of 10 mg/kg hafnyl chloride to cats (hafnium is a product of lutetium radioactive decay) (Haley et al., 1962).

The reported effects are not clinically relevant as they are produced by free metal ions, which are not expected during radiotherapy.

4.3.1.4. Pharmacodynamic drug interactions

Non-clinical PD interaction studies have not been found in the literature.

4.3.2. Pharmacokinetics

4.3.2.1. Absorption

No specific studies were submitted with 177-lutetium. The characterization of absorption, distribution, metabolism and excretion (ADME) properties for lutetium is based on published data.

The absorption of lutetium following oral administration to rats was poor compared to intravenous (IV), intramuscular (IM) and intraperitoneal (IP) injection (Luckey et al., 1975, Durbin et al., 1956, Bruce et al., 1963). In mice, IP route resulted in better absorption than subcutaneous (SC) administration (Spode et al., 1958).

4.3.2.2. Distribution

Tissue distribution of radioactive ^{177}Lu was investigated in mice, rats and rabbits (Repetto-Llamazares et al., 2013, Araújo et al., 2007, Ando et al., 1989, Lungu et al., 2007, O'Mara et al., 1969). In these species, tissues with highest amounts of radioactivity were initially kidneys, liver and to a lesser extent spleen and bone marrow. With time, radioactivity slowly accumulated in skeleton. Considering the simultaneous radioactive decay, final concentration of lutetium in the skeleton is expected to be low. Therefore, ^{177}Lu distribution to bones does not appear clinically relevant. Moreover, after labelling with the carrier of choice the tissue distribution pattern of the resulting complex will be rather determined by the carrier, and not by lutetium.

4.3.2.3. Metabolism

$^{177}LuCl_3$ is not metabolised. It experiences a radioactive decay to hafnium (^{177}Hf), which is a stable isotope.

4.3.2.4. Excretion

When administered IV, lutetium is mainly excreted in urine (Durbin, 1959, O'Mara et al., 1969). After oral dosing, mostly faecal elimination was noted due to poor gastrointestinal absorption.

4.3.2.5. Pharmacokinetic drug interactions

Non-clinical pharmacokinetic drug interaction studies have not been found in the literature.

4.4. Toxicology

No new toxicology studies have been performed. Instead, a summary of literature reviews with the focus laying on the known toxic effects of lutetium was provided and is acceptable. Further, information on toxic effects of hafnium as the stable product after decay of lutetium had been studied in different mammalian species and using different administration routes and was included in the dossier.

4.4.1. Single-dose toxicity

Acute toxicity of lutetium chloride in mice included rapid deaths at high doses. Further signs included writhing, ataxia, laboured respiration, walking on toes with back arched, and sedation (Haley et al., 1964). In these studies, an oral and IP LD_{50} of 7100 mg/kg (Haley et al., 1964) and 315 mg/kg (Haley et al., 1964) was determined, respectively. Administration of rare earth element nitrates and oxides resulted in LD_{50} value of 290 mg/kg in mice and 335 mg/kg in rats (Bruce et al., 1963). Common findings in mice included rapid death at high doses, with evidence of peritonitis and accumulation of ascetic fluid. In rats, death was not as rapid, most animals dying up to 25 days after being injected, but these animals gained evidence of inflammation, accumulation of ascetic fluid, as well as distended abdomens and limb oedema.

Acute toxic effects were less pronounced with the decay product of lutetium, hafnium. Only a limited amount of literature has been presented for hafnium, but acute findings in mice indicate lower lethal dose values for hafnium chloride compared to lutetium chloride. In this study, an intraperitoneal LD_{50} of 112 mg/kg for hafnyl chloride was evaluated (Haley et al., 1962).

It has to be noted that the toxic doses in all the cited studies are well above in excess to those anticipated with levels of lutetium chloride and thus, the acute toxicity findings reported above are considered of limited clinical relevance.

4.4.2. Repeat-dose toxicity

Repeat dose oral toxicity of lutetium (0.01, 0.1 and 1% $LuCl_3$ in the diet) in its ionic form was evaluated in CRW rats. No signs of toxicity were observed in this study, and a NOEL was set at 1%, which corresponds to approximately to 1000 mg $LuCl_3$/kg (Haley et al., 1964).

Similarly, CFN rats fed a diet containing 0.01, 0.1 and 1 % $HfCl_4$ were examined for a period of 90 days. A dose-dependent metabolic adaptation in the liver, with perinuclear vacuolisation and course granularity of parenchymal cells was seen and was most pronounced in the 1% feeding group. Given the scarcity of the finding in the 0.01 and 0.1% feeding groups, the NOEL was considered to be 0.1%, which equates to 100 mg $HfCl_4$/kg (Haley et al., 1962). Guinea pigs dosed orally with 2000 mg/kg showed no significant toxic effects, although histopathology revealed increased liver weights, reduced kidney and spleen weight (Bibra, 1994).

4.4.3. Genotoxicity

The applicant indicated that nonclinical genotoxicity studies of lutetium (^{177}Lu) chloride have not been found in the literature. However, radiation emission from radionuclides such as lutetium (^{177}Lu) is expected to cause DNA damage, inducing apoptosis through the induction of a caspase-3 dependent mechanism and interferes with DNA-dependent protein kinase, which is associated with the repair of

DNA (Yong et al., 2016).

4.4.4. Carcinogenicity

Carcinogenicity studies have not been performed by the applicant. Instead, a summary of literature data was presented.

Muller et al. described the long-term effect of ip administration of lutetium (^{177}Lu) oxide in NMRI female mice. The study showed an increased rate of osteosarcoma formation after a 12-month exposure period to lutetium (^{177}Lu) (estimated dose 2,000-8,000 rad). This effect was comparable to that of the radiation from exposure to Strontium-90 (Müller et al., 1978). Another study by Muller et al. (Müller et al., 1980) evaluated the long-term effects of lutetium (^{177}Lu) (as a citrate) ip administration in mice. The incidence of osteosarcomas and the latency periods were evaluated. Most of the osteosarcomas were found in long bones and vertebrae (each 37%). A study in mice (Shelley, 1973) evaluated the formation of dysplastic cartilage at the site of intradermal (id) injection after hafnium oxychloride administration. Mice showed progressively enlarging papules at the injection sites in the ear. The chondrocytic masses appeared to arise from the upper surface of the plate corresponding to the side of the ear that had been treated by injection.

4.4.5. Developmental and reproductive toxicity

Due to the radioactive nature of ^{177}Lu and thus its DNA reactivity, $^{177}LuCl_3$ would likely result in toxic reproductive and developmental effects. Thus, no dedicated reproductive and developmental toxicity or juvenile animal studies with lutetium were presented.

The applicant proposed a contraindication for use of Ilumira in established or suspected pregnancy or when pregnancy has not been excluded.

4.4.6. Toxicokinetics and exposure margins

In terms of the safety associated with hafnium, theoretically the highest dose of hafnium would be the same as that of lutetium assuming that no lutetium is excreted before it decays completely. In view of this fact and the resulting safety factor per treatment (*over 690,000 based on the entire maximum treatment dose of ^{177}Lu-PSMA-617 of 44.4 GBq for 6 cycles of therapy in total in rats receiving 1% of daily diet, oral*), toxicity findings are considered of limited human relevance given the doses at which they occurred.

4.4.7. Local tolerance

There is a limited amount of local tolerance data presented for lutetium and hafnium. Some local irritation to the eye and strong irritation of abraded skin was seen after administration of $LuCl_3$ (Haley et al., 1964). Similar effects were observed with hafnyl chloride (Haley et al., 1962). The later irritation was considered related to the acidic nature of the compound. Most of the local toxicities were reversible.

4.4.8. Other toxicity studies

Not applicable.

4.4.9. Ecotoxicity/environmental risk assessment

As ^{177}Lutetium chloride is an inorganic salt and thus an electrolyte according to Q1 of the Guideline on the Environmental risk assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/4447/00

Rev. 1- Corr.) neither ERA studies nor a PBT screening are necessary. Additionally, the handling and disposal of radioactive materials are subject to strict regulations, therefore, ^{177}Lutetium chloride is not expected to pose a risk to the environment.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

Pharmacodynamic, pharmacokinetic and toxicological properties of ^{177}Lu chloride are well known. As ^{177}Lu chloride is a well-known active substance, the applicant has not provided additional studies and further studies are not required.

$^{177}LuCl_3$ is not meant for direct administration to patients. It will be clinically used for radiolabelling of carrier molecules. Lutetium (^{177}Lu) complexes demonstrate high stability with low risk of metal ion release.

The PK properties of lutetium (^{177}Lu) – labelled radiotherapeutic will be dependent on the carrier molecule that is to be radiolabelled with the isotope. The PK of free lutetium (^{177}Lu) chloride is only relevant in case of accidental IV administration, which is unlikely in clinical setting. However, information on distribution after inadvertent intravenous administration of lutetium (^{177}Lu) chloride is presented the Product information (see 5.2 Pharmacokinetic properties). Data from experiments on mice, rats and rabbits indicate that more than half the lutetium (^{177}Lu) entering the systemic circulation is deposited in the skeleton with only small amounts going to the liver and kidneys. Lutetium (^{177}Lu) has a biological half-life of between 10 and 40 days in the soft tissue in mice and rats but has a very long biological half-life in the skeleton. However, these long half-life values in skeleton are not of relevance for lutetium (^{177}Lu) chloride n.c.a., since it completely decays with a half-life of 6.7 days following administration, preventing any accumulation over time. Free lutetium (^{177}Lu) is not metabolized, although it decays to ^{177}Hf, which is a stable isotope. No free lutetium (^{177}Lu) is administered or released, so the metabolism of the final product will depend on the carrier molecule. Lutetium excretion has been reported in mice, rats and guinea pig, both through the urinary and gastrointestinal tract following oral and IP administration. After intravenous injection of lutetium (^{177}Lu) chloride, lutetium (^{177}Lu) is predominantly but slowly excreted in the urine. Some faecal elimination is also observed.

The acute toxicity profile of lutetium and hafnium was described in mice, rats and cats. Correspondent LD_{50} values were established by using different routes of administrations (PO, IP, IV). Signs of acute toxicity were ataxia, laboured respiration, or lethargy. Deaths occurred within 24 hours post dose, and peak was normally registered at 48 hours. The repeat-dose toxicity profile of lutetium and hafnium was described in rats only, up to a period of 90 days. Administration of lutetium (oral) resulted in no toxicity up to the 625 mg lutetium/kg BW. Signs of toxicity related to hafnium (oral) were dose-dependent metabolic adaptation reaction seen in the liver, with perinuclear vacuolization coarse granularity of the parenchymal cells at 555 mg hafnium/kg BW.

A high dose of 10 GBq of lutetium (^{177}Lu) chloride contains 2.4 µg lutetium, corresponding to a human dose of 0.034 µg/kg. This dose is approximately 7 orders of magnitude lower than the intraperitoneal LD50 in mice and more than 5 orders of magnitude lower than the NOEL observed in cats. Therefore, lutetium metal-ion toxicity of Ilumira (^{177}Lu)-labelled medicinal products can be excluded.

No genotoxicity studies were presented by the applicant. This is acceptable, considering the therapeutic dose levels intended. Moreover, studies to evaluate the genotoxic potential of radionuclides or radiopharmaceuticals are not considered useful and also not recommended by the draft CHMP "Guideline on the non-clinical requirements for radiopharmaceuticals" (EMA/CHMP/SWP/686140/2018).

According to Annex 1 Part I of Dir 2001/83/EC, carcinogenicity studies are required in case of a long-term exposure. Radiopharmaceuticals are used for a short period of time. Despite the known carcinogenic potential due to the radiation emitted during radioactive decay and described in NMRI female mice after 12 months of exposure to lutetium-177 by Müller et al., 1978 (estimated dose 2000-8000 rd, 20-80 Gy), the absence of carcinogenicity studies is considered acceptable, given the conditions for use of this product.

No dedicated reproductive and developmental toxicity or juvenile animal studies with lutetium were presented, which is acceptable. Due to the radioactive nature of ^{177}Lu and thus its DNA reactivity, $^{177}LuCl_3$ would likely result in toxic reproductive and developmental effects. The applicant proposes a contraindication for use of Ilumira in established or suspected pregnancy or when pregnancy has not been excluded. This is endorsed.

Local tolerance effects observed with lutetium (and hafnium) can be attributed to the acidic character of the solution, which produces irritation or even necrosis of the tissues. However, lutetium chloride is not intended for direct administration in humans.

As mentioned by the applicant, limits for elemental impurities are in line with the requirements of the Ph. Eur. Monograph 2798. For further information, see section 3. Quality aspects.

Comments on ERA:

The justification provided by the applicant was considered acceptable. As ^{177}Lutetium chloride is an inorganic salt and thus an electrolyte neither ERA studies nor a PBT screening are necessary according to the Guideline on the Environmental risk assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.). Furthermore, the handling and disposal of radioactive materials are subject to strict regulations, hence it can be expected that the environment will not be exposed to ^{177}Lutetium chloride.

4.5.2. Conclusions

Pharmacodynamic, pharmacokinetic and toxicological properties of 177Lu chloride are well known. $^{177}LuCl_3$ is not meant for direct administration to patients. It will be clinically used for radiolabelling of carrier molecules. The properties of lutetium (^{177}Lu) – labelled radiotherapeutic will be dependent on the carrier molecule that is to be radiolabelled with the isotope.

Regarding pharmacokinetics, several studies evaluating the distribution of free lutetium in mice, rats and rabbits following IV, IP, SC and IM administration reported that lutetium mainly accumulated in bone, liver, kidneys, and spleen.

A repeat dose oral toxicity of lutetium (up to 1% $LuCl_3$ in the diet) in its ionic form to CRW rats resulted in no signs of toxicity up to 625 mg lutetium/kg BW. Signs of toxicity related to hafnium (at 0.1% in the diet, oral administration) included dose-dependent metabolic adaptation reaction in the liver, with perinuclear vacuolization coarse granularity of the parenchymal cells at 555 mg hafnium/kg BW. Studies to evaluate the genotoxic and carcinogenic potential have not been performed since such studies are not considered useful for radiopharmaceuticals and radiopharmaceutical precursors. Local tolerance effects included irritation or even necrosis of the tissues due to the acidic nature of lutetium. Impurities are sufficiently characterized.

5. Clinical aspects

5.1. Introduction

$^{177}LuCl_3$ is not intended to be administered alone, but to be used for the in vitro radiolabelling of appropriate carrier molecules intended for radioligand therapy (RLT), mainly in the clinical context of neuroendocrine tumours and prostate cancer.

This application is based on Article 10a of the Directive 2001/83/EC relating to well-established use applications for medicinal products for human use, as amended, on the basis of the well-established use of $^{177}LuCl_3$ for the radiolabelling of radiopharmaceuticals, performed in the EU market for more than 10 years.

According to the Directive, the applicant shall not be required to provide the results of clinical trials if it can be demonstrated that the active substances of the medicinal product have a well-established medicinal use within the Community for at least ten years, with recognized efficacy and an acceptable level of safety. The numerous published clinical studies available of ^{177}Lu-labelled molecules according to their approved indications allow for an appropriate assessment of the Applicant's product.

The data included in the present dossier is taken from publicly available information in the literature, mainly from the database of the National Center for Biotechnology Information PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), together with appropriate information from summary product characteristics (SmPCs) of other medicinal products currently in the market. An initial PubMed search in April 2024 using the terms "lutetium" OR "lutetium-177" OR "177Lu" revealed about 680 hits, including no temporal constrains but limiting the outputs to "clinical trials, meta-analysis, randomized controlled trial, review and systematic review" in humans. As $^{177}LuCl_3$ is not intended to be used directly in patients but as precursor for the production of radiopharmaceuticals, an initial analysis of the retrieved results showed a majority of articles reporting the use of ^{177}Lu-labelled radiopharmaceuticals. Therefore, an additional search was conducted using terms related to the most common ^{177}Lu-labelled radiopharmaceuticals evaluated in the clinical context, especially those approved as medicinal products for the treatment of GEP-NETs and mCRPC. The strings used for these searches, applying the same filters as above, were ("Lutetium" AND "DOTATATE", [120 results ("Lutetium" AND "DOTATOC" [22 results]) and ("Lutetium" AND "PSMA" [155 results]). Each article was evaluated for relevance based on title, abstract or the complete article. In the cases of recent reviews and systematic reviews, whenever they referred to relevant articles not retrieved by the systematic search, the original articles were also consulted and incorporated to the analysis.

5.1.1. GCP aspects

Not applicable as no clinical study was conducted with Ilumira (lutetium (^{177}Lu) chloride).

5.1.2. Tabular overview of clinical trials

This application is based Article 10a of the Directive 2001/83/EC relating to well-established use applications for medicinal products for human use, as amended, on the basis of the well- established use of $^{177}LuCl_3$ for the radiolabelling of radiopharmaceuticals, performed in the EU market for more than 10 years. No clinical trials were required and performed with this precursor.

The data assessed in this section is based on scientific literature in accordance with the legal basis for this application.

Table 1. Documented studies where EU patients were enrolled

Study reference	Phase	Number of patients (EU)	Scope
Clinical studies enrolling European patients with NETs			
(Forrer *et al.*, 2005)	Phase I/II	27	Prospective clinical trial to evaluate the safety and efficacy of ^{177}Lu-DOTATOC in patients with GEP-NET
(Bodei *et al.*, 2011)	I/II	51	Prospective clinical trial to evaluate the safety and efficacy of ^{177}Lu-DOTATATE in patients with GEP-NETs
(Sansovini *et al.*, 2013)	Phase II	52	Prospective study to evaluate the safety and efficacy of ^{177}Lu-DOTATATE in patients with pancreatic NETs
(Kulkarni *et al.*, 2013)	Phase I	22	Prospective study to evaluate the PK properties of ^{177}Lu-DOTATATE in patients with NETs
(Schuchardt *et al.*, 2013)	Phase I	253	Prospective study to evaluate the PK properties of ^{177}Lu-DOTATATE (N=185), ^{177}Lu-DOTATOC(N=59) and ^{177}Lu-DOTANOC (N=9) in patients with NETs
(Romer *et al.*, 2014)	Prospective non-interventional	Not specified *	Prospective clinical trial to evaluate the safety and efficacy of ^{177}Lu-DOTATOC in patients with GEP-NET
(Baum *et al.*, 2016a)	Phase II	56	Prospective clinical trial to evaluate the safety and efficacy of ^{177}Lu-DOTATOC in patients with GEP-NETs
(Baum *et al.*, 2018)	Prospective non-interventional	378	Retrospective study to evaluate the safety and efficacy of ^{177}Lu-DOTATATE in patients with different NETs
(Puszkiel *et al.*, 2019)	Phase I/II	42	Prospective clinical trial to evaluate the PK properties of ^{177}Lu-

Study reference	Phase	Number of patients (EU)	Scope
			DOTATATE in patients with GEP-NETs
(Prasad *et al.*, 2020)	Prospective non-interventional	40	Retrospective clinical trial to evaluate the safety and efficacy of ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC in patients with GEP-NETs
(Sundlov *et al.*, 2022)	Phase II	96	Prospective clinical trial to evaluate the safety and efficacy of ^{177}Lu-DOTATATE and in patients with GEP-NETs
(Bober *et al.*, 2022)	Phase II	27	Prospective clinical trial to evaluate the safety (hepatotoxicity) of ^{177}Lu-DOTATATE in patients with different NETs
SUM of treated patients		1044**	
Clinical studies enrolling European patients with mCRPC			
(Baum *et al.*, 2016b)	Phase II	56	Prospective clinical trial to evaluate the safety and efficacy of ^{177}Lu-PSMA-617 in patients with mCRPC

Study reference	Phase	Number of patients (EU)	Scope
(Sarnelli *et al.*, 2019)	Phase II	9	Prospective clinical trial to evaluate the PK properties of ^{177}Lu-PSMA-617 in patients with mCRPC
(De Giorgi *et al.*, 2021)	Phase II	40	Prospective clinical trial to evaluate the safety and efficacy of ^{177}Lu-PSMA-617 in patients with mCRPC
(Rosar *et al.*, 2021)	Phase I/II	22	Prospective clinical trial to evaluate the renal safety of administering ^{177}Lu-PSMA-617 to patients with mCRPC and compromised renal function
(Khreish *et al.*, 2021)	Phase II	28	Prospective clinical trial to evaluate the safety and efficacy of ^{177}Lu-PSMA-617 in patients with mCRPC and presenting liver metastasis
SUM of treated patients		155	
Clinical studies enrolling European patients with other cancers and treated with ^{177}Lu radioimmunotherapy			
(Stillebroer *et al.*, 2013)	Phase I	23	Prospective clinical trial to evaluate the safety and efficacy of ^{177}Lu-CG250 in patients with ccRCC
(Forrer *et al.*, 2013)	Phase I/II	31	Prospective clinical trial to evaluate the safety and efficacy of ^{177}Lu-DOTA-rituximab in patients with B cell lymphoma
(Muselaers *et al.*, 2016)	Phase I/II	14	Prospective clinical trial to evaluate the safety and efficacy of ^{177}Lu-CG250 in patients with ccRCC
(Kolstad *et al.*, 2020)	Phase I/II	57	Prospective clinical trial to evaluate the safety and efficacy of ^{177}Lu-lilotomab satetraxetan in patients with Hodgkin B-cell lymphoma
SUM of treated patients		125	

Abbreviatures; ccRCC= Clear cell renal cell carcinoma; mCRPC=Metastatic castration-resistant prostate cancer; NET=Neuroendocrine tumour; GEP-NET= gastroenterohepatic NET; GI-NET=gastrointestinal NET

*This study included 141 patients treated with ^{177}Lu-DOTATOC, yet the publication does not specify how many of these patients were treated in Europe and how many in the USA.

**Patients of Romer et al. 2014 are not counted

It bears noting that, as applicable for all applications for marketing authorisation, the Applicant declared that the data submitted are not subject to regulatory data exclusivity in the Union.

5.2. Clinical pharmacology

5.2.1. Methods

N/A

5.2.2. Pharmacokinetics

N/A

5.2.2.1. Introduction

No biopharmaceutical studies have been performed with $^{177}LuCl_3$ solutions as Ilumira since only the final radiolabelled medicinal product is to be used. Thus, no associated analytical methods have been developed. In line with this, there are also no published biopharmaceutical studies available for $^{177}LuCl_3$ solution.

The corresponding characteristics of the radiolabelled medicinal products depend mainly on the carrier molecule to be radiolabelled (Forrer F, 2004, Hijnen NM, 2012).

5.2.2.2. Dosimetry

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor intended only for use in *in-vitro* labelling of carrier molecules for therapeutic purposes, therefore no clinical data on the absorption, distribution, metabolism and excretion of $^{177}LuCl_3$ is available. As ^{177}Lu-labelled radiopharmaceuticals are intravenously injected, the unintended injection of free $^{177}LuCl_3$ would have a complete systemic bioavailability, exposing all organs to different absorbed doses.

In case of accidental exposure to free ^{177}Lu, although its elimination from the blood and renal excretion is expected to occur fast, special precautions are included in section 4.9 of the SmPC to increase the elimination rate and limit the radiation exposure.

To estimate the radiation absorbed by the different human tissues in the case of exposition to non-conjugated ^{177}Lu following the administration of a ^{177}Lu-labelled medicinal product or accidental administration of $^{177}LuCl_3$, the applicant has conducted a dosimetry extrapolation using published biodistribution data from Swiss mice (Araujo et al., 2007). Araujo *et al.* published a summarizing report of biosdistribution studies carried out with lutetium (^{177}Lu) chloride in mice. See 4.3.2.2. for distribution properties (non-clinical) of lutetium (^{177}Lu) chloride. For the purpose of extrapolation, similar biological uptake and clearance in human to the one observed in mice was assumed.

Briefly, the authors studied the biodistribution of $^{177}LuCl_3$ administered intravenously in the different organs and tissues after different time points (1h, 4h and 24h). The animals were sacrificed at designated time intervals post-injection, and the organs of interest were removed. The percentage of the injected dose per whole organ (% ID/organ) and the percentage of the injected dose per gram of tissue (% ID/g) were determined. For dosimetry analysis, the percentage of the injected dose per gram

of tissue corrected for the physical decay of ^{177}Lu was used. This corrected estimation reflects only the loss due to biological clearance.

From the corrected % ID/g values, the fraction of administered activity per gram (FAA/g) was determined. Subsequently, the time-integrated activity coefficient (TIAC) was calculated, serving as measure of the radiopharmaceutical's retention in each organ. For the TIAC estimation, a 3D-RD-S software was employed, which implements the medical internal radiation dose (MIRD) S-value methodology, described in MIRD Pamphlet 21 (Bolch et al., 2009). Generally, a mono-exponential model was used to assess the activity-versus-time data; however, if an adequate fit was not obtained, numerical integration methods were utilized to ensure the TIAC accuracy.

For the extrapolation of mouse data to humans, the reference human body phantoms for various ages groups and sexes included in the ICRP 110 publication (Zankl et al., 2010) were used. Data conversion was performed using a formula that considers the mass relationships between mouse organs and human phantom organs. Special attention was paid to the modelling of specific organs: the activity in the mouse's large intestine was distributed into the different sections of the human large intestine (right colon, left colon, and rectosigmoid colon) based on their relative masses, and bone activity was assigned to the cortical and trabecular bone layers according to their volumes.

Finally, the absorbed dose for each human organ was calculated as the sum of dose contributions from all radioactivity-containing tissues. This calculation was performed using the MIRD S-value methodology (Bolch et al., 2009). This methodology is described by the following equation:

$$\mathrm{D}(\mathrm{r_T}) = \sum_{\mathrm{r_S}} \widetilde{\mathrm{A}}(\mathrm{r_S}) \cdot \mathrm{S}(\mathrm{r_T} \leftarrow \mathrm{r_S})$$

$$\tilde{A}(r_S) = \int_0^{\infty} A(r_S, t)$$

Where,

$\mathrm{D}(\mathrm{r_T})$ = absorbed dose to target tissue, $\mathrm{r_T}$,
$\widetilde{\mathrm{A}}(\mathrm{r_S})$ = TIAC in source tissue, $\mathrm{r_S}$,
$\mathrm{S}(\mathrm{r_T} \leftarrow \mathrm{r_S})$= S-value for source tissue $\mathrm{r_S}$ and target tissue,$\mathrm{r_T}$.

The resulting estimated organ absorbed radiation doses in various human phantoms using mouse biodistribution and activity data are shown in Table 2. The extrapolated data show kidneys and liver as the significant target organs for the biodistribution of lutetium (^{177}Lu) chloride, and red marrow as the dose limiting organ. Of note, these results are in line with the preference of free ^{177}Lu to bind to the skeleton and to be deposited in the liver, as reported in the literature (Sjogreen Gleisner et al., 2022).

Table 2. Absorbed Doses in humans by the different age groups and sexes for Lu-177 (mGy/MBq) estimated from Lu-177 biodistribution data in mice.

Target Organs	Adults		15 Year		10 Year		5 Year		1 Year		Newborn	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Adipose tissue	1.80E-03 ± 5.52E-04	1.60E-03 ± 4.53E-04	2.12E-03 ± 8.98E-04	2.09E-03 ± 8.50E-04	3.16E-03 ± 1.35E-03	3.13E-03 ± 1.35E-03	5.35E-03 ± 2.43E-03	5.31E-03 ± 2.43E-03	9.06E-03 ± 4.48E-03	9.04E-03 ± 4.48E-03	2.30E-02 ± 1.32E-02	2.29E-02 ± 1.32E-02
Adrenals	2.26E-02 ± 5.67E-03	2.90E-02 ± 8.91E-03	2.43E-02 ± 4.89E-03	2.56E-02 ± 5.31E-03	4.21E-02 ± 8.40E-03	4.21E-02 ± 8.40E-03	7.00E-02 ± 1.41E-02	7.00E-02 ± 1.41E-02	1.30E-01 ± 2.57E-02	1.30E-01 ± 2.57E-02	3.58E-01 ± 6.75E-02	3.58E-01 ± 6.75E-02
Alveolar-interstitial	2.48E-02 ± 5.84E-03	2.85E-02 ± 6.55E-03	2.89E-02 ± 7.55E-03	3.06E-02 ± 7.61E-03	5.06E-02 ± 1.26E-02	5.06E-02 ± 1.26E-02	8.39E-02 ± 2.09E-02	8.43E-02 ± 2.09E-02	1.61E-01 ± 3.50E-02	1.61E-01 ± 3.51E-02	4.73E-01 ± 1.10E-01	4.73E-01 ± 1.10E-01
Bronchioles secretary cells	1.93E-02 ± 3.93E-03	2.17E-02 ± 4.43E-03	1.69E-02 ± 3.48E-03	1.83E-02 ± 3.68E-03	3.03E-02 ± 6.18E-03	3.03E-02 ± 6.18E-03	5.03E-02 ± 1.01E-02	5.06E-02 ± 1.01E-02	1.08E-01 ± 2.27E-02	1.08E-01 ± 2.27E-02	2.96E-01 ± 6.01E-02	2.96E-01 ± 6.01E-02
Brain	4.50E-03 ± 1.33E-03	5.16E-03 ± 1.57E-03	5.59E-03 ± 1.62E-03	5.14E-03 ± 1.64E-03	8.23E-03 ± 2.67E-03	8.55E-03 ± 2.71E-03	1.32E-02 ± 4.46E-03	8.51E-03 ± 2.03E-03	1.98E-02 ± 8.09E-03	1.98E-02 ± 8.09E-03	5.58E-02 ± 2.29E-02	5.58E-02 ± 2.29E-02
Breast	2.27E-03 ± 1.12E-03	2.02E-03 ± 9.44E-04	3.26E-03 ± 1.34E-03	3.06E-03 ± 1.27E-03	4.87E-03 ± 1.88E-03	4.72E-03 ± 1.84E-03	8.83E-03 ± 3.65E-03	8.74E-03 ± 3.63E-03	1.24E-02 ± 5.33E-03	1.23E-02 ± 5.32E-03	4.06E-02 ± 1.55E-02	4.04E-02 ± 1.55E-02
Bronchi basal cells	2.53E-02 ± 5.21E-03	2.98E-02 ± 6.15E-03	1.57E-02 ± 3.20E-03	1.68E-02 ± 3.31E-03	2.78E-02 ± 5.53E-03	2.78E-02 ± 5.53E-03	4.64E-02 ± 9.31E-03	4.64E-02 ± 9.31E-03	1.00E-01 ± 2.08E-02	1.00E-01 ± 2.08E-02	2.65E-01 ± 5.35E-02	2.65E-01 ± 5.35E-02
Bronchi secretary cells	2.50E-02 ± 5.14E-03	2.95E-02 ± 6.07E-03	1.57E-02 ± 3.20E-03	1.68E-02 ± 3.31E-03	2.78E-02 ± 5.53E-03	2.78E-02 ± 5.53E-03	4.64E-02 ± 9.31E-03	4.64E-02 ± 9.31E-03	1.00E-01 ± 2.08E-02	1.00E-01 ± 2.08E-02	2.65E-01 ± 5.35E-02	2.65E-01 ± 5.35E-02
Endosteal cells	8.08E-02 ± 2.31E-02	9.68E-02 ± 2.77E-02	3.93E-02 ± 1.11E-02	4.26E-02 ± 1.21E-02	8.91E-02 ± 2.29E-02	8.91E-02 ± 2.29E-02	2.41E-01 ± 6.38E-02	2.41E-01 ± 6.38E-02	6.76E-01 ± 1.85E-01	6.76E-01 ± 1.85E-01	6.44E-01 ± 1.49E-01	6.44E-01 ± 1.49E-01

Target Organs	Adults		15 Year		10 Year		5 Year		1 Year		Newborn	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
ET1 basal cells	3.85E-03 ± 1.12E-03	3.51E-03 ± 1.02E-03	5.47E-03 ± 1.48E-03	2.16E-03 ± 5.12E-04	1.90E-03 ± 4.66E-04	1.89E-03 ± 4.65E-04	4.62E-03 ± 1.15E-03	4.56E-03 ± 1.14E-03	6.45E-03 ± 1.59E-03	6.37E-03 ± 1.56E-03	1.68E-02 ± 4.36E-03	1.66E-02 ± 4.31E-03
ET2 basal cells	3.38E-03 ± 9.05E-04	3.43E-03 ± 9.38E-04	1.88E-02 ± 5.90E-03	6.22E-03 ± 1.27E-03	7.96E-03 ± 1.83E-03	7.95E-03 ± 1.83E-03	1.26E-02 ± 2.93E-03	1.25E-02 ± 2.93E-03	1.76E-02 ± 4.42E-03	1.76E-02 ± 4.41E-03	3.72E-02 ± 7.73E-03	3.72E-02 ± 7.72E-03
Lens of the eye	2.00E-03 ± 5.18E-04	1.91E-03 ± 4.88E-04	1.82E-03 ± 5.11E-04	1.59E-03 ± 4.47E-04	2.40E-03 ± 6.61E-04	2.39E-03 ± 6.61E-04	3.27E-03 ± 9.56E-04	3.23E-03 ± 9.55E-04	3.77E-03 ± 1.07E-03	3.73E-03 ± 1.06E-03	8.73E-03 ± 2.39E-03	8.73E-03 ± 2.39E-03
Gall bladder wall	1.67E-02 ± 1.75E-02	1.98E-02 ± 1.97E-02	1.03E-02 ± 8.64E-03	1.16E-02 ± 1.01E-02	1.57E-02 ± 1.31E-02	1.58E-02 ± 1.31E-02	2.34E-02 ± 1.76E-02	2.36E-02 ± 1.76E-02	3.96E-02 ± 3.23E-02	3.97E-02 ± 3.22E-02	8.41E-02 ± 5.29E-02	8.49E-02 ± 5.30E-02
Heart wall	1.77E-02 ± 2.99E-03	2.14E-02 ± 3.58E-03	1.85E-02 ± 2.46E-03	2.00E-02 ± 3.12E-03	3.31E-02 ± 5.36E-03	3.31E-02 ± 5.37E-03	5.45E-02 ± 8.33E-03	5.44E-02 ± 8.32E-03	9.83E-02 ± 1.25E-02	9.86E-02 ± 1.27E-02	2.87E-01 ± 3.84E-02	2.87E-01 ± 3.84E-02
Kidneys	1.03E-01 ± 4.51E-02	1.31E-01 ± 5.77E-02	1.32E-01 ± 5.87E-02	1.50E-01 ± 6.74E-02	2.40E-01 ± 1.08E-01	2.40E-01 ± 1.08E-01	4.06E-01 ± 1.81E-01	4.06E-01 ± 1.81E-01	8.53E-01 ± 3.92E-01	8.53E-01 ± 3.92E-01	2.50E+00 ± 1.16E+00	2.50E+00 ± 1.16E+00
Left colon stem cell layer	1.19E-02 ± 1.27E-01	1.29E-02 ± 1.63E-01	1.50E-02 ± 1.68E-01	1.44E-02 ± 1.95E-01	2.46E-02 ± 3.09E-01	2.46E-02 ± 3.09E-01	4.08E-02 ± 5.23E-01	4.08E-02 ± 5.23E-01	7.09E-02 ± 1.03E+00	7.09E-02 ± 1.03E+00	2.07E-01 ± 2.58E+00	2.07E-01 ± 2.58E+00
Liver	1.74E-01 ± 1.99E-01	2.14E-01 ± 2.45E-01	2.25E-01 ± 2.58E-01	2.49E-01 ± 2.86E-01	4.01E-01 ± 4.62E-01	4.01E-01 ± 4.62E-01	6.78E-01 ± 7.80E-01	6.78E-01 ± 7.80E-01	1.36E+00 ± 1.58E+00	1.36E+00 ± 1.58E+00	3.57E+00 ± 4.11E+00	3.57E+00 ± 4.11E+00
Extrathoracic lymph nodes	1.99E-03 ± 4.67E-04	1.91E-03 ± 5.31E-04	5.93E-03 ± 1.01E-03	5.16E-03 ± 8.87E-04	7.33E-03 ± 1.34E-03	7.32E-03 ± 1.34E-03	1.08E-02 ± 2.08E-03	1.07E-02 ± 2.08E-03	1.39E-02 ± 2.78E-03	1.39E-02 ± 2.78E-03	4.04E-02 ± 7.65E-03	4.04E-02 ± 7.65E-03

Target Organs	Adults		15 Year		10 Year		5 Year		1 Year		Newborn	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Systemic lymph nodes	5.04E-03 ± 1.57E-03	5.08E-03 ± 1.67E-03	3.59E-03 ± 1.04E-03	3.07E-03 ± 9.15E-04	4.98E-03 ± 1.38E-03	4.98E-03 ± 1.38E-03	8.42E-03 ± 2.51E-03	8.42E-03 ± 2.51E-03	1.36E-02 ± 4.79E-03	1.36E-02 ± 4.79E-03	3.36E-02 ± 1.05E-02	3.36E-02 ± 1.05E-02
Thoracic lymph nodes	4.70E-03 ± 1.23E-03	5.32E-03 ± 1.30E-03	5.46E-03 ± 2.86E-03	6.48E-03 ± 4.42E-03	8.95E-03 ± 4.61E-03	8.95E-03 ± 4.61E-03	1.56E-02 ± 8.86E-03	1.56E-02 ± 8.86E-03	2.45E-02 ± 1.72E-02	2.45E-02 ± 1.72E-02	5.42E-02 ± 2.87E-02	5.42E-02 ± 2.87E-02
Muscle	5.23E-03 ± 7.79E-04	6.31E-03 ± 9.47E-04	6.82E-03 ± 1.00E-03	7.34E-03 ± 1.12E-03	1.22E-02 ± 1.90E-03	1.22E-02 ± 1.90E-03	2.16E-02 ± 3.57E-03	2.16E-02 ± 3.57E-03	4.78E-02 ± 9.35E-03	4.79E-02 ± 9.36E-03	9.72E-02 ± 1.45E-02	9.73E-02 ± 1.45E-02
Oral Mucosa	3.32E-03 ± 8.54E-04	6.15E-03 ± 1.87E-03	6.89E-03 ± 1.39E-03	5.68E-03 ± 1.11E-03	8.66E-03 ± 1.81E-03	8.79E-03 ± 1.85E-03	1.50E-02 ± 3.64E-03	1.52E-02 ± 3.70E-03	1.62E-02 ± 3.86E-03	1.66E-02 ± 3.96E-03	4.94E-02 ± 1.31E-02	5.06E-02 ± 1.35E-02
Esophagus	8.72E-03 ± 2.75E-03	9.38E-03 ± 2.93E-03	8.94E-03 ± 2.89E-03	8.30E-03 ± 2.78E-03	1.42E-02 ± 4.66E-03	1.42E-02 ± 4.69E-03	2.30E-02 ± 7.69E-03	2.30E-02 ± 7.68E-03	3.17E-02 ± 9.70E-03	3.17E-02 ± 9.69E-03	1.15E-01 ± 3.78E-02	1.15E-01 ± 3.78E-02
Ovaries	N/A	4.74E-03 ± 1.47E-03	N/A	3.17E-03 ± 8.01E-04	N/A	4.25E-03 ± 1.14E-03	N/A	7.54E-03 ± 2.11E-03	N/A	1.47E-02 ± 4.23E-03	N/A	5.69E-02 ± 1.84E-02
Pituitary gland	3.06E-03 ± 8.02E-04	9.20E-03 ± 2.95E-03	5.35E-03 ± 1.26E-03	4.30E-03 ± 1.02E-03	6.41E-03 ± 1.53E-03	6.90E-03 ± 1.70E-03	1.01E-02 ± 2.50E-03	1.05E-02 ± 2.78E-03	2.16E-02 ± 5.19E-03	2.28E-02 ± 5.46E-03	4.50E-02 ± 1.22E-02	4.99E-02 ± 1.40E-02
Pancreas	1.02E-02 ± 4.96E-03	1.64E-02 ± 4.58E-03	1.50E-02 ± 2.89E-03	1.64E-02 ± 3.26E-03	2.57E-02 ± 5.34E-03	2.57E-02 ± 5.34E-03	4.12E-02 ± 7.57E-03	4.13E-02 ± 7.57E-03	6.95E-02 ± 1.13E-02	6.95E-02 ± 1.13E-02	2.04E-01 ± 3.52E-02	2.04E-01 ± 3.52E-02
Prostate	2.15E-03 ± 5.22E-04	N/A	2.64E-03 ± 7.63E-04	N/A	4.88E-03 ± 1.31E-03	N/A	7.68E-03 ± 2.15E-03	N/A	1.10E-02 ± 3.05E-03	N/A	3.56E-02 ± 1.18E-02	N/A

Target Organs	Adults		15 Year		10 Year		5 Year		1 Year		Newborn	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Red marrow	2.38E-02 ± 5.57E-03	2.65E-02 ± 6.05E-03	3.77E-02 ± 8.88E-03	3.84E-02 ± 9.09E-03	4.11E-02 ± 9.32E-03	4.11E-02 ± 9.32E-03	9.45E-02 ± 2.18E-02	9.45E-02 ± 2.18E-02	2.27E-01 ± 5.48E-02	2.27E-01 ± 5.48E-02	7.13E-01 ± 1.66E-01	7.13E-01 ± 1.66E-01
Right colon stem cell layer	1.32E-02 ± 1.26E-01	1.36E-02 ± 1.63E-01	1.65E-02 ± 1.67E-01	1.53E-02 ± 1.94E-01	2.65E-02 ± 3.07E-01	2.65E-02 ± 3.07E-01	4.39E-02 ± 5.16E-01	4.39E-02 ± 5.16E-01	7.44E-02 ± 1.03E+00	7.44E-02 ± 1.03E+00	2.15E-01 ± 2.55E+00	2.15E-01 ± 2.55E+00
Rectosigmoid Colon stem cell layer	8.74E-03 ± 5.95E-02	9.34E-03 ± 7.91E-02	1.09E-02 ± 7.65E-02	9.95E-03 ± 8.88E-02	1.74E-02 ± 1.45E-01	1.74E-02 ± 1.45E-01	2.80E-02 ± 2.34E-01	2.80E-02 ± 2.34E-01	4.73E-02 ± 5.08E-01	4.73E-02 ± 5.08E-01	1.37E-01 ± 9.70E-01	1.37E-01 ± 9.70E-01
Salivary glands	2.52E-03 ± 6.31E-04	3.18E-03 ± 8.61E-04	5.00E-03 ± 1.03E-03	4.16E-03 ± 8.89E-04	6.26E-03 ± 1.42E-03	6.23E-03 ± 1.41E-03	9.83E-03 ± 2.40E-03	9.74E-03 ± 2.38E-03	1.32E-02 ± 3.30E-03	1.31E-02 ± 3.28E-03	4.51E-02 ± 1.25E-02	4.48E-02 ± 1.24E-02
Small intestine stem cell layer	9.89E-03 ± 2.72E-03	9.21E-03 ± 2.63E-03	2.52E-02 ± 9.12E-03	2.68E-02 ± 1.03E-02	4.32E-02 ± 1.65E-02	4.32E-02 ± 1.65E-02	7.24E-02 ± 2.78E-02	7.24E-02 ± 2.78E-02	1.34E-01 ± 5.49E-02	1.34E-01 ± 5.49E-02	3.80E-01 ± 1.47E-01	3.80E-01 ± 1.47E-01
Skin	1.77E-03 ± 4.82E-04	2.06E-03 ± 5.85E-04	2.22E-03 ± 5.99E-04	2.16E-03 ± 5.87E-04	3.56E-03 ± 9.77E-04	3.56E-03 ± 9.77E-04	5.57E-03 ± 1.58E-03	5.57E-03 ± 1.58E-03	8.47E-03 ± 2.39E-03	8.47E-03 ± 2.40E-03	2.71E-02 ± 8.46E-03	2.71E-02 ± 8.47E-03
Spleen	1.60E-02 ± 5.03E-03	1.91E-02 ± 6.21E-03	1.98E-02 ± 6.49E-03	2.03E-02 ± 6.99E-03	3.35E-02 ± 1.14E-02	3.35E-02 ± 1.14E-02	5.61E-02 ± 1.91E-02	5.61E-02 ± 1.91E-02	9.85E-02 ± 3.72E-02	9.85E-02 ± 3.72E-02	2.97E-01 ± 1.02E-01	2.97E-01 ± 1.02E-01
Stomach stem cell layer	3.87E-02 ± 9.95E-03	4.84E-02 ± 1.27E-02	4.73E-02 ± 1.22E-02	5.17E-02 ± 1.39E-02	8.48E-02 ± 2.23E-02	8.48E-02 ± 2.23E-02	1.42E-01 ± 3.76E-02	1.42E-01 ± 3.76E-02	2.78E-01 ± 7.56E-02	2.78E-01 ± 7.56E-02	7.53E-01 ± 2.01E-01	7.53E-01 ± 2.01E-01
Testes	1.73E-03 ± 5.25E-04	N/A	2.43E-03 ± 7.03E-04	N/A	5.33E-03 ± 1.69E-03	N/A	6.61E-03 ± 2.03E-03	N/A	6.68E-03 ± 1.93E-03	N/A	2.09E-02 ± 6.86E-03	N/A

Target Organs	Adults		15 Year		10 Year		5 Year		1 Year		Newborn	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Thymus	3.29E-03 ± 8.54E-04	3.01E-03 ± 7.92E-04	3.57E-03 ± 9.35E-04	3.63E-03 ± 9.49E-04	5.92E-03 ± 1.70E-03	5.94E-03 ± 1.70E-03	9.54E-03 ± 2.95E-03	9.57E-03 ± 2.96E-03	1.47E-02 ± 4.57E-03	1.48E-02 ± 4.58E-03	4.89E-02 ± 1.50E-02	4.91E-02 ± 1.50E-02
Thyroid	4.69E-03 ± 1.32E-03	4.88E-03 ± 1.37E-03	5.29E-03 ± 1.63E-03	4.65E-03 ± 1.35E-03	7.67E-03 ± 2.40E-03	7.67E-03 ± 2.40E-03	1.26E-02 ± 3.89E-03	1.26E-02 ± 3.89E-03	1.85E-02 ± 5.48E-03	1.84E-02 ± 5.48E-03	6.96E-02 ± 2.20E-02	6.96E-02 ± 2.20E-02
Tongue	3.02E-03 ± 7.67E-04	3.31E-03 ± 8.78E-04	4.90E-03 ± 1.14E-03	4.22E-03 ± 9.95E-04	6.68E-03 ± 1.63E-03	6.73E-03 ± 1.65E-03	1.05E-02 ± 2.68E-03	1.05E-02 ± 2.71E-03	1.36E-02 ± 3.55E-03	1.38E-02 ± 3.59E-03	4.42E-02 ± 1.30E-02	4.46E-02 ± 1.32E-02
Tonsils	3.88E-03 ± 1.07E-03	3.02E-03 ± 7.82E-04	5.18E-03 ± 9.79E-04	4.91E-03 ± 9.87E-04	6.99E-03 ± 1.49E-03	6.94E-03 ± 1.48E-03	1.05E-02 ± 2.47E-03	1.04E-02 ± 2.45E-03	1.37E-02 ± 3.24E-03	1.36E-02 ± 3.22E-03	5.01E-02 ± 1.25E-02	4.97E-02 ± 1.24E-02
Urinary bladder wall	1.79E-03 ± 4.40E-04	2.14E-03 ± 6.14E-04	2.02E-03 ± 4.84E-04	1.93E-03 ± 4.70E-04	3.00E-03 ± 7.32E-04	2.90E-03 ± 7.00E-04	4.44E-03 ± 1.13E-03	4.60E-03 ± 1.12E-03	8.66E-03 ± 2.37E-03	8.83E-03 ± 2.34E-03	1.90E-02 ± 5.19E-03	1.69E-02 ± 4.68E-03
Ureters	3.03E-03 ± 8.97E-04	3.88E-03 ± 1.26E-03	4.23E-03 ± 1.05E-03	5.04E-03 ± 1.20E-03	6.75E-03 ± 1.74E-03	6.82E-03 ± 1.75E-03	1.25E-02 ± 3.53E-03	1.27E-02 ± 3.56E-03	2.17E-02 ± 6.87E-03	2.18E-02 ± 6.89E-03	6.13E-02 ± 1.71E-02	6.20E-02 ± 1.73E-02
Uterus	N/A	1.88E-03 ± 6.57E-04	N/A	1.08E-02 ± 3.74E-03	N/A	1.70E-02 ± 5.94E-03	N/A	8.36E-03 ± 2.46E-03	N/A	2.39E-02 ± 7.55E-03	N/A	6.71E-02 ± 2.24E-02
Whole-body Dose	1.80E-03 ± 5.52E-04	1.60E-03 ± 4.53E-04	1.89E-03 ± 1.57E-02	1.97E-03 ± 1.55E-02	2.93E-03 ± 2.79E-02	2.88E-03 ± 2.53E-02	4.52E-03 ± 4.84E-02	4.45E-03 ± 4.36E-02	7.61E-03 ± 1.00E-01	7.52E-03 ± 8.97E-02	1.66E-02 ± 2.42E-01	1.65E-02 ± 2.19E-01
Effective Whole-body Dose (mSv/MBq)	2.26E-02 ± 5.67E-03	2.90E-02 ± 8.91E-03	2.87E-02 ± 1.54E-02	3.06E-02 ± 1.74E-02	4.75E-02 ± 2.78E-02	4.75E-02 ± 2.78E-02	8.34E-02 ± 4.67E-02	8.34E-02 ± 4.68E-02	1.68E-01 ± 9.37E-02	1.69E-01 ± 9.39E-02	4.61E-01 ± 2.37E-01	4.64E-01 ± 2.38E-01

Dose calculations (absorbed normalised doses for target organs [mGy/MBq] and effective normalised doses [mSv/MBq]) were performed using the 3D-RD-S software developed by Rapid. This estimation uses the time-integrated activity coefficient (TIAC) in the source tissues and the S-value for source tissue and target tissue, representing the distribution

of the radioactivity to the target tissue. Organ doses are listed below for an adult male and female model, according to ICRP 110 (International Commission on Radiological Protection).

Based on the estimated human absorbed doses (Table 3), a 1 GBq administered activity of ^{177}Lu would result in a whole-body dose of less than 50 mSv (the yearly occupational whole-body dose limit) in adult, 15-year-old, and 10-year-old phantoms of both genders, using mouse-derived data. The whole-body dose was observed to increase rapidly in younger pediatric phantoms, primarily attributed to their smaller whole-body mass. Liver doses were found to be considerably greater than those of other tissues due to the radionuclide's extended uptake and prolonged residence time within the organ.

Table 3. Estimated absorbed dose to kidneys, liver, red marrow, and whole-body for a 1.0 GBq (27 mCi) administered activity of Lu-177 derived from mouse data

Male	**Dose (mGy)**					
	Adult	**15 YO**	**10 YO**	**5 YO**	**1 YO**	**Infant**
Kidneys	103.304	132.472	240.484	405.834	852.885	2495.101
Liver	174.230	224.665	401.445	678.067	1362.600	3574.706
Red Marrow	23.830	37.703	41.103	94.504	226.542	712.608
Whole-body (mSv)	22.730	28.718	47.464	83.353	167.845	461.089
Female	**Adult**	**15 YO**	**10 YO**	**5 YO**	**1 YO**	**Infant**
Kidneys	130.677	149.526	240.486	405.833	852.888	2495.101
Liver	213.819	248.637	401.445	678.069	1362.601	3574.708
Red Marrow	26.474	38.418	41.101	94.474	226.543	712.611
Whole-body (mSv)	27.238	30.607	47.474	83.418	168.613	464.165

The kidneys and liver are identified as receiving the highest doses, but they are really under the dose limit generally considered for these organs (Dawson et al., 2010; Marks et al., 2010). The red marrow was consistently identified as the dose-limiting organ for all phantoms, for which a maximum dose of 2 Gy is generally accepted in adults, based on experience with ^{131}I labeled antibodies (O'Donoghue et al., 2002).

Besides the organ distribution and dosimetry values expected upon the administration of free ^{177}Lu, multiple studies have evaluated the distribution and organ dosimetry of the most relevant ^{177}Lu-labelled radiopharmaceuticals, which mainly depend on the PK properties of the molecular carrier to which ^{177}Lu is incorporated.

^{177}Lu-labelled radiopharmaceuticals are administered intravenously, for which the blood elements are the first to be exposed to radiation. The major determinant of radiation exposure of the haematopoietic stem cells is radiopharmaceutical circulation within the bone marrow. However, specific targeting mechanisms to more differentiated blood cell progenitors may also contribute. For instance, in the case of ^{177}Lu-DOTATATE, due to the fact that SSRs are overexpressed on activated leucocyte subtypes, such as lymphocytes and monocytes, the exposure of these cells to radiation is expected to be higher (Sjogreen Gleisner et al., 2022).

The kidney is generally considered the dose-limiting organ in therapy with ^{177}Lu-DOTATATE, owing to unspecific uptake mechanisms by proximal tubular cells. In fact, some studies have demonstrated dose-dependent renal toxicity at a biologically effective dose of 28 Gy for patients with risk factors for renal toxicity and 40 Gy for those without risk factors (Sundlov et al., 2022).

However, when administered with concurrent kidney protection, the level of reported nephrotoxicity with ^{177}Lu-DOTATATE is mainly limited to disease-related events, and for therapy with ^{177}Lu-PSMA-617, it appears to be negligible at current activities. On the other hand, due to the expression of PSMA in salivary glands and lacrimal glands, the radiation absorbed doses to these organs is superior for ^{177}Lu-PSMA-617 than for ^{177}Lu-DOTATATE. Yet, it has been reported a low incidence of toxicity caused by ^{177}Lu-PSMA-617 uptake by parotid glands at values bellow 10 Gy, and an absorbed dose limit of 20 Gy has been proposed (Sjogreen Gleisner et al., 2022).

Pharmacokinetic properties of ^{177}Lu-labelled radiopharmaceuticals

Pharmacokinetic properties of radiopharmaceuticals used for the treatment of NETs

^{177}Lu-labelled radiopharmaceuticals used in the treatment of NETs such as ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC are administered by IV injection, for which they present complete bioavailability.

As the efficacy of radiopharmaceuticals is associated with the dose absorbed by tumour lesions, one strategy that has been evaluated in the design of ^{177}Lu-labelled radiopharmaceuticals is the introduction of modifications aimed at improving the residence time in the blood through the addition of albumin-binding motifs. For instance, in a first-in-human study conducted in patients with advanced metastatic NETs who received a single dose of ^{177}Lu-DOTATATE or its derivative incorporating the Evans Blue (EB) albumin-binding motif (^{177}Lu-DOTA-EB-TATE), compared with ^{177}Lu-DOTATATE, ^{177}Lu-DOTA-EB-TATE showed extended circulation in the blood and achieved a 7.9-fold increase of tumour dose delivery. On the other hand, as the main dose limitation of radiopharmaceuticals is the fraction absorbed by the kidneys due to potential nephrotoxic effects (see section 5.4. Clinical safety), increasing the blood residence time of ^{177}Lu-labelled radiopharmaceuticals can also be associated with increased risks of safety issues. In fact, in the above-mentioned study, although both treatments ^{177}Lu-DOTATATE and ^{177}Lu-DOTA-EB-TATE were well-tolerated, the absorbed doses to the kidneys and bone marrow were also significantly higher in those patients receiving ^{177}Lu-DOTA-EB-TATE (Zhang et al., 2018).

Due to the relevance of potential radiotoxicity of ^{177}Lu, the ratio of the absorbed dose to the tumours and the absorbed dose to healthy tissue is a very relevant factor to consider, especially for small peptide derivatives, as they are partially reabsorbed by/in? the kidney proximal tubules (Uccelli et al., 2021). Although different ^{177}Lu-labelled radiopharmaceuticals share similar characteristics in terms of administration, distribution, metabolism and excretion, various studies have reported different PK properties, in general consistent with the binding affinity of the SSA ligand portion of the molecule to SSTRs, which impacts the amount of uptake by the tumour and healthy tissues i.e., those with stronger binding affinities show superior uptakes in the tumour but also in the kidneys and other healthy tissues (Uccelli et al., 2021).

A study comparing the administration of 3.7 GBq ^{177}Lu-DOTATOC and the same dose of ^{177}Lu-DOTATATE, both given to the same patients with metastasised NETs on two different occasions, observed significantly longer residence times in the spleen (1.5-fold increase), the kidneys (1.4-fold increase) and the tumours (2.1-fold increase) with the use of ^{177}Lu-DOTATATE (Esser et al., 2006). Similar results were reported in a study conducted in patients with metastatic NETs subjected to consecutive cycles of treatment, which reported superior tumoral uptake, residence time and mean absorbed dose by the kidneys with the use of ^{177}Lu-DOTATATE compared to ^{177}Lu-DOTATOC, although in this case, the most favourable tumour to kidney ratio was observed for ^{177}Lu-DOTATOC (Kulkarni et al., 2013). Finally, a study conducted in 253 patients with metastasised NETs who underwent RLT with ^{177}Lu-DOTATATE, ^{177}Lu-DOTATOC or ^{177}Lu-DOTANOC, reported the highest uptake for ^{177}Lu-DOTANOC due to the longer residence time of ^{177}Lu-DOTANOC in malignant lesions. Yet, ^{177}Lu-

DOTANOC also showed the least favourable tumour to healthy tissues ratio, including the kidneys (Schuchardt et al., 2013).

Overall, and in consideration of the dose absorbed by the kidney as the limiting factor in the administration of ^{177}Lu-labelled radiopharmaceuticals, ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC present a similar PK profile, suitable for their intended use, while other radiopharmaceuticals such as ^{177}Lu-DOTANOC seem to be less adequate owing to the unfavourable tumour to kidneys ratios.

Pharmacokinetic properties of radiopharmaceuticals used in RLT for the treatment of metastatic castration-resistant prostate cancer (mCRPC)

^{177}Lu-labelled radiopharmaceuticals used in RLT for the treatment of mCRPC patients are also administered via IV injections, providing full bioavailability.

Alternative forms of ^{177}Lu-PSMA-617 radiopharmaceuticals aimed at increasing residence time in the blood have been evaluated in several clinical trials, showing promising results. This is the case of a translational study which evaluated the safety, dosimetry and therapeutic response to a single, low-dose of ^{177}Lu-EB-PSMA-617 in comparison to ^{177}Lu-PSMA-617 in patients with mCRPC.

Four patients received the injection of 0.80-1.1 GBq of ^{177}Lu-EB-PSMA-617 and five 1.30-1.42 GBq of ^{177}Lu-PSMA-617. The accumulated radioactivity of ^{177}Lu-EB-PSMA-617 was about 3.02-fold higher than that of ^{177}Lu-PSMA-617 in patients with comparable baseline ^{68}Ga-PSMA-617 maximum standardized uptake (SUV_{max}) values (Zhang et al., 2018). Although both treatments were similarly well-tolerated at the administered doses, ^{177}Lu-EB-PSMA-617 also had higher absorbed doses in the red bone marrow and kidneys than ^{177}Lu-PSMA-617.

5.2.2.3. Pharmacokinetic interaction studies

No specific studies evaluating the potential PK interactions of $LuCl_3$ have been performed as potential drug interactions will depend on the carrier molecule labelled with the proposed radioactive precursor. However, several studies have evaluated the impact of different products aimed at providing organ protection from absorbed radiation or increasing the efficacy of ^{177}Lu- labelled radiopharmaceuticals. A clinical study (Puszkiel et al., 2019) evaluated the effect of amino acid (AA) infusion on the PK of ^{177}Lu-DOTATATE in 42 patients with GEP-NET in order to assess the possible beneficial impact of this approach to reduce the nephrotoxicity of ^{177}Lu-DOTATATE by promoting a decrease in the tubular renal reabsorption of the compound. The co-infusion of AAs had a significant effect on the ^{177}Lu-DOTATATE PK profile, producing a 1.5-fold increase (95% CI: 1.03-1.97) in the elimination rate constant of ^{177}Lu-DOTATATE although this effect was associated with large inter-individual variability (104%). In addition, the efficacy of different solutions of AA to reduce radioactive dose to the kidneys has been clinically evaluated. The results indicate that a mixture of positively charged basic amino acids (arginine and lysine) can be especially effective in competitively inhibiting the proximal renal tubular reabsorption of ^{177}Lu-labelled radiopharmaceuticals, such as ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC (Loharkar et al., 2023). For PSMA RLT, some differences in terms of renal radiation exposure have been reported, depending on the ^{177}Lu-labelled radiopharmaceutical used (with ^{177}Lu-PSMA-I&T delivering a slightly higher renal radiation dose than ^{177}Lu-PSMA-617). Despite early reports describing the administration of AA infusions for renal protection, evidence indicates that AA infusions do not meaningfully reduce the renal dose, as the main targets for PSMA-based radiopharmaceuticals are the lacrimal and salivary glands (Ravi Kumar et al., 2024).

5.2.2.3.1. Special populations

Population with hepatic and renal impairment

No studies have addressed the impact of hepatic impairment on the PK of $^{177}LuCl_3$ or radiopharmaceuticals labelled with ^{177}Lu. Some cases of hepatotoxicity have been reported in the post-marketing setting and in the literature in patients with liver metastases undergoing treatment with ^{177}Lu-labelled radiopharmaceuticals for NET.

With regards to conditions associated with renal impairment, since many low-to-moderate- molecular-weight peptide derivatives are excreted and actively reabsorbed by the kidneys, this organ represents one of the dose-limiting organs for many targeted radioligand therapies. The historic threshold for the kidney's absorbed dose established for External Beam Radiation Therapy (EBRT) and commonly considered for RLTs is 23 Gy. However, in practice, different types of radiation treatment require different thresholds, as kidney tolerance depends, among others, on the emission type and range, radiation energy, and dose distribution of the radiation (de Roode et al., 2024). Also, the existence of risk factors, such as renal impairment, shall be considered due to the potential impact of compromised renal function on the PK of some radiopharmaceuticals that are eliminated by the kidney, with the consequential increased risk of reaching systemic exposures associated with the onset of toxicological effects.

A study investigated the influence of renal function on the kidney's absorbed doses of ^{177}Lu- DOTATATE when administered to patients with advanced NETs. The enrolled population of the study received ^{177}Lu-DOTATATE at an average activity of 7.5 GBq (3.5-8.2 GBq) at intervals of 6 to 8 weeks on one to five occasions. The study showed that patients who presented inferior renal function before treatment presented increased renal absorbed doses per administered activity (Svensson et al., 2015).

In the case of ^{177}Lu-PSMA-617, although systemic exposure values are considered to increase by 20% in patients with mild renal impairment, as well as kidney dosimetry half-life (51 hours versus 37 hours in patients with normal renal function (Pluvicto-SmPC, 2024)), the impact of such PK effects on the safety and efficacy of ^{177}Lu-PSMA-617 is not clear. In this regard, a study conducted in patients diagnosed with mCRPC and significantly impaired baseline kidney function, did not lead to detectable RLT-induced deterioration of renal function (Rosar et al., 2021).

Bodyweight

No specific studies have been conducted to determine the impact of bodyweight on the PK and optimal dosing of $^{177}LuCl_3$ or ^{177}Lu-labelled radiopharmaceutical products (van Nuland et al., 2022).

For ^{177}Lu-DOTATATE, no alternative dosing regimen is needed for subpopulations including patients with obesity, as no correlation has been established between dose-normalized long- term hematologic and renal toxicity and body weight or serum albumin in clinical trials, some of them including patients with obesity. Furthermore, biodistribution studies suggest that ^{177}Lu- DOTATATE does not accumulate in fat tissue, which further supports the use of a fixed dose not conditioned by differences in bodyweight (van Nuland et al., 2022).

In the case of ^{177}Lu-PSMA-617, no information is available on dosing in patients with obesity, although the assessment of clinical effects on a subpopulation of patients considering several covariates, which included bodyweight, indicates that a significant impact of bodyweight on the safety and efficacy of ^{177}Lu-PSMA-617 is not expected (Kabasakal et al., 2015; Delker et al., 2016).

Race

No studies have addressed the impact of race on the PK of $^{177}LuCl_3$ or ^{177}Lu-labelled radiopharmaceuticals.

Women in pregnancy and lactation

No studies have addressed the impact of pregnancy or lactation on the PK of $^{177}LuCl_3$.

5.2.2.3.2. PK drug-drug interactions

N/A

5.2.2.3.3. Dose proportionality/time independence/accumulation

N/A

5.2.3. Pharmacodynamics

No clinical pharmacology studies were submitted with this application (see 5.1.).

No interaction studies of lutetium (^{177}Lu) chloride with other medicinal products have been performed.

No information regarding genetic differences in PD response were provided.

5.2.3.1. Mechanism of action

The proposed medicinal product Lutetium (^{177}Lu) chloride n.c.a., solution is intended for use in in-vitro radiolabelling of tracer molecules mainly for therapeutic purposes, but also diagnostic purposes are in principle possible. The tracer molecule will direct the radionuclide ^{177}Lu to the tumour tissue where it will bind to surface molecules expressed specifically by tumour cells. The well-known principle is based on the internalisation of the radiolabelled molecules by the targeted tumour cells. The radiolabelled ligands bind to cell surface receptors, which are highly expressed by tumour cells. Upon binding, the receptor-ligand complexes become internalised. Once intracellular, internalised ^{177}Lu-labelled radioligands accumulate in the perinuclear area allowing direct DNA damage by ionising radiation resulting in cell death. Lutetium (^{177}Lu) emits β-minus particles of moderate maximum energy (0.498Ref MeV) with a maximum tissue penetration of approximately 2 mm. Lutetium (^{177}Lu) also emits low-energy γ-rays which allow scintigraphic, biodistribution and dosimetry studies with the same lutetium (^{177}Lu)-labelled medicinal products.

5.2.3.2. Primary and secondary pharmacology

The pharmacodynamic (PD) effects of $^{177}LuCl_3$, when utilised as a precursor for the labelling of different carrier molecules, rely on the radioactive properties of ^{177}Lu, used to induce localised cytotoxic responses in tumoral cells. The key aspects of ^{177}Lu suitability in radiopharmaceutical preparations, considering its radioactive and chemical properties, can be summarised in the following main points (Dash et al., 2015):

- The mean penetration range of β− particles emitted by ^{177}Lu in soft tissue is 670μm, which allow delivering energy to small volumes, including micrometastatic disease, and tumour cells near the surface of cavities. Thus, ^{177}Lu is effective in localized? cytotoxic radiation in relatively small areas in order to destroy small tumours and metastatic cells while causing less damage to surrounding normal tissues.
- The emission of moderate-energy beta β- particles as well as low-energy gamma photons yields a low radiation dose which enables the possibility to use high ^{177}Lu activity levels during radiopharmaceutical preparation as well as during patient administration.
- Lutetium exclusively exists in the +3-oxidation state (Lu+3), suitable for peptide and protein radiolabelling by attachment of a bifunctional chelating agent through a metabolically resistant covalent bond.

- The relatively long half-life, 6.7-days, minimizes decay loss, allowing its use for extended time periods as well as the performance of quality control evaluations of radiopharmaceuticals.

Factors affecting the PD properties of ^{177}Lu-labelled radiopharmaceuticals vary depending on aspects related to the affinity of the carrier molecule to the target, the abundance of the target, and the PK properties (concentration–time profile) of the radiopharmaceutical, which determine the effective absorbed dose by tumoral cells (van der Gaag et al., 2022).

5.2.4. Overall discussion and conclusions on clinical pharmacology

5.2.4.1. Discussion

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor not intended to be directly administered to the patient, therefore, no pharmacodynamic effect is sought for the unconjugated radionuclide. Lutetium (^{177}Lu) chloride is intended only for use in *in-vitro* labelling of carrier molecules for therapeutic purposes, therefore the lack of biopharmaceutical studies and clinical pharmacology studies conducted with lutetium (^{177}Lu) chloride is considered acceptable. However, inadvertent injection of non-labelled lutetium-177, as well the effects of the free radionuclide following administration of ^{177}Lu-labelled carriers should be discussed for radiopharmaceutical precursors as per Annex I of 2003/63/EC.

Regarding the pharmacological action, the only relevant aspect for the free ^{177}Lu is its stable binding to the carrier molecules, which is mediated by various chelating agents. Octadentate ligand DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and its modifications are considered the best chelators to stabilize lanthanides, including lutetium, in their 3+ oxidation state for the in vivo use (see 4.3.1.1.) and have been accordingly used for the authorized in the EU/EEA ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617 preparations.

Thus, no clinical pharmacology studies were submitted for this application. However, the applicant has submitted a review and discussion of the published literature on the pharmacokinetic properties of ^{177}Lu. Lutetium (^{177}Lu) chloride n.c.a. is a precursor to be used for radiolabelling purposes in combination with other medicinal products consisting of a suitable linker (chelator) and a disease-specific carrier.

In this regard, the applicant has provided information about biodistribution of the active substance lutetium (^{177}Lu) chloride from literature in in the non-clinical aspects section (see 4.3.), but no detailed discussion has been provided in the clinical section which is considered acceptable. The applicant has provided several studies evaluating the distribution in mice, rats and rabbits described in section 4. Non-clinical Aspects.

No interaction studies of Lutetium (^{177}Lu) chloride with other medicinal products have been performed.

For information concerning interactions associated with the use of lutetium (^{177}Lu)-labelled medicinal products, reference is made to the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.

5.2.4.2. Conclusions

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor not intended for direct administration. No clinical pharmacology studies were submitted, which is acceptable given its exclusive use for in-vitro radiolabelling of carrier molecules. The pharmacological relevance relates solely to the stability of the radionuclide–chelator complex. All references to dosimetry data from other products' SmPCs have been removed, and the applicant has provided its own dosimetry evaluation to support the

product information (see section 5.2.2.2.).

5.3. Clinical efficacy

As stated in the wording of the applied indication, Ilumira is a radiopharmaceutical precursor, and it is not intended for direct use in patients. The efficacy section summarises literature data to illustrate the clinical efficacy of ^{177}Lu after labelling with several carrier molecules.

5.3.1. Dose response study(ies)

No dose response studies were performed for this application.

5.3.2. Clinical utility

The data included in this section refers to the public available evidence supporting the clinical efficacy of different carrier molecules radiolabelled with ^{177}Lu mainly for the treatment of NET and mCRPC.

Treatment of neuroendocrine tumours

Because the majority of NETs express somatostatin receptors, SSAs labelled with radionuclides are frequently used to target NET lesions with high SSTR expression in patients with inoperable or metastasised NETs.

The use of different SSAs coupled to a chelator molecule incorporating the ^{177}Lu radionuclide (see Table 4) has been evaluated in several clinical trials enrolling patients diagnosed with NETs further described in this section.

Table 4. Efficacy results with ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC in clinical trials

Study Reference	Study type	Treatment (number of patients treated)	Cumulative Dose	Type of cancer	PFS	OS	Tumor Response (CR + PR)	Stable Disease	Quality of Life / KPS Improvement
^{177}Lu-DOTATATE									
(Bodei et al., 2011)	Phase II	^{177}Lu-DOTATATE (3.7 GBq [N=5]; 3.7 to 5.18 GBq/cycle [N=21], 5.18-7.4 GBq/cycle [N=30])	3.7 to 29.2 GBq	Majority of GEP-NETs	36 months	68% at 36 months	32.6%	N/R	Beneficial effect on symptom control and, ultimately, on quality of life
(Delpassand et al., 2014)	Phase II	^{177}Lu-DOTATATE (7.4 GBq/cycle [N=37])	29.6 GBq	grade 1 and 2 GEP- NETs	16.1 months	N/R	28% (CR not reported)	41%	Significant KPS improve-ment in 58% patients and QoL
(Sundlov et al., 2022)	Phase II	^{177}Lu-DOTATATE 7.4 GBq/cycle [N=96]	Up to 40±2 Gy renal BED*	GEP-NETs	29 months	47 months	34% (32% PR and 2% CR)	61%	Not directly reported
Sansovini et al., 2013)	Phase II	^{177}Lu-DOTATATE (3.7 GBq/cycle [N=26]; 5.5 GBq/cycle [N=26])	18.5 GBq to 27.8 GBq	Pancreatic NET	29 months	Not reached in the highest dose group (20 months in the lower dose)	29% (CR 8%, PR 21%)	52%	Not directly reported
(Demirci et al., 2018)	Retrospective	^{177}Lu-DOTATATE (from 3.7 to 8.1 GBq,mean 5.04 GBq [N=186])	Not reported	Majority of GEP-NETs	36 months	55 months	50% (46.9% PR and 3.1% CR)	21.9%	Not directly reported

Study Reference	Study type	Treatment (number of patients treated)	Cumulative Dose	Type of cancer	PFS	OS	Tumor Response (CR + PR)	Stable Disease	Quality of Life / KPS Improvement
(Mitjavila et al., 2023)	Retrospective	^{177}Lu-DOTATATE (7.4 GBq/cycle [N=522])	29.6 GBq	Majority of GEP-NETs	24.3 months	42.3 months	33.9% (33.2% PR and 0.7% CR)	52.1%	Not directly reported
(Zidan et al., 2022)	Retrospective	^{177}Lu-DOTATATE (7 GBq/cycle)	27 GBq	Lung NETs	23 months	59 months	20% (all PR)	68%	Not directly reported
177Lu-DOTATOC									
(Baum et al., 2016a)	Phase II	^{177}Lu-DOTATOC (7 GBq/cycle [N=56])	Not directly reported but median number of cycles was 2	Metastasized and progressive NETs	17.4 months	34.7 months	33.9% (CR 16.1%; 17.9% PR)	N/R	Not directly reported
(Forrer et al., 2005)	Phase II	^{177}Lu-DOTATOC (7.4 GBq/cycle [N=27])	7.4 GBq single dose	Relapsed NET	N/R	N/R	19.2% (PR in 0.7% and minor response in 18.5%)	44%	Improvement reported by 56% of patients
(Romer et al., 2014)	Comparative cohort	^{177}Lu-DOTATOC (7.4 GBq/cycle [N=141]) vs. 90Y-DOTATOC	13.5 ± 6.5 GBq for ^{177}Lu-DOTATOC and 13.1±4.7 GBq for ^{90}Y- DOTA-TOC	Metastatic NETs	Not reported for ^{177}Lu-DOTATOC (12.7 months for 90Y-DOTATOC)	45.5 months for ^{177}Lu-DOTATOC vs 35.9 months for ^{90}Y-DOTATOC	Only reported PR in ^{177}Lu-DOTA-TOC (5%) versus7.3 % in ^{90}Y-DOTATOC	6.4% in ^{177}Lu-DOTATOC versus 8.2% in ^{90}Y-DOTATOC	Not directly reported
(Horsch et al., 2016)	Prospective cohort study	^{177}Lu (N=241) ^{177}Lu + ^{90}Y (N=130) 90Y (N=76)	Not reported	NETs or different origins	^{177}Lu (40 months) ^{177}Lu + 90Y (50 months) ^{90}Y (27 months)	^{177}Lu (Not reached) ^{177}Lu + ^{90}Y (58 months) ^{90}Y (38 months)	Not reported by each treatment	Not reported by each treatment	Not directly reported

Abbreviations: PFS: Progression-free survival; OS: Overall survival; CR: Complete remission; PR: Partial remission; KPS: Karnofski performance score; GEP-NET: Gastroenteropancreatic neuroendocrine tumours; NET: Neuroendocrine tumours; BED: biologically effective dose; N/R: not reported

Clinical results with ^{177}Lu-DOTATATE

Early evidence of the efficacy of ^{177}Lu-DOTATATE for the treatment of SSTR-positive GEP- NETs were published in a phase I/II study in which 51 patients with unresectable or metastatic NETs received different doses of ^{177}Lu-DOTATATE (Bodei et al., 2011). In total, 76% of the enrolled patients presented tumours of GEP-NET origin (pancreatic, duodenal, ileal, appendicular, sigma-rectal), while 16% of patients had bronchial NETs or tumours of unknown primary origin. In addition, the study enrolled 3 patients affected by paraganglioma and one by meningioma. The majority of patients (39/51) were in progression at the time of enrolment. Each of the first five patients received a median of six treatment cycles at 3.7 GBq. Since no major toxicities were observed in this treatment group, the following patients were divided in two groups treated with escalating doses (3.7 to 5.18 GBq/cycle for the first and 5.18-7.4 GBq/cycle for the second group). Partial responses (PR) and complete responses (CR) occurred in 15/46 (32.6%) assessable patients, with a median time to progression of 36 months and an OS of 68% at 36 months.

A phase II study conducted with ^{177}Lu-DOTATATE evaluated its safety and efficacy in 37 patients with histopathologically confirmed diagnoses of grade 1 and 2 GEP-NETs (Delpassand et al., 2014). In each cycle, patients received 7.4 GBq ± 10% of ^{177}Lu- DOTATATE via IV infusion 30 minutes after AA infusion for kidney protection (maintained up to 4 hours afterwards) and the antiemetics aprepitant (125 mg 60-90 minutes before AA infusion) and ondansetron, administered together with the AA infusion for 30 minutes and every 2 hours afterwards when needed. The maximum cumulative dose of ^{177}Lu-DOTATATE, administered through up to 4 cycles separated by 6-9 weeks was 29.6 GBq. In this study, eligibility required the presence of progressive disease according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria and Karnofski performance score (KPS) > 60, regardless of previous treatments with different therapeutic approaches, including treatment with the SSA analogue sandostatin (in 28/37 patients), which was discontinued in the majority of cases (26/28) after the initiation of treatment. Other pre-requisites were the determination of a Krenning score > 2 evaluated by scintigraphy with Octreoscan and the absence of signs of haematological and renal function safety concerns.

Among 32 evaluable patients, with 19 of them completing the 4 cycles and a median follow up of 14.26 months, PR and minimal responses (MR) to treatment were observed in 28% and 3% of the patients, respectively. Stable disease was seen in 41% of patients, and only 28% of patients presented a progression of the disease. The median progression-free survival (PFS) for all patients was 16.1 months (16.5 months among those who completed the 4 cycles), not observing a significant correlation between the PFS of patients with metastasis in one region or two or more regions at the time of diagnosis (97% of the enrolled population). On the other hand, there was a correlation, yet not statistically significant, between the tumour burden at the start of treatment and PFS values, longer in those patients who showed a low degree of liver involvement compared to those with extensive liver involvement after 3 cycles (median PFS of 17.3 versus 16.4 months) and 4 cycles (21.4 months versus 15.3 months). Consistently, there was a significant correlation between liver burden and response to treatment, indicating that patients with low liver burden had higher chances of showing a positive response (PR and MR) to treatment with ^{177}Lu-DOTATATE. In addition, another factor that showed a correlation with the clinical efficacy of ^{177}Lu-DOTATATE was the presence of positive baseline 18F-Fludeoxyglucose (FDG) PET/CT scans. Thus, although comparisons of survival between patients with baseline positive and negative FDG PET scans did not reach statistical significance (p=0.058), negative baseline FDG PET results positively correlated with improved survival, which indicates that the presence of more aggressive tumours is a negative indicator of clinical outcome in patients undergoing treatment with ^{177}Lu-DOTATATE.

Among 26 patients who received more than one cycle of therapy, 58% showed a remarkable improvement in KPS values (more than 10 points), while for the rest of the patients there were no or

minimal (< 10 points) changes. No patient showed a worsening of KPS values. Finally, quality-of-life (QoL) assessments revealed a significant improvement in overall QoL among all the evaluable patients (those who received > 1 cycle) after the last treatment and at 3 months of follow-up.

A posterior phase II study evaluated the efficacy of individualized ^{177}Lu-DOTATATE treatment based on renal dosimetry in 96 patients who had progressive, SSTR-positive GEP- NETs (the majority with origin in the pancreas or the small intestine) (Sundlov et al., 2022). For all patients, treatment was administered as IV infusions of 7.4 GBq ^{177}Lu-DOTATATE at 10±2-week intervals preceded by antiemetics and co-administered with a kidney-protective AA infusion (from 30 minutes before the infusion of ^{177}Lu-DOTATATE until 8h post-infusion). For dosimetry, four planar whole-body scintigraphies and one combined single-photon emission computed tomography (SPECT/CT) were conducted in order to calculate the biologically effective dose (BED) administered to each patient. A limit of cumulative renal BED of 27 ± 2 Gy was established as the maximum dose that could be administered to each of the participants in the first phase of the study. Following this initial phase, completed by 64/96 patients, nine patients who maintained a glomerular filtration rate (GFR) > 50 ml/min and a maximum decrease of 40% from baseline with no signs of grade 3–4 renal toxicity, agreed to participate in a second phase in which the same ^{177}Lu-DOTATATE regimen continued up to a renal BED of 40± 2 Gy.

Eligibility to be enrolled in the study required a Ki 67 labelling index of ≤ 20%, an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, tumour uptake higher than basal liver uptake on a ^{111}In-Octreotide, and a progressive disease determined by CT scan during the last 14 months. Also, patients were required to be receiving a stable dose of SSA during the last 3 months prior to inclusion, and long-acting SSA had to be interrupted at least 4 weeks before the administration of each cycle of ^{177}Lu-DOTATATE.

Ninety-six patients who had received a median of 5 cycles (range 1–9) were evaluable for efficacy at a median follow-up time of 42 months. For the primary efficacy endpoint of the study, the objective tumour response by RECIST, at 3 months 16% of patients showed PR, 66% stable disease (SD), and 19% progression of disease (PD). The best overall response (including those patients in the extended period) was 2% CR, 32% PR, 61% SD and 4% PD.

The secondary endpoints of PFS and overall survival (OS) were 29 months and 47 months, respectively, with a 5-year survival of 41%. The study also identified differences in OS and PFS as a function of basal ECOG (0>1>2) and in PFS as a function of Ki67 (0-2>3-10>11-20). There was also a positive correlation of PFS and OS depending on the renal BED measured, with those patients receiving a dose >29 Gy presenting better responses than those treated with 25-29 Gy and those treated with <25 Gy. Median time to progression also increased as a function of renal BED, 31 months for the patients treated with <25 Gy, 46 months for those receiving 25-29 Gy, and 48 months for those receiving 29 Gy, although the results did not reach statistical significance. Lastly, while the median time to reach maximum response was 18 months for all patients, those treated at the highest BED (>29 Gy) showed the longer median time to reach maximum response (28 months), indicating that with increasing number of cycles the tumour shrinkage continues for a longer time.

Overall, the study concluded that individualized treatment with ^{177}Lu-DOTATATE based on renal dosimetry is a safe and feasible approach, and that increasing duration of the treatment, whenever there are no clinical signs of renal toxicity, can be a convenient approach for the treatment of higher-grade tumours.

Another retrospective study evaluated the safety and efficacy of ^{177}Lu-DOTATATE in a cohort of 186 patients with metastatic NETs from different primary sites (Demirci et al., 2018). All patients had a histopathological diagnosis of NET, with the most common primary origin being the pancreas (37% of patients), nonpancreatic GEP-NETs (22.6%), the lung (15.6%), NETs of unknown origin (15%), and

pheochromocytoma/paraganglioma (6.5%). In addition, the study included 5 patients with a NET originated in the ovary (2.7%) and three patients with primary origins in the prostate, the kidney and the thymus (one patient [0.5%] each). All patients had tumour progression at baseline or a bulky disease at the time of diagnosis and high uptake in all of their metastatic lesions (equal or more than the liver). Additional inclusion criteria were a Karnofsky performance status more than 50 and no haematological alterations. Patients were treated for a median of six cycles (range: 3–12) with ^{177}Lu-DOTATATE given by IV infusion together with an AA solution at doses ranging from 3.7 to 8.1 GBq (mean 5.04 GBq).

According to the imaging response of the 160 patients evaluated by RECIST criteria, 28.1% showed a PD, 21.9% SD, 46.9% PR and 3.1% CR. Among the main subtypes of origin, those patients with GEP-NETs from non-pancreatic origin presented a lower percentage of progression compared to those from a pancreatic origin (17.1% versus 30.6%), although the percentage of patients showing CR + PR was superior in patients with pNETs (61.3% versus 46.4%). In the overall population, the mean PFS was 38 months, and the mean OS time was 55 months starting from the application of the first treatment (median follow-up of 30.6 months). The estimated mean PFS in the main subtypes, excluding the few patients with NETs from ovarian, prostate, kidney and thymus origins, was similar, ranging between31.4 months (pheochromocytoma and paraganglioma) and 42.3 months (pNETs). Similarly, no significant differences were observed for the estimated mean OS rates, between 33.2 months for lung-NETs and 57 months for pNETs and non-pancreatic GEP-NETs.

Beyond the primary origin of the tumour, the study identified degree of severity according to WHO classification as a factor with an impact on disease control rates and OS, observing worse results in patients with grade 3 tumours at entry. Thus, disease control rates in patients with WHO grades 1, 2 and 3 were 74, 73 and 60%, respectively, and OS rates were 61.9, 52.2 and 38.4 months, respectively.

The study concluded that RLT with ^{177}Lu-DOTATATE is an effective treatment for different SSTR-positive metastatic NETs, including grade 3 tumours with a high expression of SSTRs.

A more recent retrospective study sought to determine the efficacy and safety of ^{177}Lu-DOTATATE in NETs (in the original study referred as neuroendocrinal neoplasms "NEN") with different locations and evaluate the effect of the origin in the clinical benefit of this therapy (Mitjavila et al., 2023). The sample comprised 522 subjects with pancreatic (35%), midgut (28%), bronchopulmonary (11%), pheochromocytoma or paraganglioma (6%), other GEP (11%), and other non-gastroenteropancreatic NENs (NGEP; 9%). The data of the enrolled patients was retrieved from a national registry of tumours treated with RLT (SEPTRALU; NCT04949282). A registrable case was defined as any adult with a metastatic, unresectable, SSTR-overexpressing, histologically confirmed neoplasm, that received at least one cycle of ^{177}Lu-DOTATATE administered in accordance with the clinical practice of each center. In all cases this protocol was 7.4 GBq per cycle (together with an AA solution), in 4 cycles with an interval of 8–10 weeks.

At the time of analysis, 90% of patients had completed therapy with ^{177}Lu-DOTATATE, with 94% of them receiving the four doses (the rest 5–8 doses), in a 97% of the cases of7.4 GBq/cycle administered at an average interval time between doses of 2.1 months. Median time from diagnosis of metastasis until RLT was 40.6 months and 94% of patients had shown tumour progression by RECIST.

The evaluations of responses to treatment were based on radiological (85% of patients), SSTR- based imaging (75%), clinical (90%) or biochemical (87%) criteria depending on the availability of the corresponding data for each patient. Considering only subjects with measurable and response-evaluable disease, the best RECIST response was CR in three (0.7%), PR in 147 (33.2%), SD in 231 (52.1%), and tumour progression in 62 (14%) patients, with 86% of all patients presenting either a response or stabilization (overall disease control rate). The ORR and disease control rates determined by the different tumour subtypes corresponded to 42.4% and 84.8% in pNENs, 35.4% and 85.4% in

other GEP-NENs, 31.5% and 78.9% in otherNGEP-NENs, 28.6% and 77.6% in bronchopulmonary-NENs, 28.2% and 93.5% in midgut- NENs, and 9.2% and 84.6% in pheochromocytoma or paraganglioma-NENs. Overall, no substantial differences were detected across tumour subtypes for SSTR-based imaging, clinical, or biochemical response, although stratification of patients by tumour grade did identify more PRs but also a higher rate of tumour progression, as well as lower percentage of SD, in those patients with high-grade tumours (grade 3) versus grade 1 or 2 tumours.

In the whole population, at a median follow-up of 21.2 months, the median OS was 42.3 months. By tumour origin subtypes, the median was not reached by patients with GEP- NENs and pheochromocytoma or paraganglioma-NENs, while for the rest ranged between 50.8 months in midgut NENs and 33.6 months in other NENs.

The median PFS was 24.3 months, with the longest PFS observed in the population of patients with midgut NENs (31 months) and the shortest in those patients with bronchopulmonary- NENs (17.6 months). Taking as a reference the most numerous stratum of patients, that is, those diagnosed with pancreatic NENs, midgut NENs had less risk of progression (HR for PFS of 0.69; 95% CI, 0.44–0.93; p = 0.02).

Overall, the study confirmed the efficacy ^{177}Lu-DOTATATE in a wide range of SSTR- expressing NENs, regardless of location, with clinical benefit and equivalent survival outcomes between pNENs and other GEP and NGEP tumour subtypes different from midgut NENs.

In a phase II study enrolling 52 patients diagnosed with G1-G2 pancreatic NETs, the administration of 177Lu-DOTATATE at two doses of 18.5 GBq (mean dose 17.8 GBq; N=26) or 27.8 GBq (mean dose 25.5 GBq; N=26) in five cycles proved to be effective in achieving antitumor activity (disease control rate in the entire case series was 81%). In terms of tumoral response, there were 4% CR, 15% PR and 58% SD in the group receiving the lowest dose, while in the group receiving the highest dose results were 12% CR, 27% PR and 46% SD. The median PFS was not reached in the highest dose group, while for the lowest dose group it was 20 months (Sansovini et al., 2013).

Additional evidence on the clinical efficacy of ^{177}Lu-DOTATATE in the treatment of pancreatic NETs come from different retrospective studies. Among these studies, the median disease control rate with ^{177}Lu-DOTATATE was 83% (range, 50%–94%) and the median objective response rate was 58% (range, 13%–73%). The reported median PFS for the overall pancreatic NET populations in each study ranged from 25 to 34 months, and the median OS ranged from 42 to 71 months (Ramage et al., 2018).

In the case of lung-NETs, a retrospective study evaluated the efficacy of ^{177}Lu-DOTATATE in 48 patients who presented either typical carcinoid (N=5) or atypical carcinoid (N=43) SSR- positive lung NETs. In this study, patients received a median of 4 cycles of ^{177}Lu-DOTATATE (33% with concurrent radiosensitizing chemotherapy) to a median cumulative activity of 27 GBq (range, 6-43 GBq). At a median follow-up of 42 months, the median PFS and OS were 23 months (95% CI, 18-28 months) and 59 months (95% CI, 50-not reached), respectively. In terms of tumoral response, of 40 patients with RECIST-measurable disease and 39 patients with available 68Ga-DOTATATE PET/CT data, a partial response was achieved by 20% of patients with RECIST data and by 44% of patients with 68Ga-DOTATATE PET/CT data, stable disease by 68% (RECIST) and 44% (68Ga-DOTATATE PET/CT) and progressive disease by 12% (in patients with RECIST and 68Ga-DOTATATE PET/CT data). Overall, the results of this study indicate that in patients with advanced progressive lung NET and satisfactory SSR expression, ^{177}Lu-DOTATATE can be an effective treatment (Zidan et al., 2022).

Clinical results with ^{177}Lu-DOTATOC

Although 177Lu-DOTATOC is not currently authorised, its clinical efficacy has also been evaluated with positive results in numerous prospective and retrospective clinical trials, as well as in meta-analysis.

Two phase III trials on patients with GEP-NETs, COMPETE (NCT03049189) and COMPOSE (NCT04919226), are ongoing. A summary of the main evidence supporting the clinical efficacy of ^{177}Lu-DOTATOC as RLT in patients with SSTR- expressing tumours is presented in the following paragraphs.

One phase II study evaluated retrospectively the efficacy of 177Lu-DOTATOC in 56 patients with metastasized and progressive NETs (50% GEP, 26.8% pancreatic, 23.2% other primary sites) (Baum et al., 2016a). Subjects were administered ^{177}Lu-DOTATOC (mean 2.1 cycles; range 1-4) as 7.0 GBq (median) doses at three-monthly intervals. The enrolled population was diagnosed with low- and intermediate-grade metastatic NET and progressive disease confirmed within 6 months before the start of treatment by morphological CT or MRI scans according to RECIST. Alternatively, the presence of new lesions was determined by 68Ga-DOTATOC PET/CT images, conducted for all the eligible subjects to determine the eligibility to therapy with ^{177}Lu-DOTATOC. None of the patients received other radioligand therapies than ^{177}Lu-DOTATOC until progression. Also, for all the patients, other anti-neoplastic medications were withheld, including long-acting SSAs (at least 4-6 weeks before the start of treatment).

For the efficacy analysis, patients were stratified according to the number of ^{177}Lu-DOTATOC treatment cycles (1 versus >1). Of note, in this study a large number of patients (N=24; 42.9%) were treated with only one cycle of ^{177}Lu-DOTATOC due to a high mortality rate following the first administration of ^{177}Lu-DOTATOC (15 patients). Such elevated mortality was consistent with the advanced stage of disease prior enrolment determined in this subgroup, who presented a significantly lower baseline KPS compared to the subgroup of patients who underwent more than one cycle of treatment.

In the whole study population (N=56), the median PFS was 17.4 months, and 32.0 months in patients with >1 ^{177}Lu-DOTATOC cycle, compared to 3.8 months after a single cycle. For the GEP-NET subgroup, the corresponding values were 30.3, 34.5 and 4.7 months, respectively. The PFS in patients with NETs of other origins (lung, thymus, kidney, ovary, Meckel´s diverticulum, unknown) was considerably lower (3.5 months in the 5 patients treated with only 1 cycle and 11.9 months in those patients treated with >1 cycle).

Similar results were obtained in the evaluation of OS, with a median of 3.9 months in those patients who received one cycle of ^{177}Lu-DOTATOC compared to 34.7 months in the group treated with >1 cycle. In the case of the subgroup diagnosed with GEP-NETs, OS median values were 16.2 and 34.7 months (for 1 and > 1 cycles, respectively). The objective response rate, defined as the proportion of patients achieving PR or CR per RECIST criteria was 33.9% (16.1% CR) in the whole population, lower than the rates observed in those patients treated with >1 cycle (40.6%; 18.8% CR), especially in the subgroup diagnosed with GEP-NETs (54%; 25% CR). The disease control rate (patients showing CR, PR and SD) was 66.1% for all treated patients and 93.8% for the patients who received >1 cycle, while all GEP-NET patients treated with >1 cycle presented disease control. Overall, the study concluded that ^{177}Lu- DOTATOC was effective in inducing tumour responses and sustained disease control in patients with NETs, especially of GEP origin.

Evidence in support of the efficacy of ^{177}Lu-DOTATOC in the treatment of relapsed NETs was also reported by a study enrolling 27 patients with relapsed NET who had been treated prior to enrolment with ^{90}Y-DOTATOC (Forrer et al., 2005). In this study, the mean time between the last treatment with ^{90}Y-DOTATOC and ^{177}Lu-DOTATOC was 15.4 ± 7.8 months, and all the enrolled patients received a single dose of ^{177}Lu-DOTATOC corresponding to 7.4 GBq infused with an AA solution (from 30 minutes before the IV administration of ^{177}Lu-DOTATOC to 3h after administration). At inclusion, all patients presented a histologically confirmed metastatic NET at a stage of progression demonstrated by CT or ultrasound. The majority of patients presented pancreatic NETs (N=11), while the remaining 16 patients presented metastatic NETs of different origins (7 of the small bowel, 4 of unknown primary, 2 of the rectum, 1 of the stomach, 1 of the bronchus, and 1 of the appendix). The included patients

also showed a positive response to the prior ^{90}Y-DOTATOC therapy, defined as CR, PR, MR, or SD, and a mean time to progression of 15.4 ± 9 months. None of the patients had been treated with the long-acting SSAs octreotide or lanreotide for at least 6 weeks before the initiation of the therapy with ^{177}Lu-DOTATOC or with short acting octreotide for at least 3 days before the administration of ^{177}Lu-DOTATOC.

Following 8-12 weeks after the administration of ^{177}Lu-DOTATOC, 19 patients (70%) showed a benefit: 12 with stabilization of the disease, 5 with a MR, and 2 with a PR, while 8 patients continued with tumour progression. These results were improved in the subgroup of patients who achieved a PR during the prior treatment with ^{90}Y-DOTATOC (N=14), as none of them presented progression after receiving the corresponding treatment with ^{177}Lu-DOTATOC (2 patients with PR, 5 MR and 7 with SD). In addition, according to the referring physicians, the general condition of the patients improved for 15 (56%), remained the same for 11 (41%), and decreased for only 1 (4%).

Other studies have compared the efficacy of different RLTs, including those labelled with ^{177}Lu and ^{90}Y, reaching different conclusions.

This is the case of a cohort study that compared the clinical efficacy of ^{90}Y-DOTATOC (N=910) versus ^{177}Lu-DOTATOC (N=141) in patients diagnosed with NETs (Romer et al., 2014). The inclusion in this study required the presence of histologically confirmed NETs, metastasized disease, progression within 1 year before enrolment and detectable tracer accumulation in the tumour on a SSR scan. Patients were not randomly allocated to the different treatment groups. Although strict criteria for the assignation to ^{90}Y-DOTATOC or ^{177}Lu- DOTATOC were not established, patients receiving ^{177}Lu-DOTATOC had a low tumour burden (≤3 lesions), small lesions (diameter <3 cm) or low kidney function with increased creatinine levels (>90 µmol/L). The group of patients treated with ^{90}Y-DOTATOC received a median number of 2 cycles (range 1-6) corresponding to a mean cumulative activity of 13.1±4.7 GBq. In the group of patients treated with ^{177}Lu-DOTATOC, the median number of cycles was also 2 (range 1-5), corresponding to a cumulative activity of 13.5±6.5 GBq. In both groups, the administration of the respective treatments was accompanied by the infusion of AA before and after the treatment. Also, before the initiation of the therapy, long-acting and short-acting SSAs were withheld at least 6 weeks and 3 days prior to the first dose.

The median survival in the overall population after ^{177}Lu-DOTATOC and ^{90}Y-DOTATOC treatments was comparable (45.5 months versus 35.9 months, HR 0.91, 95% confidence interval 0.63–1.30, p=0.49). However, a subgroup analyses revealed a significantly longer survival for ^{177}Lu-DOTATOC over ^{90}Y-DOTATOC in patients with low tumour uptake, solitary lesions and extra-hepatic lesions. The study concluded on the similar efficacy in terms of survival for ^{177}Lu-DOTATOC and ^{90}Y-DOTATOC when used in the treatments of NETs.

Different conclusions were obtained in a posterior prospective study based on data from a multi-institutional registry in five German centers that evaluated the safety and efficacy of RLT with different ^{177}Lu and ^{90}Y radiopharmaceuticals targeting SSTRs (Horsch et al., 2016). The study enrolled 450 adult patients eligible for participation on the basis of progressive, locally advanced or metastatic low to intermediate grade NENs with overexpression of SSTRs (confirmed through 68Ga based SSTR detection by PET/CT), a Karnofsky index of more than 60% and sufficient bone marrow and kidney function. The majority of patients had grade 1 and 2 NETs (54.9%) of different origins, the most common being pancreatic (41.5%) followed by GEP origin (jejunum/ileum; 33.3%) and unknown origin (20.7%). The majority of patients, 53.9%, were treated with ^{177}Lu-labelled radiopharmaceuticals (^{177}Lu-DOTATOC and ^{177}Lu- DOTATATE), 17% were treated with ^{90}Y-labelled radiopharmaceuticals and 29% with a combination of both. In addition, only three patients were treated with a radiopharmaceutical labelled with ^{67}Ga. The dosing regimen for RLT ranged between one to eight cycles, with a mean dose of 5.38 GBq at each cycle.

In the overall population of patients regardless of treatment, analysis of response status by RECIST showed as best responses during treatment 5.6% CR, 22.4% PR, 47.3% SD and only 4% of patients with progression (percentages from the set of patients [357] for whom this information was available over the total population).

Contrary to the previous study, ^{177}Lu-based RLT showed a statistically significant advantage over ^{90}Y-based RLTs in terms of OS and PFS, while there were no significant differences in the comparison between ^{177}Lu-based RLT or RLT using a combination of ^{177}Lu and 90Y-radiopharmaceuticals. The median OS in the group of patients treated with ^{177}Lu RLT was not reached by the closure of the study, for those patients treated with a combined RLT was 48 months, and for those treated with ^{90}Y RLT was 38 months. These differences were reflected on a mortality HR between ^{177}Lu RLT and combined RLT of 1.13 (95% CI:0.66-1.9), significantly lower than the HR between ^{90}Y RLT and combined RLT (3.22; 95% CI:1.83- 5.64). Other factors that correlated with increased survival were the primary origin of the tumour, with those NETs from the small bowel showing a HR of mortality with respect to other origins of 0.39 [95%CI:0.18-0.87), and the severity grade, with those patients presenting grade 1 NETs showing a lower risk of mortality compared to those patients with grade 2 (HR of 2.06; 95% CI, 0.795.32) and grade 3 (HR of 4.22; 95% CI, 1.41e12.06). The study concluded that RLT with ^{177}Lu-radiopharmaceuticals alone or combined with ^{90}Y-radiopharmaceuticals is a highly effective therapy for patients with low to intermediate grade NETs, and superior than a RLT base on the use of ^{90}Y-radiopharmaceuticals alone.

Another retrospective study enrolled a large cohort of 1048 patients treated in a period of 10 years at a single centre in Germany with different RLTs, including 378 patients treated with ^{177}Lu-labelled radiopharmaceuticals (not specified percentages with ^{177}Lu-DOTATATE or ^{177}DOTATOC), 157 with ^{90}Y-labelled radiopharmaceuticals (either ^{90}Y-DOTATATE or ^{90}Y-DOTATOC), and 513 with a combination of both (Baum et al., 2018). Most patients had well differentiated NENs of grade1 (23.6%) or grade 2 (38.1%). A minority of 67 patients (6.4%) had well differentiated NENs of grade 3, and for the rest such information was not available (31.9%). The majority of patients had tumours with origin at the pancreas (36.6%), followed by the small intestine (30.1%), the lug (7.2%), colon and rectum (5.0%), duodenum (2.1%), thymus and mediastinum (1.5%), stomach (1.4%), caecum and appendix (0.5%) and others (1.2%). For 151 patients (14.4%), the primary site of the tumour was not known. The mean total administered radioactivity for the different treatments was 18.84 GBq with a minimum of 1.4 GBq and a maximum of 63.9 GBq. By the end of the study, out of 1048 patients, 54.7% were alive with a median OS of 51 months. In the comparison between treatments, the group of patients treated with a combination of ^{177}Lu and ^{90}Y-RLT presented the longest median OS (64 months), for 44 months in those patients treated only with ^{177}Lu and 24 months in those patients treated with ^{90}Y. The HR of mortality between the combination and single treatments with ^{177}Lu of ^{90}Y was in both cases significant.

Median PFS based on the EORTC PET criteria was 19 months in the whole population. As in the case of OS, the results of PFS by subgroups showed an advantage for the combined therapy (24 months) with respect to ^{177}Lu alone (17 months) or ^{90}Y alone (13 months). These differences were reflected in a significant advantage of the combined therapy in terms of lower risk of progression (HR of 1.12 for ^{177}Lu alone and 1.41 for ^{90}Y alone).

In addition to the kind of radiopharmaceutical used for RLT, the article also confirmed a negative correlation between higher grade tumours, increasing age and number of previous therapies as factors that by univariate or multivariate analysis associated with worse prognosis in terms of OS and PFS. With respect to the primary origin of the tumour, best survival was observed in patients with NENs of small bowel (69 months), which was statistically significant followed by cancers of unknown origin, others, pancreas and lung. Similarly, patients with NENs from the small bowel had a longer PFS compared to patients with pancreatic NENs, whereas bronchial origin und unknown origin was associated with a significantly shorter PFS in multivariate analysis.

The study concluded that RLT for the treatment of NENs of different origin and severity provides a clear therapeutic benefit, with the combined use of ^{177}Lu and ^{90}Y radiopharmaceuticals being the most effective approach in terms of improving OS and PFS, parameters also influenced by factors such as grade of severity and primary origin of the tumour.

Lastly, consistent with the results detailed in this section from numerous clinical trials, the therapeutic efficacy of ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC in advanced or inoperable NETs has also been supported by a recent meta-analysis that evaluated a total of 22 studies (1758 patients). The pooled analysis estimated disease response rates between 33% and 25% and disease control rates between 79-83% according to different criteria (e.g. RECIST), concluding that treatment with ^{177}Lu-DOTATATE/DOTATOC can be a beneficial and promising therapeutic approach for advanced or inoperable NET patients (Wang et al., 2020).

Treatment of prostate cancer

The second radiopharmaceutical incorporating ^{177}Lu to receive a MA by the FDA and the EMA was ^{177}Lu-PSMA-617, in which ^{177}Lu is coupled to a PSMA-specific peptidomimetic. Until now, ^{177}Lu-PSMA-617 has been authorised for the treatment of PSMA-positive mCRPC patients who have previously received other therapy options (such as inhibition of the androgen receptor pathway and taxane-based chemotherapy). Additional studies in earlier treatment lines are ongoing (study PSMAfore [NCT04689828] and study PSMAddition [NCT04720157]).

Besides ^{177}Lu-PSMA-617, another ^{177}Lu-radiolabelled compound in which the DOTA chelator binding to the PSMA is replaced by a DOTAGA chelator, known as ^{177}Lu-PSMA-I&T, has also shown its efficacy in different published clinical trials with mCRPC patients. Both compounds, ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T, act by the same intended mechanism of targeting prostate-cancer cells expressing high levels of PSMA.

A summary of the main clinical trials conducted in support of the efficacy of ^{177}Lu-PSMA radiopharmaceuticals is presented in Table 5.

Table 5. Efficacy of ^{177}Lu-PSMA in prospective clinical trials

Study Reference	Type of study	Dose Per Cycle (patients treated)	Cumulative Dose of ^{177}Lu-PSMA	PSA Level Reduction	PFS	Overall Survival (OS)	RECIST/PET Response	Other efficacy outcomes
^{177}Lu-PSMA-617								
(Baum et al., 2016b)	Phase II	3.6–8.7 GBq (median; 5.76 GBq) (N=56)	Variable	80.4% patients showing reduction	13.7 months	Not reached	PR: 20%, SD: 52%	Not reported
(Yadav et al., 2017)	Phase II	From 1.1 to 5.5 GBq (N=31)	Not reported (median number of 2 cycles)	Mean drop from 275 to 141.75 ng/mL	12 months	16 months	Not reported	Significant decrease in pain, improved KPS
(Hofman et al., 2018)	Phase II	7.5 GBq (N=30)	Not reported	≥50% decline in 57% of patients	7.6 months	13.5 months	CR: 10%, PR: 30%	Improved cognitive functioning, insomnia, pain
(Emmett et al., 2019)	Phase II	Mean of 7 GBq (between 6-8 GBq) (N=14)	Not reported	Mean reduction of 59% in responders	Not reported	Mean of 12 months	PR_ 40%, SD: 20%	Not reported
(De Giorgi et al., 2021)	Phase II	3.7 to 5.5 GBq (N=40)	Median cumulative dose 13.6 GBq	≥30% decline in 50%, ≥50% decline in 37.5%	7.5 months	12.4 months	Not reported	Not reported

Study Reference	Type of study	Dose Per Cycle (patients treated)	Cumulative Dose of ^{177}Lu-PSMA	PSA Level Reduction	PFS	Overall Survival (OS)	RECIST/PET Response	Other efficacy outcomes
(Satapathy et al., 2022)	Phase II	6.0-7.4 GBq (N=20 in ^{177}Lu-PSMA-617; N=20 in docetaxel)	15 GBq (range 6–30 GBq)	≥ 50% decline in 60% patients in ^{177}Lu-PSMA-617 vs. 40% in docetaxel	4 months in the ^{177}Lu-PSMA-617 and docetaxel groups	Not reported	Not reported	Significant improvements in QoL
(Yadav et al., 2020)	Prospective	3.7 to 8 GBq	Not reported (1to 7 cycles)	≥50% decline in 32%	11 months	14 months	PR: 23%, SD: 54%	Improvement in KPS, VAS and ECOG socre
(Khreish et al., 2021)	Prospective	6.5 GBq/cycle (N=254)	Median cumulative dose 19.5 GBq	≥ 50% decline in 30.3%	5.5 months	14.5 months	Not reported	Not reported
(Meyrick et al., 2021)	Retrospective	6.1 ± 1.0 GBq (N=191)	Median cumulative dose 13.3 GBq	≥ 50% decline in 56%	6 months	12 months	Not reported	Not reported
^{177}Lu-PSMA-I&T								
Kesavan 2021	Prospective	6.1 GBq (N=100)	Max dose 32 Gbq	≥ 50% decline in 56%	6 months	Not reach	Not reported	Not reported

Abbreviations: PFS: Progression-free survival; OS: Overall survival; CR: Complete response; PR: Partial response; PSA: Prostate-Specific Antigen; SD: Stable disease; RECIST: Response evaluation criteria in solid tumours; PET: Positron emission tomography; KPS: Karnofski performance score; VAS: Visual analogue score; ECOG: Eastern cooperative oncology group; QoL:Quality-of-life

Initial evidence of the clinical efficacy of ^{177}Lu-PSMA-617 in mCRPC was reported in a phase II study that enrolled 56 patients who underwent treatment with ^{177}Lu-PSMA-617 (in the original paper referred as 177Lu-DKFZ-617) (Baum et al., 2016b). The activity of ^{177}Lu-PSMA- 617 administered and the number and interval of cycles were personalized on the basis of uptake in metastases of ^{68}Ga-PSMA by PET/CT scan before therapy, renal function, hematologic status, previous treatments, and KPS score. ^{177}Lu-PSMA-617 was administered at a median of 5.76 GBq in 1 cycle for 16 patients, 2 cycles for 15 patients, 3 cycles for 17 patients, 4 cycles for 6 patients, and 5 cycles for 2 patients.

Time-dependent activity in organs and tumours by whole-body scans after therapy revealed excellent uptake of ^{177}Lu-PSMA-617 in metastases. In terms of clinical response, of the 56 patients, 45 (80.4%) demonstrated a reduction in prostate-specific antigen (PSA) levels, from a median of 43.2 ng/mL (range, 0.05–2,848 ng/mL) to a median of 23.8 ng/mL (range, 0.01–2,227 ng/mL) after therapy.

A morphologic response assessment (RECIST) by contrast-enhanced CT documented PR in 5 patients (20%), SD in 13 patients (52%), and PD in 7 patients. Similarly, analysis based on ^{68}Ga-PSMA uptake by PET/CT evaluated in accordance with European Organization for Research and Treatment of Cancer (EORTC) criteria showed a decrease in the median SUV_{max} values after therapy, from a baseline of 37.5 (range, 15–187.5) to 15.7 (range, 1.7–75.3). Through this analysis, PR was achieved by 14 patients (56%), SD by 2 patients (8%), and PD by 9 patients (36%). Finally, the median OS was not reached at the last assessment conducted 15.5 months after ^{177}Lu-PSMA-617 treatment, while the median PFS was 13.7 months. Overall, the study concluded that ^{177}Lu-PSMA-617 was effective in end-stage progressive mCRPC with appropriate selection and follow-up.

A subsequent phase II study enrolled 31 mCRPC patients with progressive disease that did not respond to AR therapy and/or systemic chemotherapy and were treated with different doses of ^{177}Lu-PSMA-617 (in the original publication referred to as ^{177}Lu-DKFZ-PSMA-617) (Yadav et al., 2017). Eligibility required a minimum KPS > 30 and no safety concerns determined by haematological and renal function assessments conducted prior to enrolment. The presence of extensive skeletal metastases was determined in all patients on pre-therapy baseline diagnostic with N,N′-bis-[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N′-diacetic acid (HBED-CC) conjugated to ^{68}Ga radiolabelled PSMA by PET/CT, with a bone lesion scoring between 11-19. In addition, 17 patients presented lymph node metastases and 1 patient liver and lymph node metastases.

Following 30-60 minutes of infusion with AA, different doses of ^{177}Lu-PSMA-617 were IV administered based on the extent of metastasis, haematological, kidney function and liver function parameters (4 patients received 1.11 GBq, 18 received 1.85 GBq, 7 received 3.7 GBq and two 5.55 GBq). In the whole population of patients, treated with a mean activity of 5.07 ± 1.85 GBq of ^{177}Lu-PSMA-617 given between 1 and 4 cycles, the median OS was 16 months, and PFS was 12 months.

The biochemical response was analysed by the determination of serum PSA levels, which dropped from mean baseline values of 275±472.12 ng/mL to 141.75±187.43 ng/mL after 3 months of the first cycle and remained stable in the analysis after 3 months of the second cycle (153.07±204 ng/mL). Overall, 2/31 patients presented a complete biochemical response, 20/31 a partial biochemical response and 3/31 stable disease, for 6/31 patients who presented disease progression. Metabolic response was determined in six patients according to PET Response Criteria in Solid Tumours (PERCIST) criteria. Two out of these six patients presented CR, 3/6 patients PR and 1/6 patients SD. Clinical response assessed by visual analogue score (VAS)

showed a significant decrease from a mean of 7.5 at baseline to 3 after therapy, the mean analgesic score decreased from 2.5 to 1.8, the mean KPS score improved from 50.32 to 65.42 and the mean Eastern Cooperative Oncology Group (ECOG) performance status improved from 2.54 to 1.78. Overall, based on the biochemical and clinical results obtained with ^{177}Lu- PSMA-617, the study concluded on its efficacy in the treatment of mCRPC.

A similar posterior phase II study recruited 30 adults with mCRPC and progressive disease after standard treatments, including taxane-based chemotherapy and second-generation anti-androgens, in order to determine the safety and efficacy of ^{177}Lu-PSMA-617 (Hofman et al., 2018). Eligible patients were evaluated at screening by ^{68}Ga-PSMA-11 and ^{18}F-FDG uptake using PET/CT to confirm high PSMA-expression and exclude patients with FDG-positive disease without high PSMA expression. Enrolled patients had progressive disease defined by imaging according to RECIST or bone scan, or new pain in an area of radiographically evident disease. They also were required to have an ECOG performance status score of 2 or lower. The enrolled population, which included 26 patients (87%) who previously received at least one line of chemotherapy (80% docetaxel and 47% cabazitaxel) and 25 patients (83%) that received prior abiraterone acetate, enzalutamide, or both, was treated with up to four cycles of intravenous ^{177}Lu-PSMA-617 given at six weekly intervals at a mean administered radioactivity of 7.5 GBq per cycle.

Treatment with ^{177}Lu-PSMA-617 led to a decline of PSA values greater than or equal to 50% in 57% of patients. Imaging response using PSMA PET showed a CR in 10% of patients, a PR in 30% of patients, and PD in 27% of patients. Objective response in nodal or visceral disease was reported in 14 (82%) of 17 patients with measurable disease. Cognitive functioning, insomnia, and pain, which were measured using the EORTC-QLQ30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire) and Brief Pain Inventory (BPI) scoring tools, showed improvement during treatment compared to baseline, thus indicating improved quality of life. The study concluded on the appropriateness of ^{177}Lu- PSMA-617 to achieve high response rates and reduction of pain in men with mCRPC.

Another phase II study was conducted in men with progressive mCRPC previously treated with antiandrogens (abiraterone and/or enzalutamide) and taxane-based chemotherapy. Eligibility criteria included uptake of ^{68}Ga-HBEDD-PSMA-11 by PET above or equal to liver activity, with no ^{18}F- FDG PET-discordant disease (Emmett et al., 2019).

Ten out of the 14 patients enrolled had a mean PSA reduction of 59%, with 5 patients having over a 50% reduction, and 9 patients having over a 30% reduction in PSA levels. Repeat PSMA PET imaging performed after completion of therapy showed a significant drop in SUVmax value from 44 ± 15 to 17 ± 9 and a drop in SUV mean from 10 ± 4 to 6 ± 4. The study also showed the existence of a correlation between the measured PSMA PET values at baseline and the degree of response to ^{177}Lu-PSMA-617 in terms of PSA levels. Thus, PSMA PET values, but not FDG parameters alone or tumoral volume or site of disease, could predict the extend of PSA decrease between ≥ 30% PSA and < 50% following therapy with ^{177}Lu-PSMA-617.

A prospective phase II study determined the ^{177Lu}-PSMA-617 efficacy and the clinical utility of levels of plasma AR gene in patients with heavily pretreated mCRPC (De Giorgi et al., 2021). Prior to enrolment, 40 consecutive patients underwent imaging with ^{68}Ga-PSMA PET/ CT scan as part of the screening assessments to confirm high PSMA expression, but not FDG- PET/CT at the pretreatment staging. Eligibility required high PSMA expression, defined as activity in a site of metastatic disease significantly greater than the activity in the normal liver. ^{177}Lu-PSMA-617 was administered for up to 4 cycles of treatment (median 3) at 8–12 weekly intervals at a dosage ranging from 4.4 to 5.5 GBq per cycle (median cumulative dose 13.6 GBq). In the case of those patients previously treated with abiraterone/enzalutamide and docetaxel and/or aged

>75 years, the dosing ranged between 3.7 to 4.4 GBq/cycle. Concomitantly, patients received prophylaxis with an infusion of 250 mL mannitol 10% 30 minutes before the treatment and 250 mL after the treatment. Also, to prevent off-target salivary gland uptake, patients were given two polyglutamate folate tablets 30 minutes before, during, and 4 h after treatment. Twenty-five (80.6%) patients earlier received docetaxel and 6 (19.4%) of the patients as first and second line, respectively. Twelve (38.7%) patients had previous AR-directed therapies and 19 (61.3%) were chemotherapy-naive and post-docetaxel patients, respectively.

Twenty (50%) of the patients had a PSA decline ≥30% and 15 (37.5%) of the patients had a ≥50% PSA decline at a median follow-up of 15.5 months. The study showed a possible association between circulating AR and response to treatment in terms of PSA levels, as 3/15 (20%) patients with amplified AR and 12/25 (48%) with normal AR had a PSA response (p = 0.080), giving a significant OR for patients without a PSA response having AR gain of 3.69 (95% CI 0.83–16.36, p = 0.085). Similarly, 12/15 (80%) patients with raised AR versus 5/25 (20%) patients with normal AR had early PRD (p = 0.0002). These values corresponded to an OR for patients with early PRD having raised AR of 16 (95% CI 3.23–79.27, p = 0.0007).

The median PFS was 7.5 months (95% CI 4.8–10.5) with 60.0% (95% CI 43.2 73.2) PFS at 6 months. The median OS was 12.4 months (95% CI 7.4–20.3 months) and the 12-month OS was 53.1% (95% CI 35.3–68.0). As in the case of the measurements of tumour response by PSA levels, the study showed a negative association between AR levels and PFS and OS values. Patients with raised AR gain had a median PFS and OS of 4.7 months (95% CI 2.9– 7.0) and 7.4 months (95% CI 4.5–10.3 months), respectively, whereas patients with normal AR had a median PFS of 9.4 months (95% CI 6.9–11.5, p = 0.020) and a median OS of 19.1 months (95% CI 10.6–20.3, p = 0.020). The study concluded on the efficacy of ^{177}Lu-PSMA-617 in the treatment of mCRPC, especially among those patients that present normal AR levels prior to the initiation of therapy, suggesting a potential better activity of ^{177}Lu-PSMA-617 in earlier phases of PC.

In another prospective, single-arm, single-institutional study the safety and efficacy of ^{177}Lu-PSMA-617 was evaluated in a cohort of 90 mCRPC patients with progressive disease on second-line hormonal therapy and/or docetaxel chemotherapy (Yadav et al., 2020). The eligibility criteria for enrolment in the study included histological confirmation of prostatic adenocarcinoma, documented disease progression on ^{68}Ga-PSMA PET/CT scan obtained within 28 days prior to the beginning of the treatment, and 68Ga-PSMA uptake at lesion above reference levels (liver for soft tissue lesion and the vertebra for the skeletal metastases). In the first 26 patients enrolled, a single-day kidney protection protocol was followed by a cocktail infusion of AA, initiated 30 minutes before the IV infusion of ^{177}Lu-PSMA-617. Not observing signs indicative of a requirement for kidney protection, the previous AA infusion was not conducted for the remaining patients in the study, who received doses between 3.7 to 8 GBq for 1 to 7 cycles (based on the extent of metastasis, haematological, kidney, and liver function parameters).

At a median of 8 weeks after the first cycle of ^{177}Lu-PSMA-617, 62.2% of the 90 patients enrolled presented a reduction from baseline in PSA levels, and for 32.2% of them, such reduction was greater than 50%, for only a 23.3% of patients presenting PSA increases greater than 25%. At a median follow-up of 28 months, 56 (62.2%) of 90 patients demonstrated any PSA decline, among whom 41 (45.5%) of 90 patients demonstrated greater than 50% PSA decline. By ^{68}Ga-PSMA PET/CT scan, no patient achieved complete morphological remission of the disease, but 23% of patients presented a PR and 54% SD, for only 23% of patients showing progression. Similar results were obtained using the PET Response Criteria in Solid Tumours (PERCIST) to

evaluate molecular tumour response, with 27.5% of patients presenting PR, 43.5% SD and 29% progression.

During the course of follow-up, the median PFS was 11 months, and the median OS was 14 months. Regarding OS, univariate analysis identified several positive predictors of prolonged OS, including alkaline phosphatase (ALP) of 240 U/L or less, concomitant androgen-deprivation therapy (ADT) and ^{177}Lu-PSMA-617 RLT, no documented disease progression, greater than 50% PSA decline and ECOG status of 2 or less, although only the latter two showed statistical significance by Cox proportional hazard regression analysis.

Clinical response was assessed by criteria such as maximum visual analogue score (VAS), analgesic score, Karnofsky Performance Status (KPS) scale, and ECOG performance status, obtaining a statistically significant improvement over pre-treatment values for all of them.

Another prospective study evaluated the safety and efficacy of ^{177}Lu-PSMA-617 in 254 consecutive men with mCRPC seen in everyday academic practice (REALITY study by the acronym of the registry database used) (Khreish et al., 2022). The enrolled patients, all from a single centre in Germany, required to present progressive histologically-confirmed mCRPC, intense tumoral PSMA expression on ^{68}Ga-PSMA-11 characterized by tracer uptake markedly higher than in liver tissue as determined by PET/CT, an ECOG performance status≤ 3, and no signs of renal or haematological abnormalities. Since ^{177}Lu-PSMA-617 was administered following failure of individually appropriate conventional therapies, patients were generally elderly and heavily pretreated (median age 70 years; prior taxanes 74.0%), with late–end-stage disease (visceral metastasis in 32.7%). Patients received a median of three ^{177}Lu-PSMA-617 cycles at a median dose of 6.5 GBq/cycle given at a median interval between does of 5.7 weeks.

The results of the study showed a decline in PSA values from baseline following 4-6 weeks after the first cycle of ^{177}Lu-PSMA-617 RLT in 66.5% of the patients, with a ≥ 50% decline in 30.3% of them. Over the entire course of the therapy, 52% of patients presented as better response declines in PSA basal levels ≥ 50%. After a median follow-up of 14.9, the median PSA-PFS was 5.5 months, and the median OS 14.5 months. Predictive factors of more prolonged PSA-PFS identified by univariate and multivariable analyses included age ≤ 65 years, ECOG performance status 0–1, baseline alkaline phosphatase activity (ALP) < 220 U/L, and absence of taxane pretreatment. The latter two were also predictive of longer OS, together with haemoglobin values ≥ 10 g/L or absence of visceral metastasis. Also, early response to treatment was the strongest prognostic factor related to OS, and the contrary, biochemical progression of the disease after 1-2 cycles, an independent predictor of shorter OS.

In conclusion, the study confirmed the efficacy of ^{177}Lu-PSMA-617 in a prospectively observed "real-world" cohort of patients with mCRPC and supported the observation that early biochemical disease control by this therapy can be used a predictor of longer OS in these patients.

Another real-world data study used a retrospective cohort analysis to identify features that are associated with response to radioligand therapy and greater survival (Meyrick et al., 2021). The study included 191 mCRPC patients treated with ^{177}Lu-PSMA-ligand therapy, most of them (89.5%), patients who had previously undergone first- and second-line therapy. Criteria for eligibility included an ECOG score ≤ 2 and no affectation of renal, liver functions or haematological abnormal values. Based on 68Ga-PSMA PET/CT imaging, the majority of patients (71%) had predominantly bone metastases, 20% lymph-node metastases and 4% visceral metastases. The mean injected activity was 6.1 ± 1.0 GBq per cycle, and the mean cumulative

injected activity was 13.3 GBq. Thirty-four patients (18%) underwent one cycle, 87 (46%) two cycles, 40 (21%) three cycles, 26 (13%) four cycles and 4 (2%) underwent five cycles.

Biochemical response to treatment evaluated by ≥ 50% PSA decline from baseline was obtained in 56% of the patients (75% showing any PSA decline), while radiographic response by ^{68}Ga-PSMA PET/CT by 49.6% of patients. For the entire cohort, median OS was 12 months, PSA-PFS 6 months and ^{68}Ga-PSMA PET/CT-PFS 6 months.

Response to treatment evaluated by PSA correlated with higher cumulative and average activity administered, as well as with lower mortality rates, and longer periods of follow-up, OS, PSA-PFS and PET/CT-PFS. Kaplan–Meier survival analyses showed that among 159 patients, 75% demonstrated a statistically significant survival outcome if they had any PSA decline in contrast to no PSA decline, being the HR of death between responders and no responders 0.33 (95% CI: 0.15- 0.69). This value was even lower for those patients with ≥ 50% PSA decline compared to those with <50% decline (HR 0.1, 95%CI: 0.07-0.26), which was reflected in an 86% longer median OS. Other factors that positively correlated with improved survival outcomes were PSA baseline levels below the cohort median, patients with predominantly lymph node metastases compared to patients with predominantly bone metastases, and patients that were chemotherapy naïve compared to patients receiving prior chemotherapy. The study concluded on the efficacy of Lu-PSMA RLT to obtain significant response rates in patients with mCRPC, especially in those patients presenting predominantly lymph node metastases, as well as in individuals with chemotherapy-naïve status and lower levels of baseline PSA.

Other studies have evaluated the efficacy of ^{177}Lu-PSMA-617 in comparison to alternative therapeutic approaches, as well as the efficacy of alternative ^{177}Lu-PSMA radiopharmaceuticals, such as ^{177}Lu-PSMA-I&T.

The efficacy of ^{177}Lu-PSMA-617 has also been compared to that of docetaxel in a randomized, parallel-group, open-label, phase II, and non-inferiority study enrolling chemotherapy-naïve mCRPC patients. Patients with high PSMA-expressing lesions on ^{68}Ga- PSMA-11 PET/CT were randomly allocated to receive ^{177}Lu-PSMA-617 (6.0-7.4 GBq/cycle, every 8 weeks, up to 4 cycles) or docetaxel (75 mg/m2/cycle, every 3 weeks, up to 10 cycles).

Out of the 15 patients in the ^{177}Lu-PSMA-617 arm and 20 patients in the docetaxel arm who received treatment per protocol, those patients in the ^{177}Lu-PSMA-617 arm showed a superior PSA response rate compared to those patients in the docetaxel arm (60% versus 40%), corresponding to a non-significant 20% difference between treatments (95% CI: - 12-47, p = 0.25). Progression-free survival rates at 6 months were also non-significantly higher in the ^{177}Lu-PSMA-617 group (30%) compared to the docetaxel group (20%), with a difference between treatments of 10% (95% CI: - 18-38, p = 0.50). On the other hand, QoL outcomes improved significantly in the ^{177}Lu-PSMA-617 arm compared to the docetaxel arm (p< 0.01). Overall, the study supported the non-inferiority of ^{177}Lu-PSMA-617 compared to docetaxel in the treatment of mCRPC, indicating the suitability of ^{177}Lu-PSMA-617 earlier in the disease course rather than being solely reserved for advanced end-stage disease.

The safety and efficacy of ^{177}Lu-PSMA-I&T was evaluated in a prospective single arm study enrolling 100 mCRPC patients who completed at least one cycle with the treatment (Kesavan et al., 2021). In this study, patients were enrolled following a compassionate access palliative program, and all presented confirmed metastatic disease (61% combined nodal and bone) and a medical history of relapsed/refractory following prior surgical and or chemical castration therapy. Criteria for eligibility included ECOG performance status ≤2 and adequate bone marrow function. In this case, owing to the renal safety of ^{177}Lu-PSMA RLT, patients with renal impairment were not specifically excluded. The prescribed activity of therapy of ^{177}Lu- PSMA-

I&T was a median of 6.1 GBq per patient per cycle (up to four cycles) administered at 8-week intervals.

At the time of analysis, which corresponded to a median follow-up of 12-months, the best PSA response of ≥ 50% reduction from baseline was documented in 53% of the patients, with a median PFS of 6 months. The median OS considering the whole population was not reached, although disease control demonstrated by week-12 ^{68}Ga-PSMA-11 PET/CT was associated with a significantly improved one-year OS when compared to patients with progression (median OS not yet reached versus 10-months respectively). The study concluded on the feasibility, safety, efficacy, and adaptability of outpatient RLT with ^{177}Lu-PSMA-I&T in heavily pre-treated patients.

Other ^{177}Lu-labelled radiopharmaceuticals

^{177}Lu is the most commonly used and the most researched beta-emitting radionuclide for radiolabelling of carrier molecules intended for oncologic indications. Clinicaltrials.gov search reveals more than 300 studies with ^{177}Lu-labelled compounds including approx. 150 phase 1 studies, approx. 150 phase 2 studies and approx. 25 phase 3 studies in variety of indications, including renal cell carcinoma, breast cancer, adenoid cystic carcinoma, salivary duct carcinoma, salivary gland cancer, Cholangiocarcinoma, Colorectal Cancer, Oesophageal Cancer, Head and Neck Squamous Cell Carcinoma, Melanoma (Skin), Pancreatic Ductal Adenocarcinoma, Soft Tissue Sarcoma, paraganglioma, pheochromocytoma, lymphoma, Merkel Cell Carcinoma, meningioma, high grade glioma, small cell and non-small cell lung cancer, Nasopharyngeal Cancer, Ovarian Cancer among others.

5.3.3. Overall discussion and conclusions on clinical efficacy

5.3.3.1. Discussion

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor not intended to be directly administered to the patient, therefore, no clinical studies investigating the efficacy and safety have been conducted by the applicant. However, in line with Annex 1, Part III, point 2.2 of Directive 2001/83/EC as amended in Directive 2003/63/EC, Annex I:

"Clinical information generated from clinical studies using the precursor itself is not considered to be relevant in the specific case of a radiopharmaceutical precursor intended solely for radiolabelling purposes. However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented".

In this regard, the applicant presented comprehensive efficacy and safety data from published clinical trials, which have been conducted with ^{177}Lu-labelled tracer molecules, focussing mainly on the most established carriers used for radionuclide ligand therapy (RLT) targeting different types of tumours such as neuroendocrine tumours (NETs) with different ligands (DOTATATE, DOTATOC and DOTANOC) or prostate cancer (PCa) mainly with PSMA-617 ligand and in less extension with PSMA-I&T ligand.

<u>SSTR-positive NETs</u>

The patient population included in these studies usually required confirmed SSTR expression, measurable disease progression per RECIST criteria, and adequate organ function (i.e. normal renal and haematological values at entry). Many studies enrolled patients with an ECOG performance status ranging from 0 to 2, ensuring sufficient baseline health to undergo treatment (Horsch et al., 2016; Sundlov et al., 2022). Also many studies enrolled patients who underwent prior therapies, such as long-acting SSAs, surgery, or chemotherapy (Delpassand et

al., 2014; Romer et al., 2014). Most of them presented GEP-NETs with origin mainly in the pancreas and the small bowel, although patients with NETs from non-GEP origin were frequently included in most of the studies (Bodei et al., 2011; Horsch et al., 2016; Baum et al., 2018; Demirci et al., 2018; Zidan et al., 2022; Mitjavila et al., 2023).

Median PFS for those patients treated with either ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC ranged from 16.1 (Delpassand et al., 2014) to 36 months (Demirci et al., 2018). In the case of OS, values ranged between 34.7 months (Baum et al., 2018) and 55 months (Demirci et al., 2018). For the evaluation of tumour responses, the most frequent outcome at the different follow-up times was partial response, with a minority of patients showing as best response complete remission. The rate of non-responders was low. One study also included information related to secondary efficacy outcomes, suggesting an improvement in quality of life and performance scores with ^{177}Lu-DOTATATE RLT (Delpassand et al., 2014).

Across the different studies, some of the most relevant factors associated with the efficacy of ^{177}Lu-DOTATATE/DOTATOC RLT were the origin of the tumour and the severity of the condition at the initiation of the therapy, with patients exhibiting less aggressive tumours presenting better responses (Delpassand et al., 2014; Horsch et al., 2016; Baum et al., 2018). Also, one study suggested that personalized therapies based on renal dosimetry can be an effective approach to increase the therapeutic efficacy of RLT with ^{177}Lu-DOTATATE by increasing the administered doses up to a limit that results safe for renal function (Sundlov et al., 2022).

Some studies also compared the efficacy of ^{90}Y and ^{177}Lu-based RLTs (Romer et al., 2014; Horsch et al., 2016; Baum et al., 2018). In broader cohort studies, involving large groups of patients, ^{177}Lu-DOTATATE/DOTATOC alone or in combination with ^{90}Y-labelled radiopharmaceuticals showed superior efficacy responses in terms of PFS and OS compared to RLT based on the sole administration of ^{90}Y-labelled radiopharmaceuticals (Horsch et al., 2016; Baum et al., 2018). Another study, regardless of not observing significant differences between ^{177}Lu and ^{90}Y-labelled radiopharmaceuticals in the whole population, reported that RLT based of ^{177}Lu presented more favourable outcomes in a subgroup of patients characterised by low tumour uptake, smaller solitary lesions, and extra-hepatic lesions (Romer et al., 2014).

mCRPC

In the context of RLT for the treatment of mCRPC, treatment with ^{177}Lu-PSMA (either ^{177}Lu-PSMA-617 or ^{177}Lu-PSMA-I&T) has shown positive results for the most relevant clinical endpoints. Notably, reductions in PSA levels have been consistently observed across multiple studies (Hofman et al., 2018; Yadav et al., 2020; De Giorgi et al., 2021; Kesavan et al., 2021; Meyrick et al., 2021; Khreish et al., 2022; Satapathy et al., 2022), with a percentages of patients showing reductions of $\geqslant$50% from baseline ranging between approximately 30% (Khreish et al., 2022) and 60% (Satapathy et al., 2022). Median time to progression ranged from 4 months (Satapathy et al., 2022) to 13.7 months (Baum et al., 2016b) across the different studies, and OS between 12 months (Meyrick et al., 2021) to 16 months (Yadav et al., 2017). Tumoral response based on RECIST and PET assessments also reported a majority of patients across the different studies presenting partial remission or stabilization of the disease. Other studies reported a beneficial effect of ^{177}Lu-PSMA on the quality of life and pain of patients (Yadav et al., 2017; Hofman et al., 2018; Yadav et al., 2020; Satapathy et al., 2022).

The efficacy of ^{177}Lu-PSMA-617for the treatment of mCRPC was also compared to other therapies. In the study by Satapathy et al., PSA response rates in patients treated with ^{177}Lu-PSMA-617 surpassed those seen with docetaxel. Moreover, ^{177}Lu-PSMA-617 treatments showed non-inferior results with better quality of life outcomes in earlier disease stages, emphasizing its potential as a valid alternative to conventional therapies (Satapathy et al., 2022). Some

studies, like the one conducted by Khreish et al. also correlated the biochemical response to ^{177}Lu-PSMA-617 with longer overall survival, indicating a strategic advantage of the therapy when implemented promptly (Khreish et al., 2022).

Other indications

Finally, beyond those indications for which there are approved ^{177}Lu-labelled radiopharmaceuticals, different studies have shown promising results in other indications, including the use of ^{177}Lu-EDTMP for the treatment of painful bone metastasis, and the development of 177Lu-radiolabelled monoclonal antibodies against several types of cancer (Alvarez et al., 1997; Meredith et al., 2001; Meredith et al., 2012; Forrer et al., 2013; Stillebroer et al., 2013; Tagawa et al., 2013; Agarwal et al., 2015; Bhusari et al., 2017; Tagawa et al., 2019; Kolstad et al., 2020; Niaz et al., 2020).

The provided literature data sufficiently demonstrate the clinical utility.

5.3.3.2. Conclusions on the clinical efficacy

Overall, the discussed literature is considered sufficient to support the clinical utility of ^{177}Lu-labelled radiopharmaceuticals and clinical utility of $^{177}LuCl_3$ radionuclide precursor for the intended indication.

5.4. Clinical safety

Please refer to the table of studies in section 5.3.2.

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

No original clinical safety studies were conducted by the applicant.

No clinical data are available on adverse events from systemic exposure to $^{177}LuCl_3$, as this substance is used solely as a precursor for radiolabelling; safety considerations relate to the ionising radiation emitted by the radionuclide. Product-specific risks for ^{177}Lu-labelled radiopharmaceuticals vary according to target and off-target binding. Publicly available information on human exposure to ^{177}Lu scaled-up from the results obtained in non-clinical studies conducted in rats has shown predominant absorption of ^{177}Lu at osteogenic cells, the liver, spleen, red marrow and kidneys (see also 4.3.2.2.). As a consequence, the main AEs expected due to the systemic exposure to $^{177}LuCl_3$ would be related to potential liver damage

and the development of osteosarcoma (Lutetium (^{177}Lu) chloride Billev SmPC, 2022).

In the event of accidental injection, adverse events would depend on organ-absorbed dose; non-clinical evidence indicates that activities substantially higher than those encountered during routine handling would be required to elicit toxicity, and the overall risk is considered very low. External exposure from 113 and 208 keV gamma emissions necessitates application of standard radiation-protection measures (time, distance, shielding) in line with applicable legislation and institutional procedures, ensuring occupational doses remain within statutory limits (Cappon *et al.*, 2023).

For ^{177}Lu-labelled agents targeting somatostatin receptors or PSMA, the principal clinical risks are haematotoxicity and renal toxicity.

5.4.1. Safety data collection

As lutetium (^{177}Lu) chloride is not intended for direct administration but as a precursor for the preparation of radiopharmaceuticals, the initial screening identified that most retrieved records concerned ^{177}Lu-labelled radiopharmaceuticals. An additional targeted search was performed using terms commonly associated with clinical use, in particular agents evaluated or approved for GEP-NETs and mCRPC. Using the same filters, the following strings and yields were obtained: ("Lutetium" AND "DOTATATE") [120 results]; ("Lutetium" AND "DOTATOC") [22 results]; ("Lutetium" AND "PSMA") [155 results]. Each record was assessed for relevance based on title, abstract and, when necessary, full text. For recent reviews and systematic reviews, reference lists were screened to identify pertinent primary studies not captured by the initial search; original articles were consulted and, where eligible, included. Publications subject to regulatory data exclusivity and references to other products' SmPCs were excluded.

5.4.2. Patient exposure

No patients were currently exposed with this precursor, which is in accordance with similar products with ^{177}Lu in the intended indication.

5.4.3. Adverse events

- ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC

The most frequently used regimen remains 7.4 GBq per cycle at 6–9-week intervals, with cumulative activities commonly up to approximately 29.6 GBq.

Common adverse events (AEs) identified in the literature include acute gastrointestinal reactions predominantly attributable to the co-infused amino-acid (AA) solution used for renal protection (nausea, vomiting). Bone-marrow toxicity (myelo/haematotoxicity), generally mild to moderate and reversible, presents with transient reductions in blood counts across lineages (anaemia, neutropenia, lymphopenia, thrombocytopenia).

- ^{177}Lu-PSMA-617

Typical regimens use ~7.4 GBq/cycle for 4–6 cycles at 6–9-week intervals.

Common AEs include haematological toxicity (more frequent in patients with extensive skeletal metastases or borderline marrow reserve), fatigue, nausea/vomiting, and xerostomia, consistent with ligand uptake in salivary/lacrimal glands. Renal AEs are generally infrequent; long-term renal failure is rare in available follow-up, noting limitations from disease-related mortality. Supportive measures (e.g. hydration; institutional procedures for salivary gland care)

are applied per local protocol.

• Description of selected adverse events

Dry mouth

Transient dryness of the mouth has been reported among patients with metastatic castration resistant prostate cancer receiving PSMA-targeted lutetium (^{177}Lu)-labelled medicinal products.

Alopecia

Alopecia, described as mild and temporary, has been observed among patients receiving lutetium (^{177}Lu) based peptide receptor radionuclide therapy for neuroendocrine tumours.

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

Deaths

The majority of deaths reported in the studies conducted with ^{177}Lu-labelled radiopharmaceuticals were related to the progression of the cancer conditions presented by the subjects enrolled in clinical studies.

SAEs

Therapy-related MDS/AML is rare and generally late-occurring; pooled estimates across non-protected reviews indicate low incidence. Renal SAEs are uncommon with nephroprotection and appropriate dosimetry; isolated Grade $\geqslant$3 events occur infrequently and often in patients with baseline renal impairment or prior nephrotoxic exposures. Hormone-release crises (e.g. carcinoid, catecholamine) are infrequent; risk-minimisation includes pre-treatment optimisation and close haemodynamic monitoring per institutional protocols. Tumour lysis syndrome (TLS) is rare; baseline laboratory assessment and early supportive measures are recommended.

5.4.5. Discontinuation due to adverse events

Discontinuations are most commonly related to haematological toxicity, followed by renal events and, less frequently, gastrointestinal intolerance associated with AA co-infusion.

5.4.6. Safety in special populations

General

No studies with $^{177}LuCl_3$ were conducted in special populations (not applicable to the precursor). For ^{177}Lu-labelled products, risk factors include baseline marrow compromise, extensive bone metastases, prior myelotoxic therapy, and renal impairment.

Renal/hepatic impairment

Dose individualisation and renal protection strategies should be considered per product-specific protocols. Available literature suggests ^{177}Lu-labelled therapy can be used with caution in selected patients with renal impairment under close monitoring (Ranade et al., 2016; Rosar et al., 2021). Data in hepatic failure are limited (Bober et al., 2022); disease-related hepatic dysfunction may confound attribution.

Elderly

Use in elderly patients appears generally consistent with overall safety patterns, with heightened

vigilance for marrow and renal AEs.

Pregnancy/lactation

No clinical data are available.

Race/ethnicity

No dose adjustments are recommended based on race/ethnicity.

5.4.7. Immunological events

No immune-mediated safety signal specific to the precursor was identified.

5.4.8. Safety related to drug-drug interactions and other interactions

No studies describing drug-drug interactions with ^{177}LuCl3 have been reported in the literature. Interactions of ^{177}Lu-labelled radiopharmaceuticals depend on the characteristics and mechanism of action of each medicinal product. Reference should be made to the pharmacokinetics properties and the safety profile of the administered ^{177}Lu-labelled medicinal product.

5.4.9. Vital signs and laboratory findings

Monitoring should include full blood counts and renal parameters before and during treatment with ^{177}Lu-labelled products. Vital signs and physical findings are assessed per product-specific protocols.

5.4.10. Post marketing experience

Not applicable for the precursor; $^{177}LuCl_3$ has not been authorised as a stand-alone medicinal product.

5.4.11. In vitro biomarker test for patient selection for safety

N/A

5.4.12. Overall discussion and conclusions on clinical safety

In accordance with Annex I to Directive 2003/63 for radionuclide precursors, the focus is on the potential effects of free radionuclide and occupational exposure. Ilumira ($^{177}LuCl_3$) is not administered directly to patients; safety is assessed at the level of the radiolabelled medicinal product.

The applicant has provided its own dosimetry evaluation (see section 5.2.2.2. Dosimetry); for non-clinical-to-human extrapolation see section 4. Non-clinical aspects.

The safety profile of ^{177}Lu-labelled products is characterised principally by haematological and renal toxicity, generally manageable with established risk-minimisation measures.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases, it is necessary to ensure that the risks of the radiation are less than from the disease itself.

The presence of free lutetium (^{177}Lu) chloride in the body after an inadvertent administration of Ilumira will lead to increased bone marrow toxicity and haematopoietic stem cell damage. Therefore, in case of an inadvertent administration of Ilumira, the radiotoxicity for the patient must be reduced by immediate (i.e. within 1 hour) administration of preparations containing chelators like Ca-DTPA or Ca-EDTA in order to increase the elimination of the radionuclide from the body (see section 4.4 of the SmPC). The following preparations must be available in medical institutions, which use Ilumira for labelling of carrier molecules for therapeutic purposes: Ca-DTPA (trisodium calcium diethylenetriaminepentaacetate) or Ca-EDTA (calcium disodium ethylenediaminetetraacetate). These chelating agents help with the elimination of lutetium (^{177}Lu) radiotoxicity by an exchange between the calcium ion in the complex and the lutetium (^{177}Lu) ion. Due to the capacity of the chelating ligands (DTPA, EDTA) of forming water soluble complexes, the complexes and bound lutetium (^{177}Lu) are rapidly eliminated by the kidneys. One gram of the chelating agents should be administered by slow intravenous injection over 3 – 4 minutes or by infusion (1 g in 100 – 250 mL of glucose, or sodium chloride 9 mg/mL (0.9%) solution for injection). The chelating efficacy is greatest immediately or within one hour of exposure when the radionuclide is circulating in or available to tissue fluids and plasma. However, a post-exposure interval > 1 hour does not preclude the administration and effective action of chelator with reduced efficiency. Intravenous administration should not be protracted over more than 2 hours. In any case, the blood parameters of the patient have to be monitored and the appropriate actions immediately taken if there is evidence of radiotoxicity. The toxicity of free lutetium (^{177}Lu) due to in-vivo release from the labelled biomolecule in the body during therapy could be reduced by post-administration of chelating agents.

Careful consideration of the benefit risk ratio in patients with renal impairment and haematological disorders is required since an increased radiation exposure is possible. It is recommended to perform individual radiation dosimetry assessments of specific organs, which may not be the target organ of therapy.

Because ^{177}Lu-DOTATATE/-DOTATOC are predominantly eliminated renally and a fraction is tubularly reabsorbed, the clinically relevant risks include renal toxicity. Standard practice is co-infusion of lysine/arginine AA solutions and prophylactic antiemetics; precise brands, doses and protocols vary and have been generalised here to avoid protected or product-specific claims.

Haematological AEs mostly Grade 1–2; Grade 3–4 events are uncommon and typically transient.

Renal AEs occur infrequently with nephroprotection; risk increases with pre-existing risk factors (e.g. hypertension, diabetes, prior nephrotoxic therapy).

Hepatic AEs are uncommon; clinically relevant events usually occur in patients with liver metastases.

Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been observed after treatment with lutetium (^{177}Lu)-based peptide receptor radionuclide therapy for neuroendocrine tumours (see SmPC sections 4.4 and 4.8). This should be taken into account when considering the benefit/risk, especially in patients with possible risk factors like prior exposure to chemotherapeutic agents (such as alkylating agents).

Anaemia, thrombocytopenia, leucopenia, lymphopenia, and less commonly neutropenia may occur during radioligand therapy with lutetium (^{177}Lu). Most events are mild and transient, but in some cases patients have required blood and platelet transfusions. In some patients more than one cell line may be affected and pancytopenia requiring treatment discontinuation has been described. A blood count should be taken at baseline and monitored regularly during treatment, in accordance with clinical guidance.

Radiolabelled somatostatin analogues are excreted by the kidney. Radiation nephropathy has been reported following peptide receptor radionuclide therapy for neuroendocrine tumours using other radioisotopes. Renal function including glomerular filtration rate (GFR) should be assessed at baseline

and during treatment and renal protection should be considered, in accordance with clinical guidance of the radiolabelled medicinal product.

Cases of hepatotoxicity have been reported in the post-marketing setting and in the literature in patients with liver metastases undergoing treatment with lutetium (^{177}Lu) peptide receptor radionuclide therapy for neuroendocrine tumours. Liver function should be monitored regularly during treatment. Dose reduction may be necessary in affected patients.

There have been reports of carcinoid crisis and other syndromes associated with release of hormones from functional neuroendocrine tumours following lutetium (^{177}Lu)-based peptide receptor radionuclide therapy, which may be related to irradiation of tumour cells. Reported symptoms include flushing and diarrhoea associated with hypotension. Observation of patients by overnight hospitalisation should be considered in some cases (e.g. patients with poor pharmacologic control of symptoms). In case of hormonal crises, treatments may include: intravenous high dose somatostatin analogues, intravenous fluids, corticosteroids, and correction of electrolyte disturbances in patients with diarrhoea and/or vomiting.

Tumour lysis syndrome has been reported following lutetium (^{177}Lu)-based radioligand therapy. Patients with a history of renal insufficiency and high tumour burden may be at greater risk and should be treated with increased caution. Renal function as well as electrolyte balance should be assessed at baseline and during treatment.

There have been reports of extravasation of lutetium (^{177}Lu)-labelled ligands in the post-marketing setting. In case of extravasation, infusion of the lutetium (^{177}Lu)-labelled medicinal product should be immediately ceased, and the nuclear medicine physician and the radiopharmacist should be promptly informed. Management should be in accordance with local protocols.

Point-source approximation shows that the average dose rate experienced 20 hours after administration of a 7.4 GBq dose of lutetium (^{177}Lu)-labelled medicinal product (residual radioactivity 1.5 GBq) by a person at 1 meter distance from the patient's body centre with an abdominal radius of 15 cm is 3.5 µSv/h. Doubling the distance to the patient to 2 meters reduces the dose rate by a factor of 4, to 0.9 µSv/h. The same dose in a patient with an abdominal radius of 25 cm yields a dose rate at 1 meter of 2.6 µSv/h. The generally accepted threshold for discharge of the treated patient from the hospital is 20 µSv/h. In most countries, the exposure limit for hospital staff is set the same as for the general public at 1 mSv/year. When taking the 3.5 µSv/h dose rate as an average, this would allow hospital staff to work approx. 300 hours/year in close vicinity of patients treated with lutetium (^{177}Lu)-labelled medicinal products labeled radiopharmaceuticals without wearing radiation protection. Of course, the nuclear medicine staff is expected to wear standard radiation protection.

Any other person in close vicinity of the treated patient should be informed about possibilities to reduce his/her exposure due to radiation emitted from the patient.

For information concerning special warnings and special precautions for use of lutetium (^{177}Lu)-labelled medicinal products refer also to the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.

Before administering radiopharmaceuticals to a mother who is breastfeeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breastfeeding should be interrupted, and the expressed feeds discarded.

Effects of lutetium (^{177}Lu) chloride on male and female fertility have not been studied in animals. Low exposures could be demonstrated for male and female sexual organs. It cannot be excluded that lutetium

(^{177}Lu)-labelled medicinal products lead to reproductive toxicity including spermatogenetic damage in male testes or genetic damage in male testes or female ovaries.

Further information concerning fertility as well as the use of lutetium (^{177}Lu)-labelled medicinal products in women of child-bearing potential, during pregnancy and breast-feeding is specified in the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.

Further precautions with respect to relatives, carers and hospital staff are provided in SmPC section 6.6.

5.4.12.1.1. Adverse drug reactions in the SmPC

The ADRs as included in the SmPC are described below:

Table 6. List of adverse reactions

MedDRA system organ class	Very common	Common	Uncommon	Not known
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Refractory cytopenia with multilineage dysplasia (Myelodysplastic syndrome)	Acute myeloid leukaemia	
Blood and lymphatic system disorders	Anaemia Thrombocytopenia Leukopenia Lymphopenia	Neutropenia		Pancytopenia
Endocrine disorders				Carcinoid crisis
Metabolism and nutrition disorders				Tumour lysis syndrome
Gastrointestinal disorders	Nausea Vomiting			Dry mouth
Skin and subcutaneous tissue disorders	Alopecia			

5.4.12.2. Conclusions on clinical safety

Overall, the safety profile of Ilumira has been adequately characterised.

6. Risk management plan

6.1. Safety specification

6.1.1. Safety specification

Table 7. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia) Myelodysplastic syndrome/Acute myeloid leukaemia
Important potential risks	Osteosarcoma Radiation-induced nephropathy Radiation-induced hepatotoxicity
Missing information	None

6.1.2. Discussion on safety specification

No additional pharmacovigilance activities and no additional risk minimisation measures are proposed by the applicant. The inclusion of safety concerns is therefore based on the criterion as per GVP Module V (rev. 2) that the product information advises on specific clinical actions to be taken to minimise these risks which are reflected in the RMP as "*routine risk minimisation activities recommending specific clinical measures to address this risk*" as follows.

Important identified risks

Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient

The SmPC contains detailed information on radiation protection in section 4.4 and it is specified in section 4.2 that the product is only to be used by specialists experienced with *in vitro* radiolabelling.

A recommendation to administer the smallest quantity to the patient to achieve the appropriate outcome is included in the PL in section 3.

The product information contains information about precautions to be taken during the receipt, handling and storage of the radiopharmaceutical in the SmPC in sections 6.4, 6.6 and 12 as well as the PL in sections 3 and 5.

It is agreed that exposure to radiation generally constitutes an important identified risk.

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of the competent official organisation. Administration

procedures should be carried out in a way to minimise irradiation of the operators. Adequate shielding is mandatory and radiation protection precautions in accordance with national regulations must be taken.

Since radiopharmaceuticals are administered by highly qualified professionals in a clinical setting in a highly controlled environment, radiotoxicity due to occupational exposure is not considered to constitute a safety concern. The risk of radiation relates to *inadvertent* exposure, in particular to *persons who are not aware of the exposure when in vicinity of the patient*. SmPC section 4.4 advises that any person in close vicinity of the treated patient should be informed about possibilities to reduce his/her exposure due to radiation emitted from the patient.

Therefore, this important identified risk is correctly specified as:

"Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient".

Inclusion of this important identified risk is agreed.

Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)

It is stated in SmPC section 4.4 that anaemia, thrombocytopenia, leukopenia, lymphopenia, and less commonly neutropenia may occur during radioligand therapy with lutetium (^{177}Lu). Most events are mild and transient, but in some cases patients have required blood and platelet transfusions. In some patients more than one cell line may be affected and pancytopenia requiring treatment discontinuation has been described.

Instructions to perform a blood count test at baseline and to monitor the blood count regularly during treatment is included in the SmPC in section 4.4 and in the PL in section 2.

Inclusion of this important identified risk is agreed.

Myelodysplastic syndrome/Acute myeloid leukaemia

Section 4.4 of the SmPC provides information that myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been observed after treatment with lutetium (^{177}Lu) peptide receptor radionuclide therapy for neuroendocrine tumours.

Section 4.4 advises that this should be taken into account when considering the benefit/risk, especially in patients with possible risk factors like prior exposure to chemotherapeutic agents (such as alkylating agents).

It is agreed to include "Myelodysplastic syndrome/Acute myeloid leukaemia" as an important identified risk.

Important potential risks

Osteosarcoma

It is stated in SmPC section 12 that free lutetium (^{177}Lu) is taken up and accumulates in the bones which could potentially result in osteosarcomas.

A recommendation to use a binding agent such as DTPA prior to intravenous administration of ^{177}Lu labelled conjugates is included in SmPC section 12.

Inclusion of this important potential risk is agreed.

Radiation-induced nephropathy

It is stated in SmPC section 4.4 that radiolabelled somatostatin analogues (SSAs) are excreted by the kidney. Radiation nephropathy has been reported following peptide receptor radionuclide therapy for neuroendocrine tumours using other radioisotopes.

A recommendation for assessment of the renal function at baseline and during treatment is included in SmPC section 4.4 and PL section 2.

A recommendation to consider renal protection is included in SmPC section 4.4.

As detailed in section SVII.3 of the RMP, there is scientific evidence to suspect the possibility of a causal relationship between kidney damage and radiation of ^{177}Lu but study data are not clear-cut. Therefore, this safety concern has been correctly categorised as an important potential risk. Moreover, the wording of the safety concern indicates that nephropathy is induced by ^{177}Lu radiation.

Inclusion of this important potential risk is agreed.

Radiation-induced hepatotoxicity

It is stated in SmPC section 4.4 that cases of hepatotoxicity have been reported in the post-marketing setting and in the literature in patients with liver metastases undergoing treatment with lutetium (^{177}Lu) peptide receptor radionuclide therapy for neuroendocrine tumours.

A recommendation to monitor the liver function regularly during treatment is included in the SmPC in section 4.4 and in the PL in section 2.

A recommendation to consider dose reduction in affected patients is included in SmPC section 4.4.

Inclusion of this important potential risk is agreed.

Conclusion on the summary of safety concerns

Having considered the data in the safety specification it is agreed that the safety concerns listed by the applicant are appropriate.

6.2. Pharmacovigilance plan

Routine pharmacovigilance activities including the collection, processing and analysis of individual case safety reports, the review and reporting on aggregate data, and a signal detection system are conducted for Ilumira 37 GBq/mL radiopharmaceutical precursor, solution. Routine PV activities are consistent with the EMA Guidelines on Good Pharmacovigilance Practices (GVP). A comprehensive description of all aspects of the PV system is provided in the Pharmacovigilance System Master File (PSMF), which is available upon request.

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are in place for the product included in this RMP.

6.2.1. Pharmacovigilance plan

The applicant did not propose any additional pharmacovigilance activities.

6.2.2. Discussion on the pharmacovigilance plan

6.2.2.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities are proposed which is considered sufficient.

6.2.2.2. Additional pharmacovigilance activities

No additional pharmacovigilance activities are proposed, this is acceptable.

Overall conclusion on the pharmacovigilance plan

Based on the data submitted, routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product.

Routine pharmacovigilance is also considered sufficient to monitor the effectiveness of the risk minimisation measures.

6.3. Plans for post-authorisation efficacy studies

Clinical Utility of the product has been widely confirmed, as it has been used for more than 10 years in Europe and its safety and efficacy has been well characterised. To date, no factors which might affect the efficacy of the product in medical practice have been identified in its authorised indications and in the target population.

6.4. Risk minimisation measures

6.4.1. Risk minimisation measures

Table 8. Planned routine risk minimisation measures

Safety concern	**Routine risk minimisation activities**
Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient	Routine risk communication: Warning about exposure to radioactivity in SmPC section 4.4. and Package Leaflet (PL) section 1. Adverse reactions including induction of certain risk of cancer and development of hereditary effects included in SmPC section 4.8 and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Contains a general warning on radiation protection in SmPC section 4.4. and the indication that the product is to be used by specialists experienced with *in vitro* radiolabelling in SmPC section 4.2.

Safety concern	Routine risk minimisation activities
	Recommendation to administer the smallest quantity to the patient to achieve the appropriate outcome included in PL section 3. Contains information about precautions to be taken during the receipt, handling and storage of the radiopharmaceutical in SmPC sections 6.4, 6.6 and 12 and PL sections 3 and 5. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.
Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)	Routine risk communication: Warning concerning haematological side effects and myelosuppression included in SmPC section 4.4 and PL section 2. Anaemia, thrombocytopenia, leukopenia, lymphopenia and pancytopenia are listed as adverse reactions in SmPC section 4.8 and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Instruction to perform blood count test at baseline and monitor the blood count regularly during treatment included in SmPC section 4.4 and PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.
Myelodysplastic syndrome /Acute myeloid leukaemia	Routine risk communication: Warning about MDS and AML in SmPC section 4.4 and PL section 2.

Safety concern	Routine risk minimisation activities
	MDS is listed as common and AML as uncommon adverse reactions in SmPC section 4.8 and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: The section 4.4 included a statement encouraging to the healthcare professionals to consider this possible risk when the patient presents a risk factor. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.
Radiation-induced nephropathy	Routine risk communication: Warning concerning the excretion of radiolabelled somatostatin analogues by the kidneys in SmPC section 4.4 and PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for assessment of the renal functions at baseline and during treatment in SmPC section 4.4 and PL section 2. Recommendation to consider renal protection in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.
Osteosarcoma	Routine risk communication: Explanation in SmPC section 4.8 that exposure to ionising radiation is linked with cancer induction and may result in higher incidence of cancer.

Safety concern	Routine risk minimisation activities
	Warning in SmPC section 12 concerning the uptake and accumulation of free Lutetium ^{177}Lu in the bones, which could potentially result in osteosarcomas. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to use a binding agent such as DTPA prior to intravenous administration of ^{177}Lu labelled conjugates in SmPC section 12. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.
Radiation-induced hepatotoxicity	Routine risk communication: Warning about hepatotoxicity in SmPC section 4.4 and PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to monitor the liver function regularly during treatment in SmPC section 4.4 and PL section 2. Recommendation to consider dose reduction in affected patients in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by specialists experienced with *in vitro* radiolabelling Labelling: • The symbol "radioactive" is given on the labelling.

The applicant did not propose any additional risk minimisation measures. This is considered acceptable.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

Routine risk minimisation activities as proposed by the applicant are considered sufficient.

6.4.2.2. Additional risk minimisation measures

No additional risk minimisation measures are proposed and this is considered acceptable.

Overall conclusion on the risk minimisation measures

The proposed risk minimisation measures are considered sufficient to minimise the risks of the product in the proposed indication(s).

6.5. RMP Summary and RMP Annexes overall conclusion

RMP Part VI is considered acceptable.

The RMP Annexes are acceptable.

6.6. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan, version 0.3 is acceptable.

The Applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The proposed wording of the indication is consistent with that of other ^{177}Lu precursor products recently approved in the EU and thus justified and fully acceptable.

8.1.2. SmPC section 5.1 justification

The proposed wording of SmPC section 5.1 is consistent with that of other ^{177}Lu precursor products recently approved in the EU and thus justified and acceptable.

8.1.3. Other SmPC sections justification

N/A

8.2. Labelling

Package leaflet (PL)

8.2.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to recent similar products like Lutethium Billev and Theralugand.

8.2.1.1. Conclusion from the checklist for the review of user consultation

The bridging report submitted by the applicant has been found acceptable.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, therapeutic indication

This medicinal product Lutetium (^{177}Lu) chloride 37 GBq/mL is a radiopharmaceutical precursor and it is not intended for direct administration to patients. It is to be used solely for radiolabelling of carrier molecules that have been specifically developed and authorised for therapeutic purposes.

9.1.2. Available therapies and unmet medical need

There are other available therapies based on Lutetium-177, but due to its radioactive characteristics (decay), granting a new marketing authorisation would improve the availability of these therapies.

9.2. Main clinical studies

In line with the Annex 1 Part III of Directive 2001/83/EC, as amended, on radiopharmaceutical precursors, relevant information on the clinical utility of the radiopharmaceutical precursor Ilumira when is attached to appropriate carrier molecules has been provided. An appropriate number of published articles and meta-analyses have been presented documenting a well-established use of ^{177}Lu-based radiopharmaceuticals, mainly in neuroendocrine gastro-entero-pancreatic tumours and in prostate cancer.

9.3. Favourable effects

Clinical utility has been shown, based on the submitted review of the literature, in the treatment of patients with neuroendocrine tumours using ^{177}Lu labelled somatostatin analogues. In this regard, the use of ^{177}Lu-oxodotreotide for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive GEP-NETs in adults, is considered established, as ^{177}Lu-oxodotreotide is already authorised in this clinical setting. Moreover, there is sufficient evidence to support clinical utility of lutetium (^{177}Lu) chloride when coupled to a carrier molecule in the treatment of mCRPC based on available efficacy data on ^{177}LuPSMA compounds, in particular in Radioligand therapy RLT supported with the most robust data.

9.3.1. Uncertainties and limitations about favourable effects

Not applicable.

9.4. Unfavourable effects

Safety concerns related to $^{177}LuCl_3$ (accidental free radionuclide exposure) as well as to radiopharmaceuticals incorporating ^{177}Lu derive from the radioactive properties of the radionuclide, including haematological and renal toxicity and potential carcinogenicity/mutagenicity associated with ionising radiation. Because ^{177}Lu-labelled radiopharmaceuticals are administered by the intravenous route, systemic exposure is complete. Accidental injection of unconjugated $^{177}LuCl_3$ is considered unlikely; if it occurred,

organ-dose dependent effects would be expected, with uptake described in bone (osteogenic cells), liver, spleen, red marrow and kidneys based on non-clinical data. The principal concerns in such scenarios relate to potential liver injury and theoretical risk of osteogenic malignancy; overall risk is considered very low given handling controls and standard precautions.

Additional safety concerns are associated with the administration of ^{177}Lu-labelled products and are related to biodistribution and absorbed dose in target and non-target tissues. Specific risk associated with the use of ^{177}Lu-labelled compounds should be primarily addressed in the MAs of the corresponding medicinal products.

Moreover, radiation safety for occupational or inadvertent exposure is addressed via standard protection measures (time, distance, shielding); decreased blood cell counts, and MDS/AML are included as important identified risks in the Ilumira Risk Management Plan, while osteosarcoma, radiation-induced nephropathy and hepatotoxicity are included as important potential risks. Corresponding special warnings and precautions for use are included in the SmPC accordingly.

9.4.1. Uncertainties and limitations about unfavourable effects

Toxicity of free lutetium (^{177}Lu) due to in-vivo release from the labelled biomolecule during therapy could occur. The likelihood and extent of in-vivo release are product-specific and should be addressed in the dossiers of the respective radiolabelled products.

9.5. Effects Table

N/A

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

$^{177}LuCl_3$ solution in Ilumira is a radiopharmaceutical precursor and is not intended for direct use in patients. It is to be used only for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with $^{177}LuCl_3$. Therefore, clinical utility must be demonstrated. As required, the applicant has reviewed the literature in order to document the clinical utility of lutetium-177.

The quantity of Ilumira required for radiolabelling and the quantity of ^{177}Lu-labelled medicinal product that is subsequently administered will depend on the medicinal product to be radiolabelled and its intended use.

The two most important, most common and best described in the published literature therapeutic indications for ^{177}Lu-based radiopharmaceuticals currently are:

- treatment of SSTR-positive NETs using PRRT. PRRT targets SSTRs on NET cells utilizing a somatostatin analogue carrier molecule with a coupled to it via a bifunctional chelator (e.g., DOTA) suitable radionuclide.

- treatment of mCRPC using ^{177}Lu-labelled PSMA derivatives (^{177}Lu-PSMA-617 & ^{177}Lu-PSMA-I&T, sometimes collectively referred to as ^{177}Lu-PSMA).

In accordance with authorised ^{177}Lu products, the proposed SmPC of Ilumira recommends assessing blood cell counts and renal function of patients receiving ^{177}Lu-labelled medicinal products. Furthermore, where applicable, individual radiation dosimetry of non-target organs is

advised for patients with renal impairment or haematological diseases. Liver function should be monitored in accordance with the Product Information of the administered radiolabelled medicinal product, particularly in patients with liver metastases.

Unfavourable effects are mainly related to the radioactivity of ^{177}Lu. Inadvertent administration of free $^{177}LuCl_3$ or in-vivo release of ^{177}Lu from a radiolabelled product may occur; prevention and management are addressed through handling controls, chelation where indicated, and product-specific guidance. See also section 5.2.2.2. Dosimetry. Therapy with these medicinal products is well tolerated and toxicity is manageable if protective recommendations and dose limits are followed, which have been adequately reflected in the product information.

9.6.2. Balance of benefits and risks

The clinical utility of ^{177}Lu has been demonstrated and is considered to outweigh the risks associated. The benefits and risks of ^{177}Lu-labelled medicinal product(s) will depend on the specific ^{177}Lu-labelled medicinal product(s) in the intended indications and therefore be evaluated independently.

The risks of unintended radiation exposure to patients or inferior efficacy in the labelling of radiopharmaceuticals, with respect to specific activity and ART, cannot be considered higher than the risks of other marketed products containing $^{177}LuCl_3$, with a well-established positive benefit–risk balance.

In consideration of all these arguments, combined with the extensive clinical experience over the years, sufficient information has been provided to support the acceptability of $^{177}LuCl_3$ as a radiolabelling precursor in the proposed use.

9.6.3. Additional considerations on the benefit-risk balance

Not applicable.

9.7. Benefit-risk conclusions

9.7.1. At Day 210 – Final CHMP conclusions

The overall benefit / risk of Ilumira is positive.

10. Appendix

Not applicable.