19 September 2024
EMA/468008/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Theralugand

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

Procedure No. EMEA/H/C/005882/0000

Note

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

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Table of contents

List of abbreviations

^{111}In	indium-111
^{177}Lu	lutetium-177
^{177}Lu-DOTATATE	^{177}Lu-oxodotreotide
^{177}Lu-PSMA-617	^{177}Lu-vipivotide tetraxetan
^{90}Y	yttrium-90
^{223}Ra	radium-223
ADT	androgen deprivation therapy
AE	adverse event
AKD	acute kidney disease
AKI	acute kidney injury
ALP	alkaline phosphatase
AML	acute myeloid leukaemia
ART	active reference time
AST	aspartate transaminase
BED	biologically effective dose
BM	bone marrow
BMI	body mass index
CI	confidence interval
CgA	chromogranin A
CKD	chronic kidney disease
CR	complete response
CT	computed tomography
CTCAE	common terminology criteria for adverse events
D	day
DCR	disease control rate
DOTA	1,4,7,10-tetraazacyclododecane-N,N‘,N“,N“‘-tetraacetic acid
DOTATATE	DOTA-D-Phe^{1}-Tyr^{3}-Thr^{8}-octreotate
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area

Egfr	estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
F	female
GBq	gigabecquerel
GEP	gastroenteropancreatic
GFR	glomerular filtration rate
GHS	global health status
GMP	good manufacturing practice
Hb	haemoglobin
HP	haematological parameters
HPLC	high performance liquid chromatography
HR	hazard ratio
ICH	International Council for Harmonisation
IL	interleukin
i.m.	intramuscular
IQR	interquartile range
i.v.	intravenous
LDH	lactate dehydrogenase
M	male
MA	marketing authorisation
mCi	millicurie
mCRPC	metastatic castration-resistant prostate cancer
MDS	myelodysplastic syndrome
MIRD	medical internal radiation dose
MPN	myeloproliferative neoplasm
MR	minimal response
MRI	magnetic resonance imaging
N/A	not applicable
ND	not determined
NEN	neuroendocrine neoplasm

NET	neuroendocrine tumour
NR	not reached
OLINDA/EXM	organ level internal dose assessment/exponential modeling
OR	odds ratio
ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PHD	persistent haematologic dysfunction
Ph. Eur.	European Pharmacopeia
PPI	present pain intensity
PR	partial response
PRRT	peptide receptor radiotherapy
PRLT	PSMA radioligand therapy
PSA	prostate-specific antigen
PSMA	prostate surface membrane antigen
QoL	quality of life
RBC	red blood cells
RECIST	response evaluation criteria in solid tumours
RLT	radioligand therapy
SAE	serious adverse event
SCr	serum creatinine
SD	standard deviation
SmPC	summary of product characteristics
SPECT	single photon emission computed tomography
SST	somatostatin
SSTR	somatostatin receptor
SUV	standardised uptake value
SUVmax	maximum standardised uptake value
SWOG	Southwest Oncology Group

TEAE	treatment-emergent adverse event
US	United States of America
vs.	versus
WBC	white blood cells
WHO	World Health Organization
wks.	weeks
y	years

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eckert & Ziegler Radiopharma GmbH submitted on 28 July 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Theralugand, 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 25 February 2021.

The applicant applied for the following indication: Theralugand 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.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and/or studies and bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0433/2021 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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 because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. 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

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	28 July 2023
The procedure started on	17 August 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 November 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	23 November 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 November 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 March 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	07 May 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	30 May 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	03 September 2024
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 Theralugand on	19 September 2024

2. Scientific discussion

2.1. Problem statement

The applicant is seeking marketing authorisation for the proposed medicinal product lutetium (^{177}Lu) chloride solution in accordance with Article 8.3 of Directive 2001/83/EC - complete and independent application, based on full but mixed application with the results of a nonclinical dosimetry study and supportive scientific literature.

The applied and recommended indication is as follows: Theralugand 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 (see SmPC section 4.1).

Theralugand is only to be used by specialists experienced with *in vitro* radiolabelling (see SmPC section 4.2).

The quantity of Theralugand required for radiolabelling and the quantity of lutetium (^{177}Lu)-labelled medicinal product subsequently administered will depend on the medicinal product radiolabelled and its intended use (see SmPC section 4.2).

2.1.1. Disease or condition

Theralugand was developed as a radiopharmaceutical precursor to be clinically used for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with $^{177}LuCl_3$.

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

In order to illustrate the clinical utility of ^{177}Lu data, two indications for which recently specific products using the here applied radioligand therapy (RLT) precursor added to specific carrier molecules (octreotide and PSMA) were selected. For both indications specific products were approved in the EU. This is intended to serve as basis for the benefit-risk assessment of ^{177}Lu-based therapies as recommended in the relevant RLT guideline.

2.2. About the product

Theralugand is a sterile solution of lutetium (^{177}Lu) chloride in diluted hydrochloric acid containing 40 GBq/ml of lutetium (^{177}Lu) chloride.

Lutetium belongs to the group of lanthanides, also referred to as rare-earths elements in the historical literature that consists of 15 chemical elements, mainly trivalent, f-electronic, silvery-white metals, such as cerium, praseodymium, europium, dysprosium, ytterbium, neodymium, gadolinium, etc. (Palasz, et al. 2000)

^{177}Lu is a radioactive lutetium isotope that emits beta-particles upon decay to stable hafnium (^{177}Hf) with a half-life of 6.647 days. The primary radiation emissions of ^{177}Lu are presented in **Table 1**.

Table 1: Lutetium (^{177}Lu) principle radiation emission data

Radiation	Energy (keV)*	Abundance (%)
Beta (β−)	47.23	11.66

Beta (β−)	111.20	8.89
Beta (β−)	148.84	79.44
Gamma	112.95	6.23
Gamma	208.37	10.41

* mean energies are listed for beta particles

Source: www.nndc.bnl.gov

Lutetium (^{177}Lu) emits beta (β^-) particles of moderate maximum energy (0.498 MeV) with a maximum tissue penetration of approximately 2 mm. The beta-emission of ^{177}Lu is accompanied by several gamma-photons with energies of 208 keV and 113 keV, which makes it useful for single photon emission computed tomography (SPECT) imaging and, hence, allows dosimetry.

This solution is produced and released by Eckert & Ziegler Radiopharma GmbH in full compliance with GMP standards and requirements defined in the Ph. Eur. monograph 2798 *Lutetium (177Lu) Solution for Radiolabelling*.

Non-carrier added ^{177}Lu in the Theralugand preparation is produced via an indirect route, i.e., ytterbium (^{176}Yb) is irradiated to generate ^{177}Yb which decays with a half-life of 1.9 h to the intended ^{177}Lu. ^{177}Lu is then isolated from the irradiated target material.

2.3. Type of application and aspects on development

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application - specifically for a full but mixed application with the results of the nonclinical dosimetry study and supportive scientific literature.

No formal scientific advice was requested - for this procedure.

Several similar ^{177}Lu-RLT precursor products were approved using the same approach.

According to Annex 1 of Dir 2001/83/EC, as amended, in the specific case of a radiopharmaceutical precursor intended solely for radiolabelling purposes, the primary objective of the regulatory dossier shall be to present information, which would address the possible consequences of poor radiolabelling efficiency or *in vivo* dissociation of the radiolabelled conjugate, i.e. questions related to the effects produced in the patient by free radionuclide. Accordingly, a dosimetry study (EZ-Lu^{177}) was conducted by the applicant in rats to simulate the scenario of inadvertent direct precursor solution injection into a patient and elucidate the kinetics of the free ^{177}Lu. To provide further scientific background on the pharmacological, pharmacokinetic, and toxicological properties of lutetium and $^{177}LuCl_3$, the applicant conducted a systematic literature search in the public domain.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as solution of radiopharmaceutical precursor containing 1 mL solution which contains 40 GBq lutetium (^{177}Lu) chloride at activity reference time (ART), corresponding to maximum 10 micrograms of lutetium (^{177}Lu) (as chloride) as active substance.

The ART is set on the scheduled day of radiolabelling as indicated by the customer and can be up to 10 days starting from the day of manufacture.

Each 3 mL vial contains an activity ranging from 4 to 120 GBq at ART. The volume is 0.1 to 3 mL.

Each 10 mL vial contains an activity ranging from 12 to 200 GBq at ART. The volume is 0.3 to 5 mL.

The specific activity of the radiopharmaceutical precursor solution at ART is greater than 3 000 GBq/mg.

Other ingredients are diluted hydrochloric acid.

The product is available in colourless type I glass 3 mL vial with a V-shaped bottom or a colourless type I glass 10 mL vial with a flat bottom, closed with bromobutyl rubber stopper and aluminium crimp cap as described in section 6.5 of the SmPC. The vials are placed into a lead container with acrylic insert for protective shielding and packed in a metallic can and an outer carton.

2.4.2. Active Substance

General information

The chemical name of the active substance is [^{177}Lu]Lutetium(III) chloride corresponding to the molecular formula [^{177}Lu]$LuCl_3$. It has a relative molecular mass of 283.3 g/mol

Lutetium (^{177}Lu) chloride is a simple, inorganic substance, which does not form considerable chemical structures in solutions. The active substance is well soluble in aqueous milieu. The solubility in water at room temperature is approx. 1158 g/l.

The ^{177}Lu in the active substance is a non-carrier-added radionuclide from a non-fission source. It decays to stable hafnium (^{177}Hf) with a half-life of 6.647 days. ^{177}Lu is a medium-energy beta (β-)-emitter that co-emits low-energy gamma photons.

Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site.

The active substance is synthesised in 3 main steps: transmutation of ^{176}Yb to ^{177}Lu, chromatographic separation, and recycling of ^{176}Yb.

The active substance lutetium (^{177}Lu) chloride is produced by neutron activation of stable ytterbium (^{176}Yb) followed by chemical and chromatographic separation from the irradiated target material. The manufacture does not contain any organic chemical synthesis. The separation steps are performed in dedicated, specially designed lead-shielded and air-tight boxes providing a controlled environment to ensure radiation safety and to avoid contaminations of the active substance. Adequate in-process controls are applied during the synthesis.

The specifications and control methods for intermediate products, starting materials and reagents have been provided and they are satisfactory.

The active substance is lutetium (^{177}Lu) chloride and it is not susceptible to chemical degradation.

The described manufacturing methods of Lutetium-177 are consistent and suitable. The applicant set a frame for the irradiation conditions at the nuclear research reactors which are applicable for each irradiation site. This frame contains a common target geometry, an optimal neutron energy spectrum for the ^{176}Yb(n,γ)^{177}Yb reaction, a minimum neutron flux rate, a maximum irradiation time and a minimum cooling down time.

The formation of chemical synthesis by-products can be excluded as the active substance is not of synthetic origin. Impurities in the active substance could theoretically arise from the irradiation process of the target material or may be introduced by the substances and materials used in the manufacturing (the target material itself, mobile phase components, solvents, further materials). The risk of the formation or introduction of impurities via these routes is discussed in detail. In conclusion, the risk is however considered very low due to high quality grades and thorough quality control of all materials as well as due to the purification effect of the HPLC step in the manufacturing process.

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 (^{177}Lu) chloride, is processed to the finished product without considerable storage times. Therefore, no container closure system is used.

Specification

Since the active substance is processed by dissolution into the finished product without leaving the production line and without any substantial storage or holding times, it is not considered as isolated. Therefore, in line with the Guideline on Radiopharmaceuticals, quality control of the active substance is covered by the quality control of the finished product.

Stability

The active substance, dried lutetium (^{177}Lu) chloride, is processed to finished product without storage.

Therefore, a stability evaluation of the active substance is not applicable in this case.

2.4.3. 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 provisions of the Ph. Eur. monograph 2798 (current version) and provides suitable conditions for efficient radiolabelling reactions.

The physico-chemical characteristics of the active substance are well known. Lutetium (^{177}Lu) chloride is not susceptible to chemical degradation and can be (re-)dissolved in diluted hydrochloric acid. ^{177}Lu decays to stable hafnium (^{177}Hf) with a half-life of 6.647 days. Other instabilities or any incompatibilities are not expected. ^{177}Lu is an emitter of medium-energy beta-particles with a short tissue penetration range. The co-emitted gamma photons can be employed also for single photon emission computed tomography (SPECT) imaging and dosimetry evaluations.

In line with Ph. Eur. monograph 2798 Lutetium (^{177}Lu) Solution for Radiolabelling, dilute hydrochloric acid is used as the only excipient in the medicinal product. Hydrochloric acid is a simple inorganic acid with low potential for unintended side reactions with carrier molecules to be radiolabelled by lutetium (^{177}Lu) chloride or their buffer components.

The excipient diluted hydrochloride 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 used low concentration / acidic strength of the diluted hydrochloric acid) is sufficient to maintain ^{177}Lu in the dissolved trivalent ion state but low enough to avoid extensive buffer and pH adjustments during radiolabelling procedures. Furthermore, hydrochloric acid is not affected by sterilisation by heat.

The diluted hydrochloric acid is manufactured from high-quality-grade concentrated hydrochloric acid and water for injection (Ph. Eur.) to limit the content of metal impurities which may impair the radiolabelling performance of the medicinal product.

The strength (i.e., activity concentration) of the active substance of 40 GBq/ml was chosen to allow a sufficient range of deliverable activities per packaging unit for radiolabelling of various potential carrier molecules.

The medicinal product manufacturing process is focused on production of the lutetium (^{177}Lu) chloride solution from the active substance, whereby the solution is eventually dispensed in ready-for-use, sterile aliquots with the intended activity concentration. The manufacturing is carried out in dedicated, specially designed lead-shielded and air-tight boxes that provide a controlled environment to ensure radiation safety and to avoid contaminations of the product. The manufacture consists of three process steps: dissolution of the active substance, dispensing of the obtained solution into appropriate vials, closure of the vials and sterilisation by heat. The suitability of the process was examined in validation studies provided.

The primary packaging is colourless type I glass 3 mL vial with a V-shaped bottom or a colourless type I glass 10 mL vial with a flat bottom, closed with bromobutyl rubber stopper and aluminium crimp cap. The material complies with Ph. Eur. requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. Extractables studies and leachables study performed during development support of the chosen primary packaging components for the finished product.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site. The GMP compliance of the site has been confirmed.

The manufacturing process consists of 3 main steps: dissolution of the active substance, dispensing of the obtained solution into appropriate vials, and closure of the vials and terminal sterilisation by heat. The process is considered to be a standard manufacturing process.

The sterility of the finished product is controlled by parametric release on the basis of the sterilisation process using heat to sterilise the product vials. The vials are sterilised by heat according to pharmacopeia standard conditions. The parametric release is done in compliance with the guideline on parametric release and provide supportive justification as demanded by the guideline on parametric release, demonstrating the reliability of the sterilisation by heat which justifies a parametric release on the basis of the heat sterilisation data temperature and time. In addition, the manufacturing site has sufficient experience in the sterilisation process using heat (for a comparable centralised authorised medicinal product), which further supports the application of parametric release.

Major steps of the manufacturing process have been validated in 3 commercial scale 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 release specifications include appropriate tests for this kind of dosage form: appearance (visual), visible particles (visual), identification (gamma-ray spectrometry, physiochemical test, and thin layer chromatography), pH (pH indicator strip), chemical purity (ICP-OES), radionuclidic purity (gamma-ray spectrometry), radiochemical purity (thin layer chromatography), assay (dose calibrator/ ICP-OES), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.) which is in conformity with the applicable Ph. Eur. monograph no. 2798 (Lutetium (^{177}Lu) chloride solution for radiolabelling)

The purity profile of the lutetium (^{177}Lu) chloride solution is determined by the inherent purity profiles of the active substance and the excipient, with no degradation or interaction products to be expected from these simple inorganic substances during the manufacture or shelf-life of the finished product. The corresponding impurity risks are efficiently averted by adequate specifications and quality control measures as well as by the nature of the manufacturing process itself. No considerable impurities are also to be expected from the diluted hydrochloric acid, which is likewise subject to strict quality restrictions and through controls. All purity requirements of the Ph. Eur. monograph 2798 are included in the finished product specification and are readily met.

The ICH Q3D Guideline for Elemental Impurities is not applicable for radiopharmaceuticals.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) 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. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Lutetium (^{177}Lu) chloride solution consists of simple, inorganic components. The short half-life (i.e., 6.647 days) of the radioisotope ^{177}Lu determines the shelf life of the solution. Therefore, the stability study was designed based on the recommendations of ICH guideline Q1A (R2) adapted to the short-lived radioactive nature of the product.

Stability data from 3 commercial scale batches of finished product stored for up to 10 days (starting from the manufacturing date) under storage at room temperature conditions are presented. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

A bracketing design in line with the ICH guideline Q1D was applied to adequately cover the intended filling range of 4 – 200 GBq per vial and the two glass vial types that will be used for primary packaging (either 3 ml V-shaped vials or 10 ml flat bottom vials). All vials were closed with stoppers, crimped, autoclaved and

then stored upside-down, so that the lutetium (^{177}Lu) chloride solution was constantly in contact with the stopper (worst-case scenario).

Samples were tested for appearance, pH, and purity (chemical, radionuclidic and radiochemical). The analytical procedures used are stability indicating.

In all three batches, the pH and the appearance of the lutetium (^{177}Lu) chloride solution did not change over the examined time. No considerable changes were also detected for all purity parameters, which remained well within the specified limits at the end of the stability study.

Based on available stability data, the proposed shelf-life of up to 10 days as stated in the SmPC (section 6.3) is acceptable.

From a microbiological point of view, unless the method of withdrawal from the vial or any insertion into the vial preclude the risk of microbial contamination, the radiopharmaceutical precursor solution 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.

2.4.4. 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. 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.

2.4.5. 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.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

$^{177}LuCl_3$ is not intended to be administered directly to the patients. As a precursor, it is to be used only for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with $^{177}LuCl_3$.

A dosimetry study (EZ-Lu177) was conducted in rats to simulate the scenario of inadvertent direct precursor solution injection into a patient and elucidate the kinetics of the free ^{177}Lu. In addition, to provide further scientific background on the pharmacologic, pharmacokinetic, and toxicologic properties of lutetium and $^{177}LuCl_3$, a systematic literature search in the public domain was submitted and is summarised in the sections below.

2.5.2. Pharmacology

$^{177}LuCl_3$ is not intended to be administered directly to the patients. It is to be used only for the radiolabelling of appropriate carrier molecules that have been specifically developed and authorised for radiolabelling with $^{177}LuCl_3$ to be used for treatment.

^{177}Lu is a radioactive lutetium isotope that emits beta-particles upon decay to stable hafnium-177 (^{177}Hf) with a half-life of 6.647 days. Lutetium (^{177}Lu) emits beta (β−) particles of moderate maximum energy (0.498 MeV) with a maximum tissue penetration of approximately 2 mm. The beta-emission of ^{177}Lu is accompanied by several gamma-photons with energies of 208 keV and 113 keV, which makes it useful for single photon emission computed tomography (SPECT) imaging and, hence, allows dosimetry. ^{177}Lu is broadly used as a therapeutic radionuclide for radiolabelling of specific carrier molecules, which are developed for targeted radiotherapies of various, predominantly oncologic, diseases. $^{177}Lu^{3+}$ in form of a chloride solution for radiolabelling is particularly suitable for this purpose. Several characteristics of ^{177}Lu as a radionuclide, including low-energy beta-decay, a tissue penetration range of less than 1 mm and a comparatively long half-life of 6.647 days, result in pronounced advantages of this radioisotope in terms of logistics, handling, precise localised delivery of sufficient radiation dose to diseased tissue regions and low inadvertent radiation toxicity for patients.

Physical chemistry:

Structure of the active substance	$^{177}LuCl_3$
Molecular weight	283.3 g/mol
Solubility in water	soluble
Stability	$t_{1/2}$ = 6.647 days
Radiochemical purity	≥ 99.0%

2.5.2.1. Primary pharmacodynamic studies

Literature review

The 'primary pharmacodynamic function' of $^{177}LuCl_3$, or more specifically of $^{177}Lu^{3+}$, is to provide an isotope for stable and efficient labelling. Lanthanides tend to accumulate in tumours (Higasi, 1973). A strong affinity for tumour for ^{177}Lu, thulium (^{170}Tm), and ^{169Y}b, that was comparable to that of ^{67}Ga has been shown (Hisada

et al., 1973). All lanthanides in their 3+ oxidation state can be considered hard Lewis acid, and therefore, octadentate ligand DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and its modifications are the best chelators to stabilise them for the *in vivo* use (Maecke 2003). As all pharmacodynamic properties will be dependent of the medicinal product to be radiolabelled, the information below describes labelling specifics with the most commonly used carrier molecules in clinical practice.

Currently, two carrier molecules are considered to have proven clinical utility when used with ^{177}Lu, namely, ^{177}Lu-DOTATATE or ^{177}Lu-oxodotreotide and ^{177}Lu-PSMA-617 or ^{177}Lu-vipivotide tetraxetan. The former was approved in the EU/EEA under the brand name Lutathera for the treatment of gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in September 2017, and the latter under the brand name Pluvicto was approved for the treatment of PSMA-positive metastatic castration-resistant prostate cancer in December 2022. Both active substances utilise DOTA-based chelators as carriers.

DOTA, while having slow complexation kinetics, demonstrated minimal metal release at pH 4.5 and intermediate stability even at pH 2.0 (Stimmel et al. 1998). DOTATATE, i.e. somatostatin (cyclic peptide hormone) analogue TATE coupled with the macrocyclic chelator DOTA, is one of the most commonly used carrier molecules radiolabelled with ^{177}Lu in the current clinical practice. ^{177}Lu-DOTATATE labelling efficiency was shown to depend on the molar ratio, increasing with the excess of ligand and reaching over 99% at 5-fold ligand excess (Pawlak et al. 2007).

PSMA-617 is a urea-based PSMA-targeting small molecule that has shown superior binding affinity to PSMA compared to other PSMA-targeting molecules. Following DOTA-mediated radiolabelling with ^{177}Lu, no free activity was detected at 1 h and 24 h post-labelling, while only <0.4% and <0.6% of free ^{177}Lu were detected after 48 h and 72 h of incubation, respectively, in PBS and human serum (Benesova et al. 2015).

2.5.2.2. Secondary pharmacodynamic studies

Literature review

A few investigations have been identified in literature that assessed potential effects of lutetium on GABA channels (reversible stimulation of GABA-induced chloride channels in the primary culture of rat dorsal root ganglion neurons, Ma et al. 1993) and Ca^{2+} flow and accumulation (elevated Ca^{2+} concentrations in tissues following administration of $LuCl_3$ to rats, Nakamura et al. 1997).

2.5.2.3. Safety pharmacology programme

Since $^{177}LuCl_3$ solution is not intended to be administered directly to the patients, no safety pharmacology testing was carried out by the applicant.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been conducted.

2.5.3. Pharmacokinetics

A non-clinical distribution study was carried out by the applicant in rats to obtain extrapolated human dosimetry data after accidental intravenous administration of $^{177}LuCl_3$ (study EZ-Lu177). Furthermore, published studies on ^{177}Lu pharmacokinetics are included in each relevant section below.

Overall, however, the PK of a ^{177}Lu-radiolabelled molecule will depend on the biological and chemical properties of the molecule to be radiolabelled and its mechanism of action in the human body.

In the dosimetry study EZ-Lu177 carried out by the applicant, tissue samples were measured for the total radioactivity on a gamma counter, with exception of residual carcasses, which were analysed using SPECT/CT due to high tissue mass and radiation dose. Gamma counter and SPECT scanner were validated prior to the study conduct. No chemical analysis was carried out.

Absorption

Study EZ-Lu177 investigated PK parameters of ^{177}Lu after IV injection with 30 MBq $^{177}LuCl_3$ to 18 female and 18 male healthy, mature Sprague-Dawley rats. At 5 min, 1 h, 12 h, 2 d, 7 d, and 35 d post-injection, the animals were euthanised, and their organs and tissues were measured *ex vivo* for total radioactivity. Additionally, 6 animals (3 female, 3 male) from the 35 days' group were imaged using SPECT/CT at 1 h, 12 h, 24 h, 2 d, 5 d, and 7 d post-injection for receiving longitudinal *in vivo* PK data within the same animal. Furthermore, blood samples were drawn from these animals for *in vivo* plasma kinetics prior to each SPECT/CT up to day 2 post-injection. To account for weight and activity differences between female and male rats and between individual rats, the SUV, a standardised uptake value adapted for both injected activity and body weight, was calculated.

Rapid absorption was observed upon intravenous administration of 30 MBq lutetium (^{177}Lu) chloride to rats, with the peak of lutetium (^{177}Lu) concentration in blood plasma reached within 12 min post-injection. See Figure 1 and Table 2.

Figure 1: ^{177}Lu absorption following IV administration in rats: *in vivo* data (study EZ-Lu^{177})

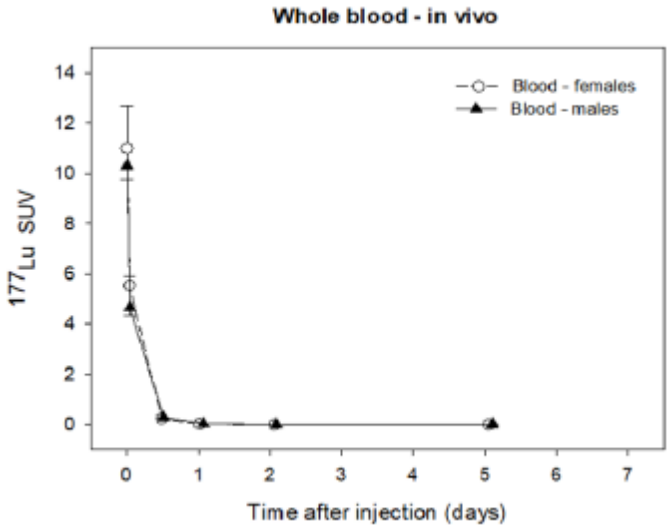


Table 2: Plasma pharmacokinetic parameters from rat ex vivo biodistribution data (study EZ-Lu^{177})

	%IA/g			SUV		
Parameter	Females	Males	Unit	Females	Males	Unit
C_0	2.762	1.595	%IA g^{-1}	8.732	10.503	SUV
C_{max}	2.376	1.512	%IA g^{-1}	8.296	7.366	SUV
T_{max}	0.161	0.206	h	0.161	0.206	h
$t_{1/2}$	0.625	2.580	h	1.813	0.356	h
k_{el}	1.108	0.269	h^{-1}	0.382	1.948	h^{-1}
$AUC_{0-\infty}$	5.387	7.497	(%IA h) g^{-1}	33.529	13.638	(SUV h) g^{-1}
CI_T	0.186	0.133	g (%IA h)$^{-1}$	0.030	0.073	g (SUV h)$^{-1}$

Distribution

Literature

Accumulation of numerous radioactive rare earth elements in tumour tissues and several organs was directly compared to the accumulation of ^{67}Ga in Ehrlich's tumour-bearing dendrin mice. $^{177}LuCl_3$ was administered via IP injection at 50 mCi/mg (n=3 per group). Lutetium accumulated with a significant increase between 28 h to 48 h in tumour, some increase in bone and kidney, and a significant decrease over time in liver and spleen (Higasi et al. 1973).

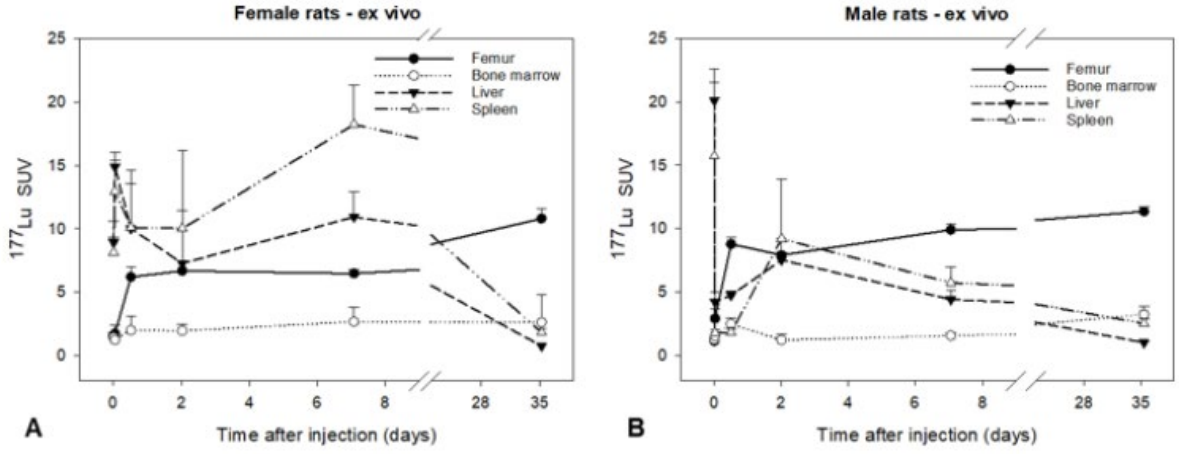
Distribution of the radioactive ^{177}Lu following IP administration to the 3-4 weeks old female mice at single doses with activity ranging from 1 µCi to 60 mCi per kg body weight, supplemented by 0.5 mg/kg stable lutetium carrier, was reported by Müller et al. 1978. Skeleton averaged almost half of the injected dose compared to the soft tissues, while between 1-5% of radioactivity was detected in liver and kidneys, and only 0.1-0.2% in the spleen and lungs in the first 24 h. While radioactivity decreased in soft tissues over time, the skeleton dose remained stable up to 14 days post-injection. About 50% of the radionuclide was excreted in

the first day. Biological half-lives averaged 5 days for the liver, spleen, and kidneys, and 50 days for skeleton.

Deposition in the organs and skeleton as well as possible late effects were further investigated in female mice by Müller et al. 1980. Various amounts of ^{177}Lu fused with $KHSO_4$ and adjusted for pH with citrate were administered via IP injection, with the addition of 0.025 or 2 mg/kg body weight stable lutetium as carrier. 60% of the injected ^{177}Lu dose was detected in the skeleton 48 h post-injection. Over 14 days, gradual decrease was observed in both liver and skeleton values.

Study EZ-Lu177 investigated tissue distribution of ^{177}Lu after IV injection with 30 MBq $^{177}LuCl_3$ to Sprague-Dawley rats (for study design see above). While initially highest ^{177}Lu amounts were found in the liver, kidneys, and spleen (i.e. organs with high blood flow), after 12 h a continuous and steady increase was observed in the bones, in both males and females (**Figure 2**). Male rats demonstrated significantly higher SUV than females for bone surface at 12 h (8.78±0.50 vs. 6.2±0.82, respectively; $p < 0.05$) and at day 7 (9.9±0.43 vs. 6.5±0.31; $p < 0.05$), while at day 35 this difference became less pronounced (11.4±0.35 vs. 10.8±0.75, respectively; $p < 0.05$). Bone marrow showed moderate uptake with no significant sex differences, with a maximum SUV of 2.7±1.17 in females and 3.2±0.63 in males over time. In liver and spleen highest SUV values were observed on day 2 in males and on day 7 in females, after which the uptake decreased for both sexes markedly.

Figure 2: ^{177}Lu distribution following IV administration in rats (study EZ-Lu177)



In **study EZ-Lu177**, a single dose of 30 MBq $^{177}LuCl_3$ was applied to both male and female rats to simulate clinical setting when the same not-weight-adjusted dose is applied to both female and male patients. Therefore, the values for %IA/g and %IA/organ were expectedly higher in female rats with substantially lower organ and body weights than in male rats. As a consequence, weight-adjusted SUV was considered more appropriate for direct comparison between the two sexes. Based on SUV, statistically significant sex-dependent differences persisting for several time points were observed in ^{177}Lu uptake in the liver and spleen, with higher doses in females vs. males. At 35 days, however, there were no significant sex differences detected.

Another study from Literature (Nakamura et al. 1997) investigated differences in distribution, their influence on minerals' concentrations in various organs, and hepatotoxicity of seven nonradioactive rare earth elements, including lutetium. Rare earth elements were administered at low (5-10 mg/kg) and high (10-20

mg/kg) doses to the 4-week-old male Wistar rats (n = 5 per group) per IV injection in chloride form. Main lutetium accumulation sites were liver, bone, and spleen. Most of the rare earth elements (including lutetium) accumulated in bones were distributed into bone marrow. Significant differences were observed for lutetium concentration in serum (85.8±1.1% for 10 mg/kg and 83.9±0.9% for 20 mg/kg) vs. blood cells (14.2±1.1% for 10 mg/kg and 16.1±0.9% for 20 mg/kg).

In the study by Durbin et al. 1956, ^{177}Lu as a citrate complex was administered at doses of 7.3 to 29 µCi, with 0.5-1.9 µg stable carrier, to the female Sprague-Dawley rats (at least 5 animals per group) via IM injection. In these experiments, over 60% of ^{177}Lu was deposited in the skeleton.

Based on **study EZ-Lu177**, human absorbed doses of ^{177}Lu after IV injected $^{177}LuCl_3$ were estimated. It should be noted, however, that the absorbed organ doses and effective dose from the *in vivo* studies in rats could be different than those from the human studies because the physiology (e.g. blood flow rate) and metabolism of rodents are not the same as of humans. Another source of potential discrepancies is allometric scaling from animals to humans on the sole basis of body weight as applied in this study.

The estimated human radiation dose by using female rat data was higher compared to values when using male rat data. (see 2.6.2.2. Dosimetry). A source of difference, translating into differences in biodistribution volumes, are size and body weight: the mean body weight of female rats was 304±18 g, and, thus, approximately 200 g lower than that of male rats with 515±42 g. As both groups, in analogy to patient treatment, received the same 30 MBq activity of ^{177}Lu, female rats are expected to present with higher organ doses and a higher effective dose than male rats. Further potential explanation may be physiology-related sex-specific differences in organ uptake and function.

Higher accumulation of ^{177}Lu in the liver and spleen of female vs. male rats observed in the present study have not been reported for a different ^{177}Lu chloride product, EndolucinBeta (EndoculinBeta EPAR, EMA 2016). However, given the small sample size (n=2 per sex per group), statistical tests on group differences are difficult.

The effective dose for an adult with 73.7 kg body weight was reported as 0.534 mSv/MBq for EndolucinBeta, which is somewhat higher than the effective dose calculated from the applicant's data for ^{177}Lu chloride of 0.190 mSv/MBq for an adult. The applicant's data does correlate better with the effective dose reported for 177Lu-PSMA-617 (Pluvicto) (**Table 3**).

For both EndolucinBeta and Theralugand, the organs with the highest organ doses are liver, bone, and spleen (**Table 3**). Importantly, the addition of the carrier molecule significantly changes ^{177}Lu and, thus, radiation distribution for both Lutathera and Pluvicto bone activity is quite low compared to the organs participating in excretion such as liver and kidneys (**Table 3**).

Table 3: Comparison of the estimated organ dose coefficients and effective doses of ^{177}Lu products in humans (study EZ-Lu^{177})

	mGy/MBq				
	EndolucinBeta[1]	**Theralugand (Study data)**		Pluvicto™ [2]	Lutathera[3]
Organ	Pooled male and female	Female	Male	Pooled male and female	Pooled male and female
Osteogenic cells	2.1500	N/A	N/A	N/A	0.15
Endosteum (bone surface)	N/A	0.2640	0.1670	0.0360	N/A
Liver	5.5600	2.2800	1.0600	0.0900	0.49
Spleen	5.7300	2.6100	0.9100	0.0670	0.80
Kidneys	0.3720	0.2760	0.2890	0.4300	0.65
Bone marrow (red)	0.5910	0.4790	0.2930	0.0350	0.03
Lungs	0.0574	0.1120	0.0804	0.1100	0.03
Muscles	0.0143	0.0358	0.0336		0.03
Effective dose 60 (mSv/MBq)	N/A	0.3040	0.1430	N/A	N/A
Effective dose 103 (mSv/MBq) [4]	0.5340	0.1900		0.1200	ND

N/A = not applicable
For Pluvicto and Lutathera, actual patient PK data were used for estimating absorbed dose coefficients.
[1] ^{177}Lu chloride
[2] (^{177}Lu)Lutetium vipivotide tetraxetan (ligand to prostate specific membrane antigen, PSMA)
[3] (^{177}Lu) Lutetium oxodotretotide (ligand for subtype 2 somatostatin receptors)
[4] Value averaged over both sexes as per ICRP Publication 103

Literature

For a standard activity of 7,400 MBq usually applied for a single treatment cycle with ^{177}Lu-labelled tumour-specific molecules such as Pluvicto and Lutathera, organ doses of 7.84 Gy, 6.73 Gy, 2.15 Gy, 1.26 Gy and 2.15 Gy would be reached for liver, spleen, bone marrow, endosteum and kidneys in male patients, respectively, in case of an accidental direct IV application of Theralugand. For kidney, liver, bone and spleen, these doses are far below critical doses as usually assumed for these organs. Such, for kidneys, an organ dose of 28-40 Gy (depending on pre-existing risk factors) is considered as critical for subsequent kidney functional impairment and risk for kidney failure (Kratochwil et al. 2019). In a recent report on kidney dosimetry in prostate cancer patients undergoing treatment with ^{177}Lu-PSMA-617, the average kidney dose per administered activity was 0.67 ± 0.24 mGy/MBq (n=176; range, 0.21- 1.60 mGy/MBq). Thus, the estimated kidney dose of 0.276 (female) and 0.289 (male) mGy/MBq for Theralugand in case of an accidental direct administration or poor radiolabelling is in the lower range of kidney organ doses acquired by standard radioligand therapy with ^{177}Lu-PSMA-617 (Mix et al. 2022).

In contrast, for red bone marrow established tolerance limits are at 2 Gy (Emami et al. 1991). Therefore, based on the data of this study, in case of the accidental direct injection of a full standard dose of 7,400 MBq of Theralugand red bone marrow with an estimated organ dose of 2.15 Gy in males and 3.55 Gy in females would be the critical organ-at-risk. This would require strict clinical surveillance and medical support.

Metabolism

Metabolism of free lutetium, independently of the radioactive status, has not been specifically investigated in animal studies. Radioactive ^{177}Lu decays to the stable isotope ^{177}Hf emitting beta-particles and gamma-photons.

Excretion

In literature, biliary excretion into the faeces was suggested to be major excretion route for all rare earth elements, including free lutetium, when injected per IV, while slight portions were rapidly excreted into urine (Nakamura et al. 1997). When administered into the muscle of rats, predominantly kidney excretion was reported for lanthanides, while liver excretion was observed with half-life of 10 to 20 days, with < 10% remaining in the liver 2 months after injection (Durbin et al. 1956).

Lutetium (^{177}Lu) excretion occurred mainly via urine, with some faecal excretion observed.

Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies relevant to the use of ^{177}Lu as a radiopharmaceutical precursor have been published.

2.5.4. Toxicology

No new toxicology studies have been performed. Theralugand is a radiopharmaceutical precursor and not intended for direct use in patients. It is to be used only for the radiolabelling of carrier molecules.

2.5.4.1. Single dose toxicity

Literature submitted showed that single-dose studies have been carried out in mice and rats (see **Table 4** and **Table 5**).

Table 4: Summary of single-dose toxicity studies in mice with lutetium

Source	**Species/ Sex/Number**	**Dose/Route**	**LD_{50}**	**Major findings**
Haley et al, 1964	CF1 male Mice	oral/up to 7590 mg/kg **$LuCl_3$**	7100 mg/kg corresponding to 197 mg/kg lutetium	
	CF1 male mice	i.p./up to 372 mg/kg **$LuCl_3$**	315 mg/kg corresponding to 197 mg/kg lutetium	Deaths, writhing, ataxia, laboured respiration, walking on toes with back arched, sedation
Bruce et al, 1963	CF1 female mice	i.p./0.5% and 0.1% of BW **Lu-nitrate**	290 mg/kg corresponding to 108 mg/kg lutetium	Depression leading to deaths Surviving animals showed generalised peritonitis

Table 5: Summary of single-dose toxicity studies in rats with lutetium and other REEs

Source	Species/ Sex/Number	Dose/Route	LD_{50}	Major findings
Bruce et al, 1963	Rats	oral/no lutetium but **other heavy lanthanides administered as nitrates** oral/**rare earths oxides**	About 3000 mg/kg N.D.	Low acute toxicity by the oral route
	SD female rats	i.p./0.1% of BW **Lutetium nitrate**	335 mg/kg corresponding to 125 mg/kg lutetium	Moderate toxicity, deaths animals had grossly distinct abdomen and limb oedemas, peritoneal inflammation, ascites fluid accumulation
	SD female rats	i.p./1000 mg/kg **Lu-oxide**	N.D.	No signs of toxicity
	SD female rats	i.v./ **heavy and light lanthanides**	30-60 mg/kg for heavy lanthanides 4.3 and 7.4 mg/kg for light lanthanides	Deaths occurred within 5 days after injection of light lanthanides, for the others mortality occurred throughout the 30-day observation period
Nakamura et al, 1997	rats	i.v./50 mg/kg **REEs**	N.D.	Necrosis at the injection site, formation of zenobiotic granulomas in spleen, deaths

Table 6: Summary of single dose studies with hafnium

Source	Species/ Sex/Number	Dose/Route/Hafnium	LD_{50}	Major findings

Haley et al, 1962	male CF1 mice/6 males and 6 females per group	i.p./various doses of **$HfCl_4$**	112 mg/kg for hafnyl chloride corresponding to an LD50 of 76 mg/kg for hafnium	Immediate urination and lethargy; deaths occurred within 24 h
	rats	Oral $HfCl_4$	2362 mg/kg	No signs of toxicity
	Rats and cats	i.v./ Hafnium-sodium mandelate	75-100 mg hafnium/kg in rats 5.56 mg hafnium/kg in cats	No signs of toxicity

2.5.4.2. Repeat dose toxicity

Lutetium (^{177}Lu) chloride solution is intended for targeted radiotherapy after in vitro binding to different targeting agents. This application results in single or repetitive single dose administration in cycles with few individual administrations of the targeting radiocomplex. No single or repeated administration of free lutetium is intended, and the administration of the targeting radiocomplex does not lead to significant exposure to free lutetium, due to the tight binding to the complexing agent. The number of administrations and the number of cycles depends on the intended clinical use and is limited by the radioactive dose administered, leading to radiation-induced toxicity. Therefore, limited data are only available describing the repeated dose toxicity of non-complexed, non-radioactive lutetium and the decay hafnium.

No studies with lutetium were reported in mice.

Table 7: Summary of repeat-dose toxicity studies in rats with lutetium and hafnium

Source	**Species/ Sex/Number**	**Dose/Route/$LuCl_3$**	**NOEL**	**Major findings**
Haley et al, 1964	CRW Rats (6 male + 6 female per group)	oral/0.01%, 0.1%, 1% within the diet for 90 days	1000 mg lutetium chloride/kg BW = 625 mg lutetium/kg BW at 1% in diet	No abnormal findings
Haley et al, 1962	CFN rats (6 male and 6 female per group)	Oral/0.01%, 0.1%, 1% within the diet for 12 weeks **$HfCl_4$**	100 mg hafnium chloride/kg BW = 55.5 mg	Liver changes/peri nuclear vacuolisation of parenchymal cells

Source	Species/ Sex/Number	Dose/Route/$LuCl_3$	NOEL	Major findings
			hafnium/kg BW at 0.1% in diet	
Hinerman et al, 1954	White rats (10)	Oral/5 to 25 mg daily for 3 to 16 days s.c and i.m. / 10 mg, 15 mg, 20 mg for 4 weeks s.c. and i.m. /35 mg for 3 weeks **hafnium sodium mandelate**		Oral: no lesions attributable to hafnium s.c. : failed to gain weight, abscesses at injection site bearing insoluble hafnium precipitates
BIBRA toxicity profile, 1994	Guinea pigs	Oral/Hafnium dioxide, up to 2000 mg/kg daily for 1 month	NO**A**EL: N.D. up to 2000 mg/kg	Increased liver weights, reduced kidney and spleen

Interspecies comparison

Table 8: Relevant safety factors based on literature NOAEL data and body surface area

Compound **Species**	**NOAEL dose,** **route of administration**	**Corresponding total dose in mg/kg**	**Human estimated dose[1]**	**Resulting safety factor per treatment[2]**
Lutetium				
Rat	1% of daily diet, oral	800	129 mg/kg	Over 690,000
Cat[3] (CVS)	10 mg/kg, IV	10	3.2 mg/kg	Over 17,000
Cat[3] (CNS)	40 mg/kg, IV	40	12.9 mg/kg	Over 69,000
Hafnium				
Rat	1% of daily diet, oral	800	129 mg/kg	Over 690,000
Ytterbium				
Rat[4]	1% of daily diet, oral	800	129 mg/kg	Over 340,000
Cat[4] (CVS)	10 mg/kg, IV	10	3.2 mg/kg	Over 8,000
Cat[4] (CNS)	40 mg/kg, IV	40	12.9 mg/kg	Over 30,000

[1] Based on FDA Guidance "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (assumes 60 kg human weight).

[2] Based on the entire maximum treatment dose of ^{177}Lu-PSMA-617 of 44.4 GBq for 6 cycles of therapy in total. Corresponds to 0.185 µg/kg metallic lutetium and hafnium and to 0.37 µg/kg metallic ytterbium. For all calculations human weight of 60 kg is assumed.

[3] Rabbit conversion factor used for human estimated dose calculations as closest possible approximation.

[4] Same NOEL values as for lutetium are assumed.

NOAEL is assumed to be equal to NOEL doses when only NOEL reported in literature.

CNS = central nervous system; CVS = cardiovascular system.

One study not discussed by the applicant in the repeated dose toxicity section but in the carcinogenicity section investigated the effects of long-term skeletal uptake of ^{177}Lu in mice (Müller et al, 1978). This study was performed to examine the incidence of osteosarcomas thought to be related to extended accumulation of lutetium in the bone tissue. The level of skeletal uptake increased with increasing dose of ^{177}Lu, along with increasing percentage of animals with osteosarcomas (ranging from 13% of animals administered 185 MBq/kg to 38% of animals administered 740 MBq/kg). Animals were given increasing doses of ^{177}Lu (185 – 740 MBq/kg), and development of osteosarcomas was examined, including mean latency period and extent of survival. Latency period also seemed to decrease with increasing dose (from 645 days at 185 MBq/kg to 534 days at 740 MBq/kg).

2.5.4.3. Genotoxicity

No studies to evaluate the genotoxic potential of Theralugand have been submitted.

2.5.4.4. Carcinogenicity

No carcinogenicity studies have been conducted.

2.5.4.5. Reproductive and developmental toxicity

No studies on reproductive and developmental toxicity have been performed with Theralugand/ $^{177}LuCl_3$, lutetium or hafnium and no data on reproductive and developmental toxicity are available in the literature.

No toxic effects on reproductive organs were observed in repeat dose toxicity studies after oral administration of lutetium chloride or hafnium chloride as a food admix for 90 days. Dosimetry data as calculated from organ distribution data indicate that lutetium does not accumulate in reproductive organs.

No studies in which the offspring (juvenile animals) are dosed and / or further evaluated have been conducted.

2.5.4.6. Local tolerance

As Theralugand is not intended for direct administration to humans, data on local tolerance have a limited significance for this application. No local effects (intravenous or other route) are to be expected from the ^{177}Lu component of the final radiolabelled product, and the local tolerance of the final product will be tested with the final product only.

Nevertheless literature from studies on local tolerance with lutetium in animals have been submitted by the applicant and are summarised below.

Table 9: Summary of local tolerance studies with lutetium

Source	Species/ Sex/Number	Dose/Route/$LuCl_3$	Major findings
Haley et al, 1964	3 guinea pigs	Intradermal, dilution up to 1:1000 Dilution $1:10^6$	Necrosis, not complete reversed within 5 weeks Irritation index 2, healing accompanied by nodule formation
	2 rabbits	Eyes, 1:1 solution	Local irritation and delayed ulceration of the cornea, complete healing after 2 weeks
	rabbits	Skin tolerance test by rubbing 0.5 g crystalline LuCl3 into abraded skin	Severe reaction, strong irritation peak after 24 h, healing with formation of scar tissue after 35 days
Garrett et al, 1981	mice	SC, 500 to 10000 µg/0.2 ml	Local calcifications

Table 10: Summary of local tolerance studies with hafnium

Source	Species/ Sex/Number	Dose/Route/	Major findings
Haley et al, 1962	rabbits	Eyes, 1 mg hafnium chloride	Increase in blinking rate and redness of the conjunctiva which was reversible after 24 h
	rabbits	Skin tolerance test by rubbing hafnium chloride crystals onto abraded skin	Strong local irritation with no healing within 14 days
Haley et al, 1964	Guinea pigs	Intradermal injection (diluted solution 1:104 and 1:108)	Transient local irritation, complete remission within 7 days

2.5.4.7. Other toxicity studies

Table 11: Ex vivo studies with lutetium

Source	**Species/ Sex/Number**	**Dose/Route/$LuCl_3$**	**Major findings**
Haley et al, 1964	Isolated rabbit ileum	10 – 40 mg $LuCl_3$ + acetylcholine (2.5 µg) 10-40 mg $LuCl_3$ + nicotine (0.5 µg)	$LuCl_3$ induced an increasing depression of intestinal tonus and contractility of the ileum resulting in a non-reversible paralysis. This effect counteracted the spasmogenic effect of acetylcholine and nicotine

Table 12: Studies evaluating hepatotoxicity of REEs

Source	**Species/ Sex/Number**	**Dose/Route/non-radioactive Lu and other REEs**	**Major findings**
Nakamura et al, 1997	Male Wistar KY rats (3-5 animals)	i.v., 10 mg/kg $LuCl_3$ cerium, praseodymium	$LuCl_3$: no significant changes in hepatic lipids, GOT, GPT, serum bilirubin, total bile acids concentrations whereas cerium and praseodymium resulted in changes due to their accumulation in the liver

Table 13: Studies evaluating nephrotoxicity of 177Lu-DOTATATE

Source	**Species/ Sex/Number**	**Dose/Route/**	**Major findings**
Rolleman et al, 2007	Tumour-bearing rats	278 + 555 MBq ^{177}Lu-DOTATATE	Renal damage
Schuler et al, 2014	Nude BALB/c mice	0.26, 2.4, 8.2 MBq ^{177}Lu-DOTATATE 90, 120, 150 MBq ^{177}Lu-DOTATATE	Minor morphological changes in kidney cortex Long-term renal toxicity

Forrer et al, 2007	Male Lewis rats	278 + 555 MBq ^{177}Lu-DOTATATE	555 MBq: severe damage of tubular function 278 MBq: histological findings comparable to the higher dose

Studies on impurities

Theralugand is a sterile solution with 40 GBq/ml of ^{177}Lu in 0.04 mol/l hydrochloric acid. This solution is produced and released by Eckert & Ziegler Radiopharma GmbH in full compliance with the GMP & quality standards defined by the Ph. Eur. monograph 2798 Lutetium (^{177}Lu) Solution for Radiolabelling.

Theralugand is produced via an indirect route, i.e., the isotope ytterbium (^{176}Yb) is irradiated with neutrons to generate ^{177}Yb, which decays with a half-life of 1.9 h to the intended ^{177}Lu. ^{177}Lu is then isolated from the irradiated target material by preparative chromatography.

2.5.5. Ecotoxicity/environmental risk assessment

The applicant applied for a waiver with regards to the ERA. The submitted justification was that 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. […] Any unused medicinal product or waste material must be disposed in accordance with local requirements. Finally, Product Information contains adequate warnings and precautions regarding handling and disposal.

Additionally, ^{177}Lutetium chloride is an inorganic salt for which an ERA was considered not required according to the Guideline on the Environmental risk assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/4447/00_corr2).

2.5.6. Discussion on non-clinical aspects

$^{177}LuCl_3$ is intended as a precursor for radiolabelling of carrier molecules specifically designed for this purpose and further use of the resulting conjugate in the clinic. The primary pharmacodynamic effect is thus a stable and efficient labelling.

At present, two ^{177}Lu-containing radiotherapeutics, Lutathera (^{177}Lu oxodotretotide or ^{177}Lu-DOTATATE) and Pluvicto (^{177}Lu vipivotide tetraxetan or ^{177}Lu-PSMA-617), are approved in the EU. Both of them have demonstrated highly efficient labelling of ^{177}Lu (more than 99%) and proved to be stable with minimal metal release.

Non-radioactive lutetium was reported to reversibly potentiate GABA response and to increase tissue accumulation of Ca^{2+} in rats.

No safety pharmacology testing was carried out by the applicant which is considered acceptable as $^{177}LuCl^3$ is not intended for direct use in patients. No pharmacodynamic drug interaction studies have been conducted for the same reason, which is also considered acceptable based on the same rationale.

Following IV administration to rats, $^{177}LuCl^3$ was rapidly absorbed from plasma and distributed to the organs (see 2.5.3. Distribution). The methods of analysis in the so-called dosimetry study EZ-Lu177 have been considered suitable for their purpose and acceptable.

Rapid absorption was observed upon intravenous administration of 30 MBq lutetium (^{177}Lu) chloride to rats, with the peak of lutetium (^{177}Lu) concentration in blood plasma reached within 12 min post-injection. Overall, the highest lutetium (^{177}Lu) uptake was detected in spleen, liver, and bone. In particular, at 1-hour post-injection, lutetium (^{177}Lu) predominantly accumulated in spleen and liver, reaching the highest values in these organs at day 2 in male and day 7 in female rats. Prominent accumulation in bone occurred at 12-hours post-injection and further increased unsteadily up to day 35, obviously partly counteracted by the radioactive decay. Distribution of lutetium (^{177}Lu) to reproductive organs was rather low at all analysed post-injection time points.

Based on the results of the distribution study in the rat, the applicant estimated human absorbed doses of ^{177}Lu after accidental IV injection of $^{177}LuCl_3$ to patients. The doses reached in this case in the liver, spleen, endosteum and kidneys are below critical doses usually assumed for these organs. However, for red bone marrow established limits would be exceeded making it a critical organ-at-risk. This would require clinical monitoring and support. Nominal differences between EndolucinBeta and Theralugand observed in liver and spleen, i.e. organs with a high blood reservoir, may be attributed in part to differences in the handling of organs and blood and the respective losses during the autopsy procedure, but also are likely due to the small number of animals examined per time point. Nevertheless, both the organ doses and the effective doses are in a comparable order of magnitude for both ^{177}Lu chloride preparations.

Lutetium (^{177}Lu) excretion occurred mainly via urine, with some faecal excretion observed.

It should be noted, however, that the PK of a ^{177}Lu-radiolabelled molecule will also depend on the biological and chemical properties of the molecule to be radiolabelled and its mechanism of action in the human body.

No pharmacokinetic drug interaction studies relevant to the use of ^{177}Lu as a radiopharmaceutical precursor have been provided as none was published, it was considered acceptable.

The toxicity of non-radioactive lutetium chloride has been studied in different mammalian species and using different administration routes. The intraperitoneal LD50 in mice was found to be approximately 315 mg/kg. In cats, no pharmacological effects on respiration and cardiovascular function were observed up to a cumulative intravenous dose of 10 mg/kg. 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 Theralugand-labelled medicinal products can be excluded. Toxicology is described by literature in accordance with Annex I Part III of Dir 2001/83/EC, as amended. In the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes, the primary objective shall be to present information which would address the possible consequences of poor radio-labelling efficiency or *in vivo* dissociation of the radio-labelled conjugate, i.e. questions related to the effects produced in the patient by free radionuclide. Thus, a summary of literature reviews laying the focus 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 was included in the original dossier. The main toxicological feature of radioactive lutetium chloride, concerns its uptake in bone and subsequent the development of osteosarcoma and its latency observed in rats and mice studies after long-term exposure, although Lutetium-177 is intended for short-term use. 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, toxicity findings are considered of limited human relevance given the doses at which they occurred.

Studies to evaluate the genotoxic potential or the carcinogenic potential of Theralugand have not been submitted as according to Annex 1 Part III of Dir 2001/83/EC, amended, studies to evaluate the genetic toxicity of the radionuclide of a radiopharmaceutical precursor intended solely for radiolabelling purposes are not considered necessary.

Based on the low exposure and the lack of accumulation in reproductive organs, no reproductive or developmental metal-based toxicity related to ^{177}Lu or ^{177}Hf is to be expected with Theralugand use, but the potential toxicity and distribution of the carrier molecule should be considered. Furthermore, radiation is a known mutagen and carcinogen, hence general radiation considerations apply. The lack of reproduction and developmental toxicity studies for Theralugand is acceptable for the same reason. Effects of lutetium (177Lu) 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 (177Lu)-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 childbearing potential, during pregnancy and breast-feeding will be specified in the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.

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. ^{177}Lutetium-labelled medicinal products are contraindicated in established or suspected pregnancy or when pregnancy has not been excluded. This is adequately reflected in the SmPC in 4.3 (Established or suspected pregnancy or when pregnancy has not been excluded (see section 4.6).) and 4.6 (The use of lutetium (^{177}Lu)-labelled medicinal products is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded due to the risk of ionising radiation to the foetus (see section 4.3)).

No data has been presented for the use of $^{177}LuCl_3$ in juvenile animals. Due to the intended use of Theralugand for in vitro radiolabelling such studies are not considered necessary.

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 only was with $LuCl_3$. Similar effects were observed with hafnyl chloride. The later irritation was considered related to the acidic nature of the compound. Most of the local toxicities were reversible.

Application of $LuCl_3$ on isolated rabbit ileum induced an increasing depression of intestinal tonus and contractability of the ileum resulting in a non-reversible paralysis counteracting the spasmogenic effect of acetylcholine and nicotine. As seen in the distribution study, an increased uptake of ^{177}Lu in liver and spleen was detected. However, evaluation of the non-radioactive $LuCl_3$ up to the dose of 10 mg/kg in rats demonstrated no adverse effects on liver and hepatic enzymes. Nephrotoxicity is a known effect of ^{177}Lu-labelled radiopharmaceuticals (^{177}Lu-DOTATATE and ^{177}Lu-PSMA). However, the effects on kidney damage could be counteracted by the addition of lysine.

The toxicological properties of lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with Theralugand prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled.

Of note, the drug product is a sterile 0.04 M HCl solution with controlled level of bacterial endotoxins and has a very low content of metal impurities (see also 2.4.).

The applicant's waiver application with regards to the ERA 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_corr2). 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.

2.5.7. Conclusion on the non-clinical aspects

There are no objections against the approval of Theralugand from a non-clinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

This is an application submitted under the legal basis of Article 8.3 of Directive 2001/83/EC, as amended with a full but mixed application (nonclinical dosimetry study and supportive scientific literature). The clinical aspects are therefore relying on a review of literature.

In line with the provisions of the Commission Directive 2001/83/EC on radiopharmaceutical precursors for radiolabelling, the main purpose of this clinical overview is to demonstrate the clinical utility of ^{177}Lu attached to relevant carrier molecules. While numerous carrier molecules to be radiolabelled with ^{177}Lu are currently in their preclinical and clinical development, in total only 2 molecules, ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617, are approved for marketing. Therefore, the selection of literature was limited to the currently established for routine clinical use ^{177}Lu-based applications, i.e., radioligand therapies with ^{177}Lu-DOTATATE and ^{177}Lu-PSMA (incl. PSMA-617 and PSMA-I&T). The literature searches were carried out in PubMed and include literature up to March 27th, 2023. Search terms used were ("Lu-177") OR ("177Lu") OR ("(177)Lu") OR ("Lu 177") OR ("177 Lu") OR ("LuCl3") OR ("Lutetium" AND ("177" OR "PSMA")) OR ("LuPSMA") OR ("Lu-PSMA") OR ("LuDOTA") OR ("Lu-DOTA"). This search resulted in over 3,000 hits including articles containing nonclinical data (see 2.5. Non-clinical aspects).

Clinical articles have been then individually selected based on the following criteria for further review and discussion:

• completed clinical studies with 177Lu-DOTATATE, 177Lu-PSMA-617 or 177Lu-PSMA I&T with main focus on efficacy and safety of the three radiolabelled compounds (as such, pure PK/dosimetry/computer modelling studies were excluded); for exclusively efficacy-focused studies, only most conclusive studies with ≥100 patients were included.

• clinical papers other than primary clinical studies reports, e.g., reviews and meta-analyses, that describe safety aspects specific to 177Lu-DOTATATE, 177Lu-PSMA-617 or 177Lu-PSMA I&T.

• relevant clinical guidelines and treatment recommendations.

Reference lists of the originally extracted articles were examined for further relevant publications and the latter ones were similarly reviewed. In total, 99 publications have been identified as relevant based on the applied criteria and included in the application.

GCP aspects

No clinical studies were performed and required for this type of RLT precursor. Therefore no GCP statement was provided.

2.6.2. Clinical pharmacology

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.

No clinical studies referring to clinical pharmacology for Lutetium (^{177}Lu) chloride n.c.a were provided in the application (see 2.6.3. Discussion on clinical pharmacology).

2.6.2.1. Pharmacokinetics

No clinical pharmacology studies were submitted with this application (see 2.6.3. Discussion on clinical pharmacology).

2.6.2.2. Dosimetry

The radiation dose received by various organs following intravenous administration of a lutetium (^{177}Lu)-labelled radiopharmaceutical is dependent on the specific molecule being radiolabelled.

Information on radiation dosimetry of each different medicinal product following administration of the radiolabelled preparation is available in the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

The dosimetry tables below are presented in order to evaluate the contribution of non-conjugated lutetium (^{177}Lu) to the radiation dose following the administration of a lutetium (^{177}Lu)-labelled medicinal product or resulting from an accidental intravenous injection of Theralugand.

The dosimetry estimates are extrapolated from a rat distribution study. Single dose of 30 MBq Theralugand was used in the study. Post-injection time points for measurements were 5 min, 1 h, 12 h, 2 days, 7 days, and 35 days. Organ absorbed radiation doses (mGy/MBq) listed below for adult, 15-year, 10-year, 5-year, 1-year and newborn male and female human models are derived from the distribution data in rats using IDAC-Dose 2.1 v1.01 (for adults) and OLINDA/EXM v1.0 (for children and adolescents) software. Sex-specific effective dose coefficients (mSv/MBq) were calculated according to ICRP 60 (International Commission on Radiological Protection) provisions. The adult sex-averaged effective dose coefficient for accidentally injected lutetium (^{177}Lu) chloride, calculated according to ICRP 103 provisions, lays at 0.19 mSv/MBq.

In case of an accidental direct injection of lutetium (^{177}Lu) chloride, the organs with the highest absorbed doses based on rat data would be liver, spleen, bone, and kidneys.

Table 14: Estimated organ absorbed radiation doses and effective doses after inadvertent intravenous administration of 177LuCl3 in women, based on data collected in rats (n=18)

Absorbed dose per administered unit of activity (mGy/MBq)						
Organ	**Adult[1] (60 kg)**	**15 years[2] (50 kg)**	**10 years[2] (30 kg)**	**5 years[2] (17 kg)**	**1 year[2] (10 kg)**	**Newborn[2] (5 kg)**
Adipose/residual tissue	0.029	0.274	0.464	0.771	1.55	4.14

Adrenals	0.199	0.184	0.266	0.365	0.565	0.549
Bone marrow (red)	0.479	0.229	0.394	0.799	1.97	6.73
Bone surface (endosteum)	0.264	ND	ND	ND	ND	ND
Brain	0.034	0.020	0.024	0.034	0.045	0.098
Colon wall	0.043	0.062	0.110	0.185	0.359	0.865
Heart wall	0.064	0.043	0.066	0.102	0.187	0.408
Kidneys	0.276	0.356	0.511	0.76	1.39	3.72
Liver	2.28	2.93	4.6	6.95	13.8	33.2
Lungs	0.112	0.177	0.253	0.392	0.782	2.14
Muscle	0.036	0.029	0.051	0.131	0.255	0.386
Osteogenic cells	6.66[2]	6.53	10.7	18.1	43.6	142.0
Ovaries	0.094	0.102	0.316	0.566	1.35	2.94
Pancreas	0.071	0.076	0.136	0.189	0.372	1.08
Salivary glands	0.068	ND	ND	ND	ND	ND
Skin	0.032	0.018	0.028	0.045	0.089	0.214
Small intestine wall	0.064	0.075	0.132	0.220	0.43	1.08
Spleen	2.61	3.98	6.31	10.1	19.1	53.2
Stomach wall	0.115	0.058	0.091	0.152	0.3	0.851
Thymus	0.048	0.026	0.03	0.039	0.061	0.132
Thyroid	0.118	0.166	0.257	0.579	1.110	1.560
Urinary bladder wall	0.047	0.02	0.034	0.055	0.109	0.256
Uterus/cervix	0.048	0.046	0.668	1.03	1.920	0.822
Effective dose ICRP 60[3] (mSv/MBq)	0.304	0.325	0.55	0.91	1.97	5.27
Effective dose ICRP 103[4] (mSv/MBq)	0.19	ND	ND	ND	ND	ND

ND = not determined as organ/tissue/data not available in OLINDA/EXM v1.0.

[1] calculations made in IDAC-Dose 2.1 v1.01 software.

[2] calculations made in OLINDA/EXM v1.0 software.

[3] sex-specific doses derived according to ICRP Publication 60.

[4] sex-averaged dose derived according to ICRP Publication 103.

Table 15: Estimated organ absorbed radiation doses and effective doses after inadvertent intravenous administration of $^{177}LuCl_3$ in men, based on data collected in rats (n=18)

Absorbed dose per administered unit of activity (mGy/MBq)						
Organ	**Adult[1] (73 kg)**	**15 years[2] (50 kg)**	**10 years[2] (30 kg)**	**5 years[2] (17 kg)**	**1 year[2] (10 kg)**	**Newborn[2] (5 kg)**
Adipose/residual tissue	0.031	0.258	0.436	0.724	1.46	3.89
Adrenals	0.172	0.245	0.355	0.488	0.749	0.625
Bone marrow (red)	0.293	0.174	0.297	0.594	1.46	5.0
Bone surface (endosteum)	0.167	ND	ND	ND	ND	ND
Brain	0.032	0.024	0.029	0.04	0.053	0.115
Colon wall	0.053	0.08	0.14	0.234	0.462	1.15
Heart wall	0.056	0.068	0.105	0.166	0.301	0.605
Kidneys	0.289	0.465	0.668	0.994	1.82	4.94
Liver	1.06	1.77	2.77	4.19	8.33	20.0
Lungs	0.08	0.157	0.225	0.348	0.696	1.91
Muscle	0.034	0.045	0.087	0.26	0.515	0.725
Osteogenic cells	5.27[2]	6.89	11.3	19.1	45.9	149.0
Pancreas	0.061	0.088	0.171	0.228	0.483	1.58
Salivary glands	0.08	ND	ND	ND	ND	ND
Skin	0.103	0.022	0.036	0.059	0.116	0.288
Small intestine wall	0.068	0.105	0.184	0.307	0.607	1.56
Spleen	0.91	1.67	2.65	4.24	8.0	22.3
Stomach wall	0.113	0.081	0.124	0.212	0.427	1.3
Testes	0.035	0.077	0.579	0.675	0.919	1.35
Thymus	0.074	0.056	0.057	0.068	0.098	0.206
Thyroid	0.144	0.252	0.392	0.888	1.710	2.39
Urinary bladder wall	0.071	0.031	0.052	0.083	0.166	0.407
Effective dose ICRP 60[3] (mSv/MBq)	0.143	0.255	0.496	0.769	1.55	4.11

Absorbed dose per administered unit of activity (mGy/MBq)						
Organ	**Adult[1] (73 kg)**	**15 years[2] (50 kg)**	**10 years[2] (30 kg)**	**5 years[2] (17 kg)**	**1 year[2] (10 kg)**	**Newborn[2] (5 kg)**
Effective dose ICRP 103[4] (mSv/MBq)	0.19	ND	ND	ND	ND	ND

ND = not determined as organ/tissue not available in OLINDA/EXM v1.0.

[1] calculations made in IDAC-Dose 2.1 v1.01 software.

[2] calculations made in OLINDA/EXM v1.0 software.

[3] sex-specific doses derived according to ICRP Publication 60.

[4] sex-averaged dose derived according to ICRP Publication 103.

2.6.2.3. Pharmacodynamics

No clinical pharmacology studies were submitted with this application (see 2.6.3. Discussion on clinical pharmacology).

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.

2.6.3. Discussion on clinical pharmacology

The lack of biopharmaceutical studies and clinical pharmacology studies is considered acceptable. This approach is consistent with the one followed for the three other approved radiopharmaceutical products containing Lutetium (^{177}Lu) chloride as the precursor is not intended to be directly administered to the patient.

The clinical pharmacology of such radiopharmaceutical products dependent essentially on the carrier molecule labelled with Theralugand. Similarly, also the pharmacodynamics of a radiopharmaceutical precursor dependents on the carrier molecule and on the method of conjugation used to link it to the radioisotope.

In view of 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 stabilise lanthanides, including lutetium, in their 3+oxidation state for the *in vivo* use (Maecke, 2003) and have been accordingly used for the authorised in the EU/EEA ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617 preparations.

However, according to annex I, point 2.2 of Directive 2001/83/EC as amended in Directive 2003/63/EC, for radionuclide precursors, "the primary objective shall be to present information which would address the possible consequences of poor radio-labelling efficiency or *in vivo* dissociation of the radio-labelled conjugate, i.e. questions related to the effects produced in the patient by free radionuclide. In addition, it is also necessary to present relevant information relating to occupational hazards, i.e. radiation exposure to hospital staff and to the environment."

In this regard, the provided clinical pharmacology discussion is considered acceptable, same than for the pharmacokinetics of free Lutetium (^{177}Lu) due to poor radio-labelling efficiency or *in vivo* dissociation of the radiolabelled conjugate with its consequences in patients.

Pharmacokinetics of free ^{177}Lu injected as 30 MBq of ^{177}LuCl3 solution was investigated in the dosimetry study (EZ-Lu^{177}) conducted in rats by the applicant. The main purpose of this study was to estimate human radiation dosimetry in case of the accidental injection of unbound ^{177}Lu. Therefore, dosimetry extrapolation from rats to humans is presented in the clinical safety section (see 2.6.8. Clinical safety).

$^{177}LuCl_3$ has no primary pharmacodynamic function and only very few data are available on the general pharmacodynamics of lutetium as a metal ion and $^{177}LuCl_3$, administered as a free soluble radioactive metal salt. Ionic lutetium in general appears to have no pharmacological function, but radioactive lutetium salts have been investigated for a few clinical applications.

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

The pharmacodynamic properties of Lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with Theralugand, prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled.

2.6.4. Conclusions on clinical pharmacology

Adequate information was provided about $^{177}Lu^{3+}$ biodistribution and dosimetry calculations, showing bone, liver, kidneys, red marrow and spleen as the main target organs.

It is accepted that the clinical pharmacology of Theralugand is dependent on the carrier molecule and therefore data specifically for Theralugand itself is not required. The relevant clinical pharmacology data with Theralugand will have to be submitted separately with the application for the different carrier molecules. Thus, the lack of studies in pharmacology for this application is acceptable. For the purpose of an application for a radiopharmaceutical for radiolabelling, the clinical pharmacology of Theralugand has been adequately addressed.

The same approach was in principle already agreed for the approval of other similar radiopharmaceutical products containing ^{177}Lutetium chloride in the identical indication during other centralised procedures (e.g. EMEA/H/C/003999 Endolucin Beta and EMEA/H/C/002749 Lumark) by CHMP.

2.6.5. Clinical efficacy

No original clinical efficacy studies were conducted by the applicant as information related to clinical efficacy obtained from the precursor alone is not considered relevant in the present case. Information on the clinical utility of the radiopharmaceutical precursor (^{177}Lu) when attached to appropriate carrier molecules has been provided. (See 2.6.1. Introduction).

Instead, as required for radiopharmaceutical precursors for radiolabelling purposes in the EU (Directive 2001/83/EC, Annex I, Part III section 2.2), information on the most important therapeutic applications has been provided, to demonstrate the clinical utility of ^{177}Lu when attached to relevant carrier molecules:

- ^{177}Lu-DOTATATE for treatment of SSTR positive Neuroendocrine tumours (NETs)
- ^{177}Lu-PSMA-617 for treatment of mCRPC.

2.6.5.1. Dose response study(ies)

The applicant did not submit studies on dose response (see clinical efficacy discussion).

2.6.5.2. Clinical utility

2.6.5.2.1. ^{177}Lu-DOTATATE for treatment of SSTR positive Neuroendocrine tumours (NETs)

NETs can occur at any age, with the median age at diagnosis in the late fifth decade and an age-related incidence increase. The overall incidence of NETs was approximately 2.5 per 100,000 per year for the white population and approximately 4 per 100,000 per year for the black population in the US from 1992-1999, according to an analysis of the Surveillance, Epidemiology and End Results Registries of the National Cancer Institute (Modin et al., 2003).

In that same period, the overall 5-year survival rate was 67.2%, but was much better for localised (78.2%) or regional (71.7%) disease than for distant (38.5%) disease. Additionally, the survival rate for patients with unstaged disease was only 48.3%. Thus, early detection and staging to allow appropriate treatment to reduce or prevent progression is highly desirable.

About two-thirds of NETs involve the GEP tract. The incidence of GEP-NETs increased in the last decades from 1.0 to 5.25/100,000 per year, with an estimated prevalence of 35/100,000 reported in 2014 (Grimaldi et al., 2014). Physicians' awareness, endoscopic screening and increased sensitivity of diagnostic tools may at least in part explain this growing trend.

Radiolabelled SST analogue therapy for the treatment of advanced, well-differentiated NETs was first described approximately 30 years ago (Horsch et al., 2016; Krenning et al., 1994; Krenning et al., 1993; Kwekkeboom et al., 2008). Initial efficacy results were based on very high doses of ^{111}In-DTPA0-octreotide, but more promising results were subsequently found with 90Y-DOTA0-Tyr3-octreotide (^{90}Y-DOTATOC) (Valkema et al., 2006) and with ^{177}Lu-DOTA0-Tyr3-octreotate (^{177}Lu-DOTATATE) (Kwekkeboom et al., 2008).

^{177}Lu-DOTA-conjugated somatostatin analogues have become an established procedure for the treatment of patients suffering from inoperable NETs overexpressing somatostatin receptors. The radiolabelled peptides ^{177}Lu-DOTATATE, ^{177}Lu-DOTATOC and ^{177}Lu-DOTANOC have the highest affinity to the subtype 2 of the somatostatin receptor family, which is also most commonly expressed by most NET (Breeman et al., 2016).

Additionally, the results of numerous uncontrolled prospective and retrospective studies involving NETs of different origin are summarised in the clinical AR in order to complete the available knowledge as documented in literature regarding the efficacy profile of ^{177}Lu-DOTATATE.

The standard protocol for ^{177}Lu-DOTATATE for treatment of SSTR-positive NETs comprised four cycles of treatment with an activity of 7.4 GBq per cycle (Kwekkeboom et al., 2008; Strosberg et al., 2017; Brabander et al., 2017). The cycles were repeated every 8 to 12 weeks. As the major organs at risk for unintended adverse effects are the kidneys and bone marrow, individualised protocols were developed which allow a cumulative absorbed dose of 23 Gy to the kidneys and of 2 Gy to bone marrow (Sandstrom et al., 2013).

This adaption allows for additional treatment cycles in selected patients and is essential to optimise therapy. Furthermore, therapy with ^{177}Lu-DOTATATE is generally combined with antiemetics and nephroprotective treatment.

Comparative Clinical Trials with ^{177}Lu-DOTATATE

NETTER-1

This was a large, representative open-label, randomised, comparator-controlled Phase 3 trial (NETTER-1) which investigated efficacy and safety of 4 cycles ^{177}Lu-DOTATATE in 231 patients with advanced,

inoperable, well-differentiated SSTR-positive midgut NETs compared with long-acting octreotide administered intramuscularly.

A total of 231 patients (114 female, 117 male) were randomly assigned to receive either four cycles of ^{177}Lu-DOTATATE with an activity of 7.4 GBq (200 mCi) plus concomitant 30 mg octreotide (every 8 weeks combined, after last ^{177}Lu-DOTATATE cycle only octreotide administered every 4 weeks), or high-dose octreotide (60 mg) administered as a single treatment every 4 weeks. ^{177}Lu-DOTATATE was administered per intravenous infusion. Two out of 231 patients were randomly assigned after the primary PFS analysis data cutoff. Demographic and baseline disease characteristics were generally well balanced between the study groups.

In total, 200 (87%) of 231 patients entered long-term follow-up, including 101 (86%) of 117 patients in the ^{177}Lu-DOTATATE group and 99 (87%) of 114 patients in the control group.

The primary endpoint was PFS at the data-cutoff date; secondary endpoints included safety, OS and ORR.

Progression-Free Survival

At the time of the data cutoff for the primary analysis (July 24, 2015; almost 3 years after study start), 23 events of disease progression or death had occurred in the ^{177}Lu-DOTATATE group vs. 68 such events had occurred in the control group (Strosberg et al., 2017).

At the data-cutoff for the primary analysis, the median PFS had not yet been reached in the ^{177}Lu-DOTATATE group and was 8.4 months (95% CI, 5.8 to 9.1) in the control group (hazard ratio for disease progression or death with ^{177}Lu-DOTATATE vs. control, 0.21; 95% CI, 0.13 to 0.33; p<0.001), which represented a 79% lower risk of disease progression or death in the ^{177}Lu-DOTATATE group than in the control group. The estimated rate of PFS at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the ^{177}Lu-DOTATATE group and only 10.8% (95% CI, 3.5 to 23.0) in the control group.

Objective Response Rate

The ORR was defined as the percentage of patients who had a response according to RECIST (sum of partial responses and complete responses). Within the population of patients who could be evaluated for objective tumour response (n=201), the response rate was 18% in the ^{177}Lu-DOTATATE group vs. 3% in the control group (p<0.001) (Strosberg et al., 2017).

Overall Survival

The prespecified final OS analysis was conducted 5 years after the last patient was randomly assigned, when 142 deaths had occurred [16]. Median follow-up was 76.3 months (range 0.4- 95.0) in the ^{177}Lu-DOTATATE group and 76.5 months (0.1-92.3) in the control group. Out of 142 patients who died there were 73/117 (62%) in the ^{177}Lu-DOTATATE group and 69/114 (61%) patients in the control group. Death due to disease progression was the leading cause of death in both groups.

Median OS was 48.0 months (95% CI 37.4-55.2) in the ^{177}Lu-DOTATATE group and 36.3 months (25.9-51.7) in the control group. This longer median OS in the ^{177}Lu-DOTATATE group compared with the control group was clinically relevant, but not statistically significant (HR 0.84 [95% CI 0.60-1.17]; two-sided p=0.30).

ILUMINET

These beneficial results of treatment with ^{177}Lu-DOTATATE were confirmed in a single-arm Phase 2 trial (ILUMINET) investigating personalised ^{177}Lu-DOTATATE therapy (Sundlov et al., 2022). Safety and efficacy

of individualised, dosimetry-based ^{177}Lu-DOTATATE treatment in 96 patients (42 female, 54 male) with NETs irrespective of origin was evaluated based on the hypothesis that treatment may be optimised by adjusting the number of cycles to the individually estimated renal BED.

The patients received cycles of 7.4 GBq of ^{177}Lu-DOTATATE preceded by antiemetics and co-administered with a kidney-protective amino acid infusion at 10±2-week intervals until a predefined radiation dose to the kidneys was reached. All patients were planned for treatment up to a cumulative renal BED of 27±2 Gy (step 1). Thereafter, patients with partial response or stable disease were offered further treatment up to a renal BED of 40±2 Gy (step 2). The median number of treatment cycles for all patients was 5 (range 1 to 9), with 51 patients (53%) receiving more than 4 cycles, and the median follow-up at the time of analysis was 42 months.

In patients with NETs of different origin, the objective tumour response 3 months after step 1 was 16% partial response (95% CI, 8.1 to 23%), 66% stable disease (95% CI, 56 to 75%), and 19% progressive disease (95% CI, 11 to 27%).

The median PFS and OS were 29 months and 47 months, respectively, with a 5-year survival of 41% (95% CI, 31 to 54%). PFS and OS were significantly correlated with kidney dose, performance status, and Ki 67 levels but not with tumour origin.

Such, the median time to progression was 41 months (95% CI, 29 to 48 months) for all patients and 31 (95% CI, 22 to 46 months), 46 (95% CI, 26 months to not reached), and 48 months (95% CI, 36 months to not reached) for the renal BED groups <25 Gy, 25-29 Gy, and >29 Gy, respectively.

2.6.5.2.2. Metastatic Castration-Resistant Prostate Cancer

The current therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) includes several treatments to prolong OS, including docetaxel, androgen receptor-directed therapies such as abiraterone, and enzalutamide.

Among possible treatment options is the RLT, where a radionuclide is coupled to a ligand that specifically binds to the tumour cells. For treatment of mCRPC, the radionuclide ^{177}Lu is coupled to a PSMA analogue, e.g., PSMA-617 (see Pluvicto EPAR).

The knowledge about the efficacy of ^{177}Lu-PSMA for treatment of mCRPC is predominantly based on the comparative open-label Phase 3 trial VISION (Sartor et al., 2021) and the comparative Phase 2 trial TheraP (Hofman et al., 2021) (see below section relative to Comparative Clinical Trials with ^{177}Lu-PSMA). Additionally, the results of numerous prospective and retrospective studies summarised in 2.6.5.2.4. complete the efficacy profile (see Table 18).

The recommended RLT regimen for treatment of mCRPC consists of intravenous infusions of ^{177}Lu-PSMA for up to a total of 6 cycles unless there is disease progression or unacceptable toxicity (Pluvicto SmPC 2022).

Comparative Clinical Trials with ^{177}Lu-PSMA

VISION

In the VISION trial, the pivotal trial for MAA of Pluvicto, a total of 831 patients with mCRPC who were previously treated with at least one androgen-receptor-pathway inhibitor and one or two taxane regimens were randomised in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 (7.4 GBq every 6 weeks for 4-6 cycles) plus protocol-permitted standard care (n=551) or standard care alone (n=280) (Sartor et al., 2021). Standard-care therapies could not include cytotoxic chemotherapy, systemic radioisotopes (e.g., radium-223 [^{223}Ra]),

immunotherapy, or drugs that were investigational when the trial was designed (e.g., olaparib). These constraints were used because of a lack of safety data on combining the investigational drug with these agents. Permitted treatments included but were not restricted to the approved hormonal treatments (including abiraterone and enzalutamide), bisphosphonates, radiation therapy, denosumab, or glucocorticoid at any dose. The alternate primary end points were imaging-based PFS and OS. Key secondary end points were objective response, disease control, and time to symptomatic skeletal events. AEs during treatment were those occurring no more than 30 days after the last dose and before subsequent anticancer treatment.

The baseline characteristics of the patients were balanced between the groups. The median follow-up was 20.9 months. The analysis of OS included all the patients who had undergone randomisation (n=831), whereas imaging-based PFS and key secondary efficacy outcomes were analysed in a subgroup of these patients (n=581).

Results

Progression-Free Survival and Overall Survival

^{177}Lu-PSMA-617 plus standard care significantly prolonged, as compared with standard care, imaging-based PFS. Among the 581 patients in the analysis set, the median imaging-based PFS was 8.7 in the ^{177}Lu-PSMA-617 group and 3.4 months in the control group (hazard ratio for progression or death, 0.40; 99.2% CI, 0.29 to 0.57; p<0.001).

Among all 831 patients who underwent randomisation, median OS was 15.3 months in the ^{177}Lu-PSMA-617 group vs. 11.3 months in the control group (hazard ratio for death, 0.62; 95% CI, 0.52 to 0.74; p<0.001).

PSA Response

The proportions of patients with confirmed decreases in the PSA level of at least 50% from baseline were higher in the ^{177}Lu-PSMA-617 group (46.0%) than in the control group (7.1%). Similarly, the proportions of patients with confirmed decreases in the PSA level of at least 80% were 33.0% versus 2.0% in the ^{177}Lu-PSMA-617 group and the control group, respectively. All other key secondary end points significantly favoured ^{177}Lu-PSMA-617.

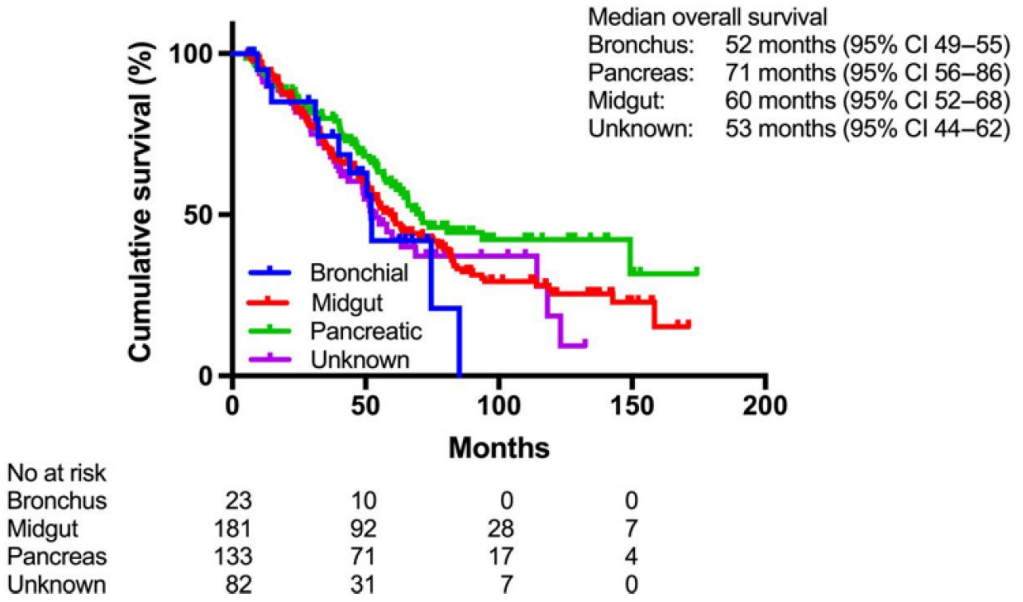
2.6.5.2.3. Supportive Studies and Analyses with ^{177}Lu-DOTATATE

Response to PRRT in NETs of Different Origin

Study by Brabander et al. (2017)

Brabander et al. (2017) retrospectively investigated the treatment effect of ^{177}Lu-DOTATATE in patients with NETs of different origin. A group of 443 Dutch patients who were treated with a cumulative dose of at least 600 mCi (22.2 GBq) ^{177}Lu-DOTATATE was analysed for efficacy and survival.

Best ORR in the entire patient group was 39% – defined as the proportion of patients achieving CR and PR at follow-up according to the RECIST 1.1 criteria. In patients with midgut NETs and pancreatic NETs with progressive disease at baseline, radiologic disease control was observed in 84% and 81%, respectively. Stable disease was reached in 43% of all NET patients, and progressive disease as treatment outcome was observed in 12% of patients and 5% of patients had non-evaluable treatment outcome. PFS and OS for all NET patients were 29 months [95% CI, 26-33 months] and 63 months (95% CI, 55-72 months), respectively. The median time to progression was 36 months (95% CI, 32-40 months). Patients with a primary NET in the pancreas had the longest OS (see Figure 3).



Source: Brabander et al. (2017) [19]

Note: Not shown are patients with primary tumour of the hindgut (n=12) and other foregut (n=12) due to the small number of patients. OS=overall survival

Figure 3: Median OS in 419 NET patients treated with ^{177}Lu-DOTATATE by location of primary tumour: Study by Brabander et al. (2017)

For comparison with the NETTER-1 study described, patients with NETs of the midgut and progressive disease at baseline that received a cumulative dose of >100 mCi (3.7 GBq) ^{177}Lu-DOTATATE were selected. The median PFS in this study was 24 months (95%CI, 18-30 months), whereas it had not been reached in the ^{177}Lu-DOTATATE group in the NETTER-1 trial at data cut-off point. OS was 46 months (95% CI, 32–60 months), which is comparable to the results of the NETTER-1 trial (OS: 48 months). The OS was significantly worse for patients with progressive disease at baseline (median 46 months) as compared with patients without progressive disease at baseline (median 82 months) (HR 0.49, 95% CI 0.31-0.71; p<0.01).

Tumour response also varied among NET types in the prospective observational study reported by Garske-Roman et al. (2018). Patients with small intestinal NETs showed a significantly lower ORR than patients with pancreatic and rectal NETs.

SEPTRALU registry study

The SEPTRALU registry study evaluated data of 522 patients with pancreatic (35%), midgut (28%), bronchopulmonary (11%), pheochromocytoma/paraganglioma (6%), other GEP (11%), and other non-GEP (9%) NENs (Mitjavila et al., 2023). The patients were treated with 4 cycles of ^{177}Lu-DOTATATE administered at an activity of 7.4 GBq/cycles every 8 weeks. The best RECIST 1.1 responses were complete response in 3 patients (0.7%), partial response in 147 patients (33.2%), stable disease in 231 patients (52.1%), and tumour progression in 62 patients (14%), with activity conditioned by the tumour subtype, but with benefit in all strata (see **Table 16**). The overall disease control rate (responses and stabilisations) was 86% (n=381). ORR and disease control rate broken down by tumour subtype was 42.4% and 84.8% in pancreatic NENs, 35.4% and 85.4% in other GEP-NENs, 31.5% and 78.9% in other non-GEP-NENs, 28.6% and 77.6% in bronchopulmonary NENs, 28.2% and 93.5% in midgut, and 19.2% and 84.6% in

pheochromocytoma/paraganglioma. Median PFS was 31.3 months (95% CI, 25.7 to 'not reached') in midgut, 30.6 months (14.4 to 'not reached') in pheochromocytoma/paraganglioma, 24.3 months (18.0 to 'not reached') in other GEP, 20.5 months (11.8 to 'not reached') in other non-GEP, 19.8 months (16.8 to 28.1) in pancreatic, and 17.6 months (14.4 to 33.1) in bronchopulmonary NENs. Median OS was 50.8 months (95% CI, 39.1 to 'not reached') in midgut NENs, 44.8 months (19.9 to 'not reached') in bronchopulmonary NENs, 34.2 months (30.4 to not reached') in pancreatic NENs, 33.6 months (21.0 to 'not reached') in other non-GEPs, and not-reached in other GEP-NENs and pheochromocytoma/paraganglioma (log-rank test, p=0.3).

Table 16: Response assessment according to tumour subtype: SEPTRALU registry study by Mitjavila et al. 2023

Tumour type	Progressive disease	Disease control	Stable disease	Partial response	Complete response	Total
N (%)						
pancreatic NENs	24 (15.2)	134 (84.8)	67 (42.4)	66 (41.8)	1 (0.6)	158 (100)
midgut NENs	8 (6.5)	116 (93.5)	81 (65.3)	34 (27.4)	1 (0.8)	124 (100)
bronchopulmonary NENs	11 (22.4)	38 (77.6)	24 (49.0)	14 (28.6)	0	49 (100)
pheochromocytomas/ paragangliomas	4 (15.4)	22 (84.6)	17 (65.4)	5 (19.2)	0	26 (100)
other GEP-NENs	7 (14.6)	41 (85.4)	24 (50.0)	17 (35.4)	0	48 (100)
other non-GEP-NENs	8 (21.1)	30 (78.9)	18 (47.4)	11 (28.9)	1 (2.6)	38 (100)
Total	62 (14.0)	381 (86.0)	231 (52.1)	147 (33.2)	3 (0.7)	443 (100)

Source: Mitjavila et al. (2023) NEN=neuroendocrine neoplasm

Study by Kwekkeboom et al. 2008

Of 310 GEP-NET patients evaluable for efficacy in a retrospective analysis, complete and partial tumour remissions occurred in 2% and 28%, respectively (see **Table 17**). Minor tumour response (decrease in size >25% and <50%) occurred in 16%. Median time to progression was 40 months. Median OS from start of treatment was 46 months, median OS from diagnosis was 128 months. Overall objective tumour response rate, comprising complete, partial, and minimal responses, was 46%.

Response rates in patients with gastrinomas, insulinomas, vasoactive intestinal peptide-secreting tumours and nonfunctioning pancreatic NETs were higher than in carcinoid tumour patients.

Table 17: Response assessment according to tumour subtype: Study by Kwekkeboom et al. 2008

Tumour subtype	Complete Response	Partial Response	Minimal Response	Stable disease	Progressive disease	Total
N (%)						
Carcinoid	1 (1)	41 (22)	31 (17)	78 (42)	37 (20)	188 (100)
Nonfunctional pancreatic	4 (6)	26 (36)	13 (18)	19 (26)	10 (14)	72 (100)
Unknown origin	-	10 (32)	3 (10)	7 (23)	11 (36)	31 (100)
Gastrinoma	-	5 (42)	4 (33)	2 (17)	1 (8)	12 (100)
Insulinoma	-	3 (60)	-	1 (20)	1 (20)	5 (100)
VIPoma	-	1 (50)	-	-	1 (50)	2 (100)
Total	5 (2)	86 (28)	51 (16)	107 (35)	61 (20)	310 (100)

Source: Kwekkeboom et al. (2008) VIPoma=vasoactive intestinal peptide-secreting tumour

Study by Demirci et al. 2018

In patients treated with at least 3 cycles of ^{177}Lu-DOTATATE, the estimated mean OS was longest in patients with a primary tumour originating from pancreas (57.4 months), followed by nonpancreatic GEP-NETs (57.3 months), pheochromocytoma and paraganglioma (51.8 months), unknown primary (48.3 months), lung (44.3 months) and other sites (25.4 months) (Demirci et al., 2018).

Study by Horsch et al. 2016

Patients with small NENs of small bowel had significantly increased survival (hazard ratio, 0.39; 95% CI, 0.18-0.87) compared to NENs of other locations as determined in a registry study with prospective follow-up (Horsch et al., 2016). Interestingly, PFS was not influenced by the location of the primary tumour in this study.

Study by Baum et al. 2018

Similarly to the study above, in a retrospective analysis of 1048 patients with NENs, best OS was observed in patients with NENs of small bowel (69 months), which was statistically significant followed by carcinoma of unknown primary, others, pancreas and lung (Baum et al., 2018). In contrast to the studies described in this section, no significant differences in median PFS or OS were identified according to tumour origin in the ILUMINET trial (Sundlov et al., 2022).

Treatment Response by Risk Factors, Progression-Free Survival and Overall Survival

As reported above, PFS as well as OS after treatment with ^{177}Lu-DOTATATE are dependent on the location of the primary tumour. However, several risk factors associated with shorter survival were identified in retrospective analyses.

The OS was significantly shorter in NEN patients with liver or bone metastases at baseline (Brabander et al., 2017). Also, patients with increased ALP levels (>120 IU/L) and patients with extensive disease as scored with the OctreoScan had a worse prognosis.

In studies evaluating personalised dose regimens, there were significant differences in OS and PFS according to renal BED, ECOG performance status and Ki 67 levels (Sundlov et al., 2022). The median time to maximum response was 18 months for all patients (95% CI, 16 to 22) and 13 (95% CI, 11 to 19 months), 23 (95% CI, 18 to 31 months), and 28 months (95% CI, 17 to 36 months) for the three renal BED groups <25 Gy, 25-29 Gy, and >29 Gy, respectively. The median time to progression was 41 months (95% CI, 29 to 48 months) for all patients and 31 (95% CI, 22 to 46 months), 46 (95% CI, 26 months to not reached), and 48 months (95% CI, 36 months to not reached) for the renal BED groups <25 Gy, 25-29 Gy, and >29 Gy, respectively.

Type of radionuclide, location of primary tumour and proliferation index were identified as risk factors of OS and PFS in a registry study with prospective follow-up (Horsch et al., 2016). A total of 450 patients with progressive low- or intermediate grade NENs were included and followed for a mean of 24.4 months. Primary NENs were mainly derived of pancreas (38%), small bowel (30%), unknown primary (19%) or bronchial system (4%). The somatostatin- analogues/chelators DOTATATE and DOTATOC were applied in most therapy cycles. ^{177}Lu was predominantly used as radionuclide, either alone (in 54% of patients) or in combination with ^{90}Y (in 29% of patients). ^{90}Y alone was used in 17% of patients. Median OS of all patients was 59 (95% CI ,49 to 68.9) months and PFS was 41 months. Both OS and PFS were significantly inferior in the patients treated with ^{90}Y solely compared to any PRRT with ^{177}Lu. Patients with small NENs of small bowel had significantly increased survival (hazard ratio, 0.39; 95% CI, 0.18e0.87) compared to NENs of other locations. Grade II (hazard ratio, 2.06; 95% CI, 0.79 to 5.32) and grade III (hazard ratio, 4.22; 95% CI, 1.41 to 12.06) NENs had significantly worse OS than grade I neuroendocrine neoplasms. In contrast, sex, age groups or number of previous therapies did not affect survival.

In a retrospective analysis of 1048 patients with NENs, best OS was achieved by a combination of ^{90}Y- and ^{177}Lu- for PRRT (Baum et al., 2018). Shortest survival was observed in patients treated exclusively with ^{90}Y, while treatment with solely ^{177}Lu resulted in an intermediate survival between the two extreme curves.

Extended liver metastases (liver tumour burden >50%), more than one line of chemotherapy, and elevated alkaline phosphatase >2x the upper normal limit were independent risk factors for both progression and death (Fross-Baron et al., 2021). Presence of bone metastases and elevated CgA levels were linked to shorter PFS. Surgery of the primary tumour and ECOG status 0 were independent positive prognostic factors for OS.

In addition, a significant predictor of poor PFS was a baseline platelet-lymphocyte ratio ≥173.1 in 42 NET patients (Satapathy et al., 2022). However, this association was not significant on multivariate analysis.

Long-term survival outcomes were evaluated in a retrospective review of 104 patients with advanced NETs treated on 4 Phase 2 clinical trials with ^{177}Lu-DOTATATE (Kennedy et al., 2022). Median follow-up was 68 months. Median PFS and OS were 37 months and 71 months, respectively. The site of the primary tumour correlated with survival, with median OS of 81 months for intestinal origin, 73 months for lung origin, 69 months for pancreatic origin, 50 months for gastric origin, and 47 months for unknown origin. Similarly, the median PFS was 43 months for patients with intestinal primary tumours, 40 months for gastric, 33 months for pancreatic, 27 months for unknown, and 11 months for lung primary tumours.

5- and 10- year OS were 62% and 29%, and 5- and 10- year PFS were 36% and 21%, respectively, demonstrating ^{177}Lu-DOTATATE can provide durable responses.

Objective Response Rate

ORR was affected by the NET type, the amount of radiation delivered to the kidneys, as well as the tumour proliferation rate (Garske-Roman et al., 2018). Of patients in whom the dose to the kidneys reached 23 Gy, 30.9% obtained an objective response (CR/PR) compared with 13% of patients in whom the dose to the kidneys did not reach 23 Gy for any reason ($p<0.0001$). The response rate of 10.6% in patients with tumours with a low proliferation rate (Ki-67 index ≤2%) was lower than in patients with higher proliferation rates (30.6% and 31.3% for Ki-67 index 3 to 20% and >20%, respectively). Furthermore, patients with small intestine NETs showed a significantly lower ORR than patients with pancreatic and rectal NETs.

Long-term response was evaluated in a retrospective analysis of 468 metastatic/advanced NET patients who underwent at least 2 cycles of ^{177}Lu-DOTATATE PRRT (Sitani et al., 2021). Median follow-up was 46 months, ranging from 4 to 97.6 months. Molecular imaging response (by PERCIST criteria) showed complete response in 29 patients (6%), partial response in 116 patients (25%), stable disease in 267 patients (57%) and progressive disease in 56 patients (12%). On RECIST 1.1 criteria, complete response was observed in 14 patients (3%), partial response in 126 patients (27%), stable disease in 282 patients (60%) and progressive disease in 46 patients (10%).

Quality of Life

QoL of patients is one of the most important aspects of any cancer therapy. In the Phase 3 NETTER-1 trial, QoL was evaluated according to the European Organization for Research and Treatment of Cancer QoL questionnaires EORTC QLQ-C30 and G.I.NET-21 (Strosberg et al., 2018). EORTC QLQ-C30 was developed to assess the QoL of cancer patients. Patients completed the questionnaire at baseline and every 12 weeks until tumour progression. QoL scores were converted to a 100-point scale according to European Organisation for Research and Treatment of Cancer instructions, and individual changes from baseline scores were assessed. Time to QoL deterioration was significantly longer in the ^{177}Lu-DOTATATE arm (n=117) versus the control arm (n=114) for the following domains: global health status (HR 0.406), physical functioning (HR 0.518), role functioning (HR 0.580), fatigue (HR 0.621), pain (HR 0.566), diarrhoea (HR 0.473), disease-related worries (HR 0.572), and body image (HR 0.425). Differences in median time to QoL deterioration were clinically significant in several domains: 28.8 months versus 6.1 months for global health status, and 25.2 months versus 11.5 months for physical functioning.

In a different study, EORTC QLQ-C30 questionnaires of a total of 265 patients were evaluated in a retrospective analysis. 241 of these patients completed the whole treatment and received 22.2 to 29.6 GBq of ^{177}Lu-DOTATATE. The baseline questionnaires were compared with questionnaires completed at the first visit after completion of therapy (Khan et al., 2011). Regardless of the treatment outcome, GHS/QoL, emotional and social functioning, insomnia, appetite loss, and diarrhoea improved significantly in the total group. These improvements were also seen in patients with bone metastases or a decrease of 50% or more in chromogranin A.

Improvement in the scores by at least 10 points was also analysed in a subgroup of patients with decreased GHS/QoL or symptoms at the start of therapy: in 36% of these patients, GHS/QoL improved after therapy; in 49%, fatigue; in 70%, nausea plus vomiting; in 53%, pain; in 44%, dyspnoea; in 59%, insomnia; in 63%, appetite loss; in 60%, constipation; and in 67%, diarrhoea.

Additionally, there was no statistically significant deterioration in patients who had GHS/QoL 100, KPS 100, or no symptoms at the start. In patients with initial stable disease or remission after treatment, GHS/QoL and KPS decreased significantly when regrowth of the tumours occurred.

QoL was evaluated in a study including 144 consecutive patients with histologically confirmed NETs using the European Organization for Research and Treatment of Cancer questionnaire (EORTC QLQ-C30) (Hamiditabar et al., 2017). Among them, 132 were deemed evaluable by having at least 1 cycle of treatment with ^{177}Lu-DOTATATE and a post-treatment MRI or CT scan for assessment based on modified RECIST. Both quantitative and qualitative assessments of changes in QoL following PRRT were assessed. Out of 97 evaluable EORTC-QLQs, 46 (47.4%) patients reported improvement, 47(48.4%) patients reported worsening, while 4 (4.1%) patients reported no change in their quality of life (p=0.59). Among patients who experienced improvement in their QoL, the average improvement from the baseline was 12% (range: 1 to 42) while patients who experienced worsening in QoL, the average of worsening from the baseline was 6.7% (range: -1 to -28).

2.6.5.2.4. Supportive Studies and Analyses with ^{177}Lu-PSMA

TheraP study

PSA response rate, defined as the proportion of participants with PSA reduction of 50% or more from baseline, was the primary endpoint in the TheraP trial (Hofman et al., 2021). In this randomised, unblinded Phase 2 trial, a total of 200 men were randomly assigned in a 1:1 ratio to ^{177}Lu-PSMA-617 (6.0-8.5 GBq intravenously every 6 weeks for up to six cycles) or cabazitaxel (20 mg/m² intravenously every 3 weeks for up to ten cycles). Study treatment was received by 98/99 (99%) men in the ^{177}Lu-PSMA-617 group and by 85/101 (84%) men in the cabazitaxel group.

PSA response

The characteristics of participants at baseline were similar in the two groups. PSA responses were more frequent among men in the ^{177}Lu-PSMA-617 group (65/99, 66%) than in the cabazitaxel group (37/101, 37%) in the intention to treat analysis set (difference 29%; 95% CI 16 to 42; p<0.0001). Using the "by treatment received" analysis set, 66% of patients in the ^{177}Lu-PSMA-617 group and 44% of patients in the control group had PSA responses (difference 23%; 9 to 37; p=0.0016).

Radiographic Response

Among the 248 patients who had measurable target lesions according to RECIST, version 1.1, on independent central review at baseline, a complete response was noted in 17 of 184 patients (9.2%) in the ^{177}Lu-PSMA-617 group and in none of the 64 patients in the control group. A partial response was noted in 77 patients (41.8%) in the ^{177}Lu-PSMA-617 group and in 2 (3%) in the control group.

Study by Garske-Roman, 2018

A prospective observational study also showed that OS was longer in patients who reached an absorbed dose to the kidneys of 23 Gy compared to those patients who did not reach this dose (Garske-Roman et al., 2018).

Of 200 consecutive patients with metastasised SSTR-positive progressing NETs, 123 patients (61.5%) reached an absorbed dose to the kidneys of 23 Gy with 3 to 9 cycles during first-line therapy. In no patient a dose to the bone marrow of 2 Gy was reached. The best responses (according to RECIST 1.1) were a CR in 1 patient (0.5%), a PR in 47 (23.5%), stable disease in 135 (67.5%) and progressive disease in 7 (3.5%). Of patients in whom the dose to the kidneys reached 23 Gy, 30.9% obtained an objective response (complete response and partial response) compared with 13% of patients in whom the dose to the kidneys did not reach 23 Gy for any reason (p<0.0001).

Median PFS was 27 months (95% CI 22 to 30 months) in all patients, 33 months in those in whom the absorbed dose to the kidneys reached 23 Gy vs. 15 months in those in whom it did not. Median OS was 43 months (95% CI 39 to 53 months) in all patients, 54 months in those in whom the absorbed dose to the

kidneys reached 23 Gy vs. 25 months in those in whom it did not. Median OS was 60 months in patients with a best response of partial response or complete response, 42 months in those with stable disease and 16 months in those with progressive disease.

Tabulated summary of efficacy results in published studies conducted with ^{177}Lu-PSMA

Overview of the efficacy results per study in a chronologic order up to January 27th, 2023 is included in Table below:

Table 18: Efficacy results of studies with ^{177}Lu-PSMA for the treatment of mCRPC

Study	Number of patients / Treatment	Efficacy Measures		Summary of results/Author's conclusions
		Median OS*	Median PFS/ PSA-PFS*	
Ahmadzadehfar et al. (2017)	100	60 wks (95% CI: 47.3–72.7)	-	Sixty-nine patients (69%) showed a PSA decline 2 months after the first cycle, 38 (38%) of which showed a PSA decline of ≥ 50%.
Rahbar et al. (2017)	145	-	-	The overall biochemical response rate was 45% after all therapy cycles, whereas 40% of patients already responded after a single cycle. Elevated ALP and the presence of visceral metastases were negative predictors and the total number of therapy cycles positive predictors of biochemical response.
Rahbar et al. (2018)	104	56.0 wks (95% CI: 50.5–61.5)	-	A total of 51 patients (49%) died during the observation period. Any PSA decline occurred in 70 (67%) and a PSA decline ≥50% in 34 (33%) of patients after the first cycle. Initial PSA decline ≥50%, initial Lactate dehydrogenase (LDH),

Study	Number of patients / Treatment	Efficacy Measures		Summary of results/Author's conclusions
		Median OS*	**Median PFS/ PSA-PFS***	
				visceral metastases, second line chemotherapy or prior radium-223 did not have an effect on survival, whereas any initial PSA decline, initial alkaline phosphatase <220 U/L and cumulative injected activity ≥18.8 GBq were associated with a longer survival. PSA decline ≥20.87% was the most noticeable cut-off prognosticating longer survival.
Barber et al. (2019)	167	10.7 months (95% CI: 7.9-13.5 months) for T-pre-treated patients and 27.1 months (95% CI: 18.4-35.8 months) for T-naive patients.	6.0 months (95% CI: 3.2-8.8 months) for Tpre-treated patients and 8.8 months (95% CI: 7.1-10.6 months) for T-naive patients.	PSA response assessment was evaluable in 132 patients and seen in 25 of 62 (40%) T-pre-treated patients and 40 of 70 (57%) T-naive patients.
Gafita et al. (2020)	Response (≥30% decline) in PSA at 6 wks.	16.7 month; (95% CI, 14.4–19.0)	7.1 month; (95% CI, 4.7–9.5)	A ≥30% decline in PSA at 6 wks. was associated with longer OS than stable PSA (P=0.007) or PSA progression (P<0.001). A ≥30% decline in PSA at 6 wks. was associated with longer imaging-
	Progression (≥25%	6.5 month; (95% CI, 5.2–7.8)	1.2 month; (95% CI, 1.1–1.3)	

Study	Number of patients / Treatment	Efficacy Measures		Summary of results/Author's conclusions
		Median OS*	**Median PFS/ PSA-PFS***	
	increase) PSA at 6 wks.			based PFS than stable PSA (P=0.01) or PSA progression (P<0.001). Patients with a ≥30% decline in PSA at 6 wks. also had a lower risk of imaging based progression than patients with stable PSA (hazard ratio [HR], 0.60; 95% CI, 0.38–0.94) (P=0.02), whereas patients with PSA progression had a higher risk of imaging based progression than patients with stable PSA (HR, 3.18; 95% CI, 1.95–5.21) (P<0.001).
	Stable (<30% decline and <25% increase) PSA at 6 wks.	11.8 month; (95% CI, 8.6–15)	2.0 month; (95% CI, 0.1–4.1)	
Yadav et al. (2020)	90	14 months	11.8 months	Followed up over a median duration of 28 months. At 2- to 3-month interval after the first therapy and the end of the assessment, greater than 50% decline in PSA was observed in 32.2% and 45.5%, respectively. Radiographic response by diagnostic CT revealed partial remission in 23% (16/69), stable disease in 54% (37/69), and progressive disease in 23% (16/69) of patients. Molecular tumour response by PET Response Criteria in Solid Tumour 1 criteria revealed 19 (27.5%) of 69 patients with partial remission, 30 (43.5%) of 69 with stable disease, and 20 (29%) of 69 with progressive disease. The disease control rates according to the radiographic and molecular response were 77% and 71%, respectively.

Study	Number of patients / Treatment	Efficacy Measures		Summary of results/Author's conclusions
		Median OS*	**Median PFS/ PSA-PFS***	
Yadav et al. (2021)	121	16 months (95% CI: 13-17)	12 months (95% CI: 10.3-13)	The median follow-up duration was 36 months (6-72 months). Any PSA decline and PSA decline >50% was achieved in 73% and 61% of the patients, respectively. Multivariate analysis revealed only failure to achieve >50% PSA decline as a significant factor associated with a poor PFS.
WARMTH Study Ahmadzadehfar et al. (2021)	319	11.6 months (95% CI: 10.3–12.9)	-	The extent of bone metastases and PSA response did not correlate significantly. Any PSA decline was observed in 73% patients; 44% showed a decline of ≥50%. The median OS of patient in the different subgroups was 18 months (20 lesions) and 8 months (diffuse involvement), respectively
Calais et al. (2021)	71-included 43-results reported	Whole cohort-14.0 months (95% CI 10.1–17.9 months), 6.0-GBq group-15.8 months (95% CI 11.8–19.4 months), 6.0-GBq group-13.5 months (95% CI 10.0–17.0 months)	3.7 months in the overall study population (95% CI 2.0–5.4) 2.9 months in the 6.0-GBq group (95% CI 0.0-9.0) and 3.7 months in the 7.4-GBq groups (95% CI 1.9– 5.6)	The PSA response rates after 2 cycles and at any time were 11/40 (28%), 6/13 (46%), and 5/27 (19%), and 16/43 (37%), 7/14 (50%), and 9/29 (31%) in the whole cohort, the 6.0-GBq group, and the 7.4-GBq group, respectively.

Study	Number of patients / Treatment	Efficacy Measures		Summary of results/Author's conclusions
		Median OS*	**Median PFS/ PSA-PFS***	
TheraP Study Hofman et al. (2021)	98/ ^{177}Lu-PSMA-617 85/ cabazitaxel	-	5.1 months (3.4-5.7) 5.1 months (2.8-6.0)	PSA responses were more frequent among men in the ^{177}Lu-PSMA-617
Kesavan et al. (2021)	100	median overall OS has not been reached	6-months (95% CI; 4.11–7.89)	54% achieved a PSA response. Disease control rate by PET/CT was 64% (29% stable disease, 34% partial response, and 1% complete response). Disease control by PET/CT was associated with an improved one-year OS compared to non-responders, median OS not-reached vs 10-months (p<0.0001; 95% CI:0.08-0.44). Regarding haematologic toxicity, 11% experienced a grade ≥3 cytopenia (self-limiting).
Meyrick et al. (2021)	191	12 (5-18)	PSA PFS (n=132) 4 (3–8) months and PET/CT PFS 6 (3–10) months	A ≥50% PSA decline was observed in 89 (56%) patients, while any PSA decline occurred in 120 (75%) men. Better survival in responders. Predominantly lymph node metastatic disease and chemotherapy-naive status were significant pre-therapy factors associated with longer survival. Lower baseline PSA predicted a lower risk of death and disease progression. TEAEs included grade 3 or 4 haematological (12%), grade 1 or 2 renal (4.5%), and grade 3 or 4 other clinical events (5.7%).

Study	Number of patients / Treatment	Efficacy Measures		Summary of results/Author's conclusions
		Median OS*	**Median PFS/ PSA-PFS***	
VISION Study Sartor et al. (2021)	551 patients/ ^{177}Lu-PSMA-617 plus protocol-permitted standard care (^{177}Lu-PSMA-617 group) or 280 patients/ standard care alone (control group)	15.3 vs. 11.3 months HR for death, 0.62 (95% CI, 0.52-0.74; P<0.001)	8.7 vs. 3.4 months HR for progression or death, 0.40 (99.2% CI, 0.29-0.57; P<0.001)	The median follow-up was 20.9 months. The incidence of AEs of grade 3 or above was higher with 177Lu-PSMA-617 than without (52.7% vs. 38.0%), but quality of life was not adversely affected.
Seifert et al. (2021)	110	Lesion number, total tumour volume, and total lesion quotient were prognosticators of OS (HR=1.255, p=0.009; HR=1.299, p=0.005; HR=1.326, p=0.002)	-	In a stepwise backward Cox regression only LDH and total lesion quotient remained independent and statistically significant negative prognosticators of OS (HR=1.632, p=0.011; HR=1.239, p=0.024) in contrast to PSA value.
Derlin et al. (2022)	208- initial 26- treatment extension	-	450 d (276– 1,742 d)	During treatment extension (≤13 cycles), 50% of patients achieved an additional PSA decline (-52%±34%; range -1% to -100%), with 8% of patients achieving a congruent PSA– based and imaging-based CR. Acute toxicity, including myelosuppression, was mild

Study	Number of patients / Treatment	Efficacy Measures		Summary of results/Author's conclusions
		Median OS*	**Median PFS/ PSA-PFS***	
				(≤grade 2). Xerostomia and CKD became more common with repetitive dosing.
REALITY Registry Khreish et al. (2022)	254	14.5 (95%CI 11.5–17.5) months	5.5 (95% CI 4.4-6.6) months	Best response was ≥50% PSA reduction in 52.0% of patients (132/254). In multivariable Cox proportional hazards modelling, response to the initial ≤2 RLT administrations was the strongest significant prognosticator related to OS (HR 3.7 [95% CI 2.5–5.5], p<0.001). No RLT-related deaths or treatment discontinuations occurred; the most frequent RLT-related grade ¾ AEs were anaemia (18/254, 4.3%), and lymphopenia (7/254, 2.8%). RLT-related xerostomia, all grade ½, was noted in 53/254 (20,9%).
Mader et al. (2023)	26	29 (95% CI: 18–40) months	19 (95% CI: 15–23) months	Further PSA decline of 33±28% during the extended treatment was observed in 21/26 (81%) patients, whereas 5/26 (19%) patients showed a PSA increase; correspondingly in 11/21 patients with an initial response to extended cycles, treatment was discontinued due to progressive disease, whereas six (23%) patients achieved low-volume residual disease. Two (8%) patients died without showing progression, and two (8%) patients are still under therapy.

* unless otherwise stated

^{177}Lu=Lutetium-177, RLT=radioligand therapy, OS=overall survival, PFS=Progression-free survival, wks.=week(s), d=day(s), CI=confidence interval, CKD=chronic kidney disease, AKD=acute kidney disease, HR=hazard ratio, OR=odds ratio, ^{223}Ra=Radium-223, LDH=Lactate dehydrogenase, HP=haematological parameters, CT=computed tomography, PET=positron emission tomography, PSA=prostate-specific antigen, PSMA=prostate-specific membrane antigen, SUV_{max}=maximum standardised uptake value.

2.6.6. Discussion on clinical efficacy

In accordance with the Annex 1 Part III of Directive 2001/83/EC, as amended, 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 radiopharmaceutical precursor when attached to relevant carrier molecules shall be presented.

In support of the clinical utility of ^{177}Lu, the applicant performed a bibliographical search and presented comprehensive efficacy from published clinical trials (until January 2023), which have been conducted with ^{177}Lu-labelled tracer molecules. This approach is acceptable and consistent with previously centralised procedures for similar Lutetium (^{177}Lu) chloride radiopharmaceutical precursor products already marketed in the EU (e.g. EndolucinBeta).

Clinical utility is considered demonstrated in treatment of patients with neuroendocrine tumours using ^{177}Lu-labelled somatostatin analogues as well as in the treatment of mCRPC using ^{177}Lu labelled PSMA compounds.

2.6.7. Conclusions on the clinical efficacy

It is concluded that there is enough evidence to support the clinical utility of ^{177}Lu coupled to suitable carrier molecules.

2.6.8. Clinical safety

No original clinical safety studies were conducted by the applicant. Safety is considered with respect to the radiation product itself and in order to provide data allowing an risk assessment in already well established ^{177}Lu-RLT indications (SSTR-pos NETS and mCRPC) approved in the EU. However, since Theralugand is only a precursor, specific risks of the intended administration of ^{177}Lu added to other carrier molecules may be also different. It will need an independent product specific benefit risk assessment in the intended indication.

2.6.8.1. Patient exposure

Patient exposure information is based on published studies with ^{177}Lu-labelled tracers.

Accidental injection of free ^{177}Lu

No non-clinical studies investigated radiation dosimetry in case of the accidental injection of unbound ^{177}Lu to get a glance of the effects in patients. Extrapolating from the rat data, the estimated absorbed dose coefficients were the highest for the spleen (2.61 mGy/MBq vs. 0.91 mGy/MBq), liver (2.28 mGy/MBq vs. 1.06 mGy/MBq), bone marrow (0.48 mGy/MBq vs. 0.29 mGy/MBq), kidneys (0.28 mGy/MBq vs. 0.29 mGy/MBq), and bone surface (0.26 mGy/MBq vs. 0.17 mGy/MBq) for female vs. male adults. Hence, while numerical differences were observed between sexes in rats, the organs with the highest ^{177}Lu3+ accumulation were the same. (See 2.5. Non-clinical aspects).

Occupational and other inadvertent exposure

Theralugand is a subject to the restricted medical prescription and is intended for use in designated nuclear medicine facilities only. Furthermore, the *in vitro* radiolabelling procedure should only be handled by experienced specialists (see SmPC Section 4.2).

Data on radiation exposure to free ^{177}Lu was not available in literature. Studies investigating the radiation exposure of family members and of the public (Kurth et al., 2028; Levart et al., 2019) from patients treated with ^{177}Lu-PSMA-617 or ^{177}Lu-DOTATATE report that cumulative radiation doses in close proximity to the patients could potentially exceed over time the ICRP-recommended annual limit of 1 mSv per year in the absence of contact restrictions.

Although the actual risk is limited by the short distances which emitted β-particles can travel and their rather low tissue penetration depth (Hosono et al., 2018), the patients should be given precise recommendations upon release to further reduce inadvertent radiation exposure for others, especially for young children and pregnant women (Nelson et al, 2019).

Point-source approximation shows that the average dose rate experienced 20 hours after administration of a dose of 7.4 GBq Theralugand-labelled radiopharmaceutical (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 Theralugand-labelled radiopharmaceuticals without wearing radiation protection. Of course, the nuclear medicine staff is expected to wear standard radiation protection.

Based on the above calculations for the highest currently applied in therapies single-dose ^{177}Lu activity, the expected radiation exposure of medical personnel, patient's family members and general public is considered acceptable in line with ICRP recommendations (Lutetium (^{177}Lu) chloride Billev RMP, 2022). However, procedural guidelines setting standards for radiation safety of nuclear-medicine employees (Cappon et al., 2023) and for the management of radiotherapy patients (Nelson et al., 2019) should be followed to reduce the risks of excess and inadvertent exposure

2.6.8.2. Adverse events

The safety evaluation of ^{177}Lu-DOTATATE therapy for **treatment of SSTR-positive NETs** is illustrated best from the following two prospective clinical trials:

NETTER-1

This trial was a large, representative open-label, randomised, comparator-controlled Phase 3 trial investigated safety of ^{177}Lu-DOTATATE plus long-acting octreotide compared to high dose long-acting octreotide in a total of 231 patients (114 female, 117 male) with advanced inoperable, well-differentiated SSTR-positive midgut NETs

During the whole study, seven (6%) of 111 patients in the ^{177}Lu-DOTATATE group had a grade 3 or worse treatment-related SAE, whereas SAEs were not collected in the control group during long-term follow-up. The incidence of treatment-related SAEs was low during long-term follow-up (in three [3%] of 111 patients). Notably, no new treatment-related SAEs were reported after the safety analysis cut-off, which was approximately 46 months after study start. Two (2%) patients developed MDS. No cases of acute myeloid leukaemia were reported in the trial population.

Table 19: Overview of AEs: Study NETTER-1 (Pivotal trial for Lutathera EMEA/H/C/4123)

	^{177}Lu-DOTATATE group	**Control group (n=110)**	**p value**
	number of patients (percent)		
AE			
Any	106 (95)	95 (86)	0.02
Related to treatment	95 (86)	34 (31)	<0.001
SAE			
Any	29 (26)	26 (24)	0.76
Related to treatment	10 (9)	1 (1)	0.01
Withdrawal from trial because of AE			
Because of any AE	7 (6)	10 (9)	0.46
Because of AE related to treatment	5 (5)	0	0.06

Source: Strosberg et al. (2017) E=adverse event

Table 20: Adverse events occurring in ≥10% of patients*: Study NETTER-1

Event SOC **PT**	**^{177}Lu-DOTATATE group (n=111)**		**Control group (n=110)**		**p value#**
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**	**Any Grade**
	number of patients (percent)				
Any AE	105 (95)	46 (41)	92 (84)	36 (33)	0.01
Gastrointestinal disorders					
Nausea	65 (59)	4 (4)	13 (12)	2 (2)	<0.001
Vomiting	52 (47)	8 (7)	11 (10)	1 (1)	<0.001
Abdominal pain	29 (26)	3 (3)	29 (26)	6 (5)	1.00
Diarrhoea	32 (29)	3 (3)	21 (19)	2 (2)	0.11
Distension	14 (13)	0	15 (14)	0	0.84
General disorders					
Fatigue	44 (40)	2 (2)	28 (25)	2 (2)	0.03
Oedema peripheral	16 (14)	0	8 (7)	0	0.13

Event SOC PT	^{177}Lu-DOTATATE group (n=111)		Control group (n=110)		p value#
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**	**Any Grade**
Blood disorders					
Thrombocytopenia	28 (25)	2 (2)	1 (1)	0	<0.001
Anaemia	16 (14)	0	6 (5)	0	0.04
Lymphopenia	20 (18)	10 (9)	2 (2)	0	<0.001
Leukopenia	11 (10)	1 (1)	1 (1)	0	0.005
Neutropenia	6 (5)	1 (1)	1 (1)	0	0.12
Musculoskeletal disorders					
Musculoskeletal pain	32 (29)	2 (2)	22 (20)	1 (1)	0.16
Nutrition disorders					
Decreased appetite	20 (18)	0	9 (8)	3 (3)	0.04
Nervous system disorders					
Headache	18 (16)	0	5 (5)	0	0.007
Dizziness	12 (11)	0	6 (5)	0	0.22
Vascular disorders					
Flushing	14 (13)	1 (1)	10 (9)	0	0.52
Skin disorders					
Alopecia	12 (11)	0	2 (2)	0	0.01
Respiratory disorders					
Cough	12 (11)	0	6 (5)	0	0.22

Source: Strosberg et al. (2017)

* Shown are all AEs that were reported in at least 10% of the patients in the ^{177}Lu-DOTATATE group, with the exception of neutropenia, which was reported in less than 10% of the patients in the ^{177}Lu-DOTATATE group. The safety population included all patients who underwent randomisation and received at least one dose of trial treatment.

P values were calculated with the use of Fisher's exact text.

AE=adverse event; PT=preferred term; SOC=system organ class

The most common AEs among patients in the ^{177}Lu-DOTATATE group were nausea (65 patients [59%]) and vomiting (52 patients [47%]). Other common AEs in the ^{177}Lu- DOTATATE group included fatigue or asthenia, abdominal pain, and diarrhoea; however, the majority of patients in whom these events were reported

(≥97%) had events of grade 1 or 2 (**Table 20**). The rates of grade 3 or 4 AEs were similar in the two groups; however, transient grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia were reported in 1%, 2%, and 9% of patients, respectively, in the ^{177}Lu-DOTATATE group versus in no patients in the control group.

ILUMINET

A personalised, dosimetry-based ^{177}Lu-DOTATATE therapy was investigated by Sundlöv *et al.* (2022) in 96 patients (42 female, 54 male) with NETs.

Table 21: Adverse events: Study ILUMINET (n=96)

Event	**Early AEs n (%)**		**Late AEs n (%)**	
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
	number of patients (percent)			
Clinical AE				
Fatigue	60 (62)	1 (1.0)	9 (9.4)	-
Nausea / Vomiting	48 (50)	1 (1.0)	-	-
Pain	21 (22)	1 (1.0)	-	-
Diarrhoea	19 (20)	-	-	-
Abdominal pain	18 (19)	1 (1.0)	-	-
Flushing	7 (7.3)	-	-	-
Alopecia	6 (6.2)	-	-	-
Constipation	5 (5.2)	-	-	-
Depression	5 (5.2)	-	-	-
Infection	5 (5.2)	1 (1.0)	-	-
Ileus	2 (2.1)	1 (1.0)	-	-
Thromboembolic disease	2 (2.1)	2 (2.1)	1 (1.0)	1 (1.0)
Weight loss	2 (2.1)	1 (1.0)	-	-
Biliary tract infection	1 (1.0)	1 (1.0)	-	-
Dehydration	1 (1.0)	1 (1.0)	-	-
Laboratory AE				
Thrombocytopenia	58 (60)	9 (9.4)	10 (10)	-
Anaemia	51 (53)	1 (1.0)	20 (21)	-

Leukopenia	32 (33)	4 (4.2)	8 (8.3)	1 (1.0)
Neutropenia	28 (29)	6 (6.2)	9 (9.4)	1 (1.0)
Liver enzyme increase	6 (6.2)	1 (1.0)	-	-

Source: Sundlov et al. (2022)

Note: Early AEs included events from the start of therapy to 3 months after completing step 1 and late AE events 12 months after the last treatment

AE=adverse event, n=number of patients.

Also in ILUMINET the overall toxicity was described as mild, with few grades 3-4 AEs detailed in the Table above (see **Table 21**).

The most common clinical events were grade 1-2 fatigue, nausea, pain, diarrhoea, abdominal pain, flushing, and alopecia. Haematological AEs were common, with grade 1-2 anaemia and thrombocytopenia occurring in >50% of the patients. Grade 3-4 laboratory findings were observed in 1-9% of patients, including haematological AEs and liver enzyme increase. Grade 3-4 toxicity occurred in <10% of patients and was mostly haematological, with no grade 3-4 renal toxicity.

Regarding late AEs, the only clinical AE occurring in >5% of the patients and persisting 12 months after treatment was grade 1 fatigue. There was one grade 3-4 clinical AE, a thromboembolic event. The only persisting laboratory findings were grade 1-2 haematological AEs, whereas all grade 3-4 AEs occurred in <5% of the patients at 12 months.

During follow-up, two patients were diagnosed with acute myeloid leukaemia 2 and 4 years after the first cycle of ^{177}Lu-DOTATATE.

Plasma creatinine levels increased over time, leading to an increase in the frequency of grade 1 nephrotoxicity. Compared to baseline, less patients had a GFR >60 after treatment. There was one case of grade 3 toxicity related to intercurrent nephrolithiasis. There was one case of grade 2 renal toxicity and no grade 3-4 events.

In addition, numerous further studies, predominantly retrospective analyses, investigated the safety and toxicity profile of ^{177}Lu-DOTATATE for treatment of SSTR-positive NETs and generally are in line with the findings of the prospective clinical trials mentioned above. Very informative is also the large retrospective analysis from Kwekkeboom et al (2008) also included in the Lutathera application for long term safety evaluation from 504 patients with NETs.

Acute AEs were nausea after 25% of administrations, vomiting after 10% of administration, and abdominal discomfort or pain after 10% of administrations. 2 patients were hospitalised within 2 days of the administration because of hormone-released crisis. Temporary hair loss occurred in 62% of patients.

Haematotoxicity: Any haematologic toxicity grade 3 or 4 occurred in 9.5% of patients after at least one of several treatments. MDS occurred in 4 patients (0.8%) and was likely attributable to treatment in 3 of them.

Nephrotoxicity and hepatotoxicity: Two SAE cases of renal insufficiency were reported, both of which were probably unrelated to ^{177}Lu-DOTATATE treatment. 3 patients experienced serious liver toxicity: 2 cases were likely treatment-related and non-lethal; 1 lethal case was considered unlikely related to treatment.

^{177}Lu-PSMA-617 in metastatic castration resistant prostate cancer

The safety risks of ^{177}Lu-PSMA-617 therapy for treatment of mCRPC is paradigmatic illustrated from the VISION trial, pivotal for the approval of Pluvicto in the EU (EMEA/H/C/005483). With respect to the safety outcome of other trials in this indication it appears that the findings are generally in line with the outcome in VISION.

PSMA is expressed in all types of prostate tissues. As it has been shown to be overexpressed in prostate tumours including its metastatic cells, as well as in mCRPC, it is an ideal target for prostate cancer diagnosis and therapy (Silver et al., 1997; Sweat et al., 1998). However, PSMA is not prostate specific and several other organs such as the kidneys, salivary glands, lacrimal glands, or small intestine also express PSMA (Sweat et al., 1998; O'Keefe et al., 2004). Therefore, proximal renal tubules and salivary glands, among others, are considered critical organs in patients receiving PSMA-RLT. Since ^{177}Lu-PSMA agents are predominantly excreted by kidneys, additional concerns relating to their potential nephrotoxicity and renal outcomes exist.

As already known from PRRT in NETs with ^{177}Lu-DOTATATE myelosuppression is the most important potential dose-limiting factor in RLT also relevant for ^{177}Lu-PSMA. Toxic effects to haematopoietic cells are mediated by both blood-driven recirculating β-irradiation and scatter radiation from bone metastases.

The results of 3 prospective clinical trials and several other supportive safety results are available in this indication. Most studies have monitored AEs and any other safety-relevant parameters along with the efficacy of ^{177}Lu-PSMA as a radioligand for treatment of mCRPC.

VISION (pivotal trial for approval of Pluvicto EMEA/H/C/005483)

This trial evaluated the clinical safety profile of ^{177}Lu-PSMA-617 in 831 patients with mCRPC who were previously treated with at least one androgen-receptor pathway inhibitor and one or two taxane regimens. This is the largest randomised study with ^{177}Lu-PSMA-617 that became pivotal for its approval in EU in Dec 2022.

Median duration of exposure to ^{177}Lu-PSMA-617 was 6.9 months (range, 0.3 to 10.2 months), with patients receiving a median of 5 cycles (range, 1 to 6) and with a median cumulative dose of 37.5 GBq (range, 7.0 to 48.3 GBq). The incidence of AEs of grade 3 or above was higher with ^{177}Lu-PSMA-617 than without it (52.7% vs. 38.0%), but quality of life was not adversely affected (see **Table 22**).

Fatigue, dry mouth, and nausea were the most common AEs in the ^{177}Lu-PSMA-617 group, and these AEs were nearly all of grade 1 or 2. Grade 5 TEAEs occurred in 5/529 patients (0.9%) in the ^{177}Lu-PSMA-617 plus standard care arm (pancytopenia, n=2; bone marrow failure, n=1; subdural haematoma, n=1; intracranial haemorrhage, n=1) and none in the control arm.

The incidence of SAEs was 31.9% in the ^{177}Lu-PSMA-617 treatment group and 25.4% in the standard care group, and drug-related SAEs were reported by 8.1% in the ^{177}Lu-PSMA-617 treatment group and 2.4% in the standard care group.

Table 22: Summary of Adverse Events: Study VISION

Event	**^{177}Lu-PSMA-617 plus Standard Care (n=529)**		**Standard Care Alone (n=205)**	
	All Grades	**Grade ≥3**	**All Grades**	**Grade ≥3**
	number of patients (%)			
Any AE	519 (98.1)	279 (52.7)	170 (82.9)	78 (38.0)
AE that occurred in >12% of patients				
Fatigue	228 (43.1)	31 (5.9)	47 (22.9)	3 (1.5)
Dry mouth	205 (38.8)	0	1 (0.5)	0
Nausea	187 (35.3)	7 (1.3)	34 (16.6)	1 (0.5)
Anaemia	168 (31.8)	68 (12.9)	27 (13.2)	10 (4.9)
Back pain	124 (23.4)	17 (3.2)	30 (14.6)	7 (3.4)
Arthralgia	118 (22.3)	6 (1.1)	26 (12.7)	1 (0.5)
Decreased appetite	112 (21.2)	10 (1.9)	30 (14.6)	1 (0.5)
Constipation	107 (20.2)	6 (1.1)	23 (11.2)	1 (0.5)
Diarrhoea	100 (18.9)	4 (0.8)	6 (2.9)	1 (0.5)
Vomiting	100 (18.9)	5 (0.9)	13 (6.3)	1 (0.5)
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.9)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)
AE that led to reduction in ^{177}Lu-PSMA-617 dose	30 (5.7)	10 (1.9)	NA	NA
AE that led to interruption of ^{177}Lu-PSMA-617[#]	85 (16.1)	42 (7.9)	NA	NA
AE that led to discontinuation of ^{177}Lu-PSMA-617[#]	63 (11.9)	37 (7.0)	NA	NA
AE that led to death[*]	19 (3.6)	19 (3.6)	6 (2.9)	6 (2.9)

Source: Sartor et al. (2021)

Patients who had been randomly assigned to receive ^{177}Lu-PSMA-617 plus standard care and who did not receive 177Lu-PSMA-617 but did receive standard care were included in the control group (standard care alone) of the safety

population; 3 patients had AEs during cycle 1 of ^{177}Lu-PSMA-617 therapy that led to the interruption (in 2 of 205 patients [1.0%]) or discontinuation (in 1 [0.5%]) of that therapy.

* Five AEs that led to death in the ^{177}Lu-PSMA-617 group were considered by the investigators to be related to the drug: pancytopenia (in 2 patients), bone marrow failure (in 1), subdural haematoma (in 1), and intracranial haemorrhage (in 1).

AE=adverse event

In a retrospective cohort analysis by Meyrick et al (2021), TEAEs during RLT with 177Lu-PSMA in patients with mCRPC included grade 3 or 4 haematological (12%), grade 1 or 2 renal (4.5%), and grade 3 or 4 clinical events (5.7%) (Meyrick et al., 2021). The following table shows treatment related adverse events with 177Lu-PSMA-617:

Table 23: Treatment-related adverse events in study by Meyrick et al. (2021*)*

Adverse event	**Number of patients (%)***
Haematological AE (grade 3 or 4 only)	21 (12)
Thrombocytopenia	6 (3.4)
Anaemia	9 (5.1)
Lymphopenia	10 (5.7)
Neutropenia	1 (0.6)
Renal AE (grade 1 or 2 only)	8(4.5)
Acute kidney disease	3 (1.7)
Chronic kidney disease	5 (2.8)
Clinical AE (grade 3 or 4 only)	9 (5.1)

Source: Meyrick et al. (2021) [50]

*total number of patients, n=175

=adverse event

Table 24: Tabulated list of adverse reactions in Theralugand SmPC

Adverse reactions are divided into groups according to the MedDRA convention frequencies: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 ,000 to < 1/100), rare (≥ 1/10 ,000 to < 1/1 ,000), very rare (< 1/10 ,000), not known (cannot be estimated from the available data).

MedDRA system organ class	**Frequency**			
	Very common	**Common**	**Uncommon**	**Not known**
Neoplasms benign, malignant and unspecified **(incl cysts and polyps)**		Refractory cytopenia with multilineage dysplasia (Myelodysplastic syndrome) (see section 4.4)	Acute myeloid leukaemia (see section 4.4)	
Blood and lymphatic system disorders	Anaemia Thrombocytopenia Leucopenia 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			

Description of selected adverse reactions

Dry mouth

Transient dryness of the mouth has been reported among patients with metastatic castration resistant prostate cancer receiving PSMA-targeting 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.

2.6.8.3. Serious adverse event/deaths/other significant events

No data were submitted by the applicant. Reference is made to the literature review below by indication.

NETS: From NETTER-1 it reported that sixty-seven patients (30.0%) from both arms experienced at least one SAE, 37 (33.0%) patients in the Lutathera arm, 30 (27.0%) patients in the Octreotide LAR arm. The number of patients with at least one TESAE was 35 (31.3%) patients in the Lutathera arm, 27 (24.3%) patients in the Octreotide LAR arm, differences between the treatment arms in the occurrence of TESAEs were not statistically significant ($p>0.05$). The number of patients who experienced TESAEs considered by the Investigator to be related to study treatment was 13 (11.6%) patients in the Lutathera arm and 3 (2.7%) patient in the Octreotide LAR arm.

In the NETTER-1 study, one patient of the Lutathera arm died due to a non-treatment emergent AE. Sixteen other patients (7.2%) died due to TEAEs in the course of this study: 7 patients (6.3%) of the Lutathera and 9 patients (8.1%) of the Octreotide LAR arm. None of these fatal TEAEs was related to the study medication.

mCRPC: From Pluvicto in the VISION trial more patients in the 177Lu-PSMA-617+BSC/BSoC arm than in the BSC/BSoC only arm had SAEs (177-Lu-PSMA: 36.3% vs BSC/BSoC only: 27.8%). However, this could be expected in a trial using BSC/BSoC as comparator. The impact of radiation toxicity on safety becomes even more clearly in the frequency of drug-related SAEs, which occurred threefold in 9.3% patients in the 177Lu-PSMA-617+BSC/BSoC arm and 2.4% patients in the BSC/BSoC only arm.

The SOCs with TEAEs reported in at least ≥5% of the patients in either arm were (^{177}Lu-PSMA vs BSC/BSoC only) were infections and infestations (9.8% patients vs. 4.4% patients).

SAEs with fatal outcomes occurred only slightly more in the 177Lu-PSMA-617+BSC/BSoC arm: 19 (3.6%) patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm (including 1 disease progression and 1 COVID-19); and 6 (2.9%) patients in the BSC/BSoC only arm (including 1 disease progression). However, again the difference of treatment duration on randomised treatment between the arms need to be considered for interpretation, since it was significantly shorter in the BSC/BSoC only arm.

2.6.8.4. Laboratory findings

No data were submitted by the applicant. Reference is made to the literature review below by indication.

NETS:

In the Lutathera arm, 49 patients (43.8%) had a lymphopenia (Grade 3 or 4) and 22 patients (19.7%) had an increased GGT (Grade 3 or 4) diagnosed post randomisation. In each of the following categories, between 4 and 7 patients (3.6% to 6.3%) showed post randomisation Grade 3 or 4 hyperglycaemia, hyperuricemia, hypokalaemia, alkaline phosphatase increased, ASAT increased and ALAT increased. In the comparator arm, the following toxicities were notable: lymphopenia (5 (4.5%) patients), hyperuricemia (7 (6.3%) patients), GGT increased (18 (16.2%) patients), and alkaline phosphatase increased (10 (9%) patients).

Regarding the Grade 3 or 4 laboratory toxicities, no relevant differences were observed between the 2 arms, except for lymphopenia, leukopenia, neutropenia, and thrombocytopenia. A trend towards stabilisation then improvement in patients with longer follow-up is observed.

For the lymphocyte toxicity observed following PRRT it was demonstrated that only B lymphocytes are affected, with no opportunistic infection being reported after PRRT. Additionally, in the NETTER-1 study lymphopenia in the Lutathera arm was not associated with an increased rate of infections compared to the control arm. The majority of thrombocytopenia in the Lutathera arm was mild to moderate.

mCRPC (VISION):

With respect to **haematology,** the most frequent myelosuppression-related adverse events were anaemia, thrombocytopenia, lymphocytopenia, leukopenia, and neutropenia, which may be attributed to the effects of ionizing radiation on sensitive precursor cells in circulation or in the bone marrow close to metastatic bone lesions, but which may also be impacted by bone marrow impairment at baseline from prior therapy. These shifts were mainly by 1 or 2 grades up, with some shifts to grade 4. None of these haematological parameter shifts caused any unexpected safety concerns.

Clinical chemistry abnormalities observed during randomised treatment were generally similar in both treatment arms (≤10% differences) with few noteworthy exceptions of hyponatremia (38.2% patients vs. 24.9% patients); hypocalcaemia (43.1% patients vs. 31.7% patients); and AST increased (31.2% patients vs. 21.0% patients). In both treatment arms, grade 3 / 4 abnormalities were infrequent (<3.0% patients). Some shifts to higher grades were observed during the randomised treatment period but there was no trend; and none of these shifts raised any safety concerns.

The liver function parameters were similar in both arms, and no notable high frequency was observed for any of the hepatic laboratory categories. The laboratory data did not raise any hepatic safety concerns. No patient in either arm had a constellation of values indicative of Hy's law during the randomised treatment. Also, during long term follow-up, liver function parameters were similar between both the groups of patients and similar to what was observed during the randomised treatment.

2.6.8.5. Safety in special populations

Pregnant and lactating women

According to the SmPCs of authorised medicinal products containing lutetium-177, those medicinal products are contraindicated in established or suspected pregnancy or when pregnancy has not been excluded.

Paediatric population

The proposed medicinal product is not intended for use in children and adolescents. As medicinal products containing ^{177}Lu are currently not authorised for use in the paediatric population, data on the safety of ^{177}Lu-labelled tracers in this vulnerable population are scarce.

Elderly

Due to the nature of the underlying diseases, a significant number of patients above the age of 65 years have been treated with ^{177}Lu-labelled tracers in the course of published clinical studies.

Renal impairment

Radiolabelled peptides are mainly excreted by the kidney. Radiation nephropathy has been reported following peptide receptor radionuclide therapy for neuroendocrine tumours using radioisotopes.

2.6.8.6. Immunological events

No information provided.

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

No data were submitted by the applicant.

^{177}Lu-PSMA-617 is metabolically stable both *in vitro* and *in vivo*, passively cleared through the kidneys and not a substrate of any of the investigated uptake or efflux transporters (i.e. MATE1, MATE2-K, OAT1, OAT3,

OCT2, P-gp and BCRP) based on *in vitro* assessments. Therefore, it is unlikely to become subject to any metabolic- or transporter-mediated drug interactions.

2.6.8.8. Discontinuation due to adverse events

No data were submitted by the applicant.

Discontinuation from ^{177}Lu-RLT in both indication were mostly due to adverse events related to haematological toxicity, followed by renal toxicity and to a lesser extent GI toxicity (possibly as a result of the amino acids infused for renal protection).

2.6.8.9. Post marketing experience

Theralugand is not marketed as a drug in any country world-wide. Thus, no there is no postmarketing experience available. Information from medicinal products authorised in the EU containing the radionuclide lutetium-177 was presented. The applicant summarised the adverse events reported with these products. (See 2.6.8.2.)

2.6.9. Discussion on clinical safety

In accordance with the Annex 1 Part III of Directive 2001/83/EC, as amended, in the specific case of a radiopharmaceutical precursor intended solely for radiolabelling purposes, the primary objective shall be to present information which would address the possible consequences of poor radiolabelling efficiency or *in vivo* dissociation of the radiolabelled conjugate, i.e. questions related to the effects produced in the patient by free radionuclide. These aspects have been adequately addressed in the dosimetry of ^{177}Lu chloride section (above), focusing on the accumulation of free lutetium-177 ($^{177}Lu^{3+}$) in target organs. Furthermore, safety information from already authorised medicinal products containing the active substance lutetium (^{177}Lu) chloride was evaluated.

The safety data available for $^{177}LuCl_3$ have been thoroughly summarised and it is agreed that data allow an adequate characterisation of ^{177} $LuCl_3$ as a precursor added to two clinical relevant carrier molecules in the currently already approved indications (NETs and mCRPC).

As a radiopharmaceutical precursor, Theralugand is not administered directly to the patient and therefore has no clinical safety concerns associated with its stand-alone use. In general, adverse reactions following the administration of a ^{177}Lu-labelled medicinal product prepared by radiolabelling with the proposed medicinal product will be mainly dependent on the specific medicinal product being used. Such information will be supplied in the SmPC/package leaflet of the medicinal product to be radiolabelled.

Safety concerns for the radiolabelling with ^{177}Lu might arise due to unstable labelling, resulting in the release of ionic ^{177}Lu into the body. However, complexing with the most commonly used for radiolabelling chelators like DOTA appears to be irreversible and the applicant thus stated that no free ^{177}Lu is administered or released from Theralugand. A summary of the available study data and the corresponding human estimates of the absorbed ^{177}Lu doses was submitted. Nevertheless, it is emphasised that *in vitro* and *in vivo* stability of the resulting complex needs to be thoroughly tested by the developer of each new ^{177}Lu-labelled compound; since this is, an essential prerequisite for its successful clinical application.

Since the safety can be assessed only for the final radiolabelled medicinal product and depends from the pharmacokinetics and the distribution of the carrier molecule radiolabelled with Theralugand, only non-clinical dosimetry data is available for $^{177}LuCl_3$ itself or other ionic forms of ^{177}Lu.

Importantly, the safety of any ^{177}Lu-labeled carrier molecule will be needed to be addressed in a potential MA procedure of any of these newly developed radiopharmaceuticals. This aspect is generally beyond the scope of the application for authorisation of the radiopharmaceutical precursor $^{177}LuCl_3$.

In the very implausible case of a direct injection, the main safety concern is radiation toxicity to the bone marrow. Based on the animal dosimetry results for direct injection, bone marrow would be the most sensitive organ as it could receive a higher than acceptable radiation dose. This risk is adequately addressed in the Theralugand Risk Management Plan (see 2.7. Risk Management Plan) as well as in SmPC section 4.9. In case of an inadvertent administration of Theralugand, 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. The following preparations must be available in medical institutions, which use Theralugand 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.

Nevertheless, as with respect to efficacy, safety evaluation of Theralugand can be assessed from literature data and clinical trial for Somatostatin-Receptor positive Neuroendocrine tumours (SSTR-pos.NETs) NETs using ^{177}Lu-DOTATATE and treatment of metastatic castration resistant prostate cancer using ^{177}Lu-labelled PSMA derivatives (^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T). In both indications specific products (Lutathera and Pluvicto) have been meanwhile approved in the EU.

It is noted that with both already approved therapies with ^{177}Lu-DOTATATE and ^{177}Lu-PSMA the safety profile is acceptable overall. The most common non-haematological AEs included nausea and vomiting, fatigue or asthenia, abdominal pain, and diarrhoea. The majority of these events are mild or moderate in intensity, and generally transient.

Haematological toxicity is a known risk of treatment with both ^{177}Lu-DOTATATE and ^{177}Lu- PSMA, with myelosuppression being a potential dose-limiting factor in RLT. Toxic effects to haematopoietic cells are mediated by both blood-driven recirculating ß-irradiation and scatter radiation from bone metastases. Indeed, haematological AEs were among the most common treatment-related side effects reported during therapy and predominantly presented as anaemia, leukopenia, and/or thrombocytopenia. However, haematological toxicity was mostly mild or absent (in over 60% of patients), and often transient. Of note, most patients already had impaired haematological function prior to ^{177}Lu-based therapy due to preceding chemotherapy or other anticancer treatment. Women treated with ^{177}Lu-DOTATATE developed more frequently grade ≥2 thrombocytopenia or grade ≥3 anaemia compared with men. 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 section 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).

Bone marrow toxicity, presenting in severe haematological effects (grade 3 or 4), occurred in 8 to 15% of patients treated with ^{177}Lu-DOTATATE or ^{177}Lu-PSMA. It was generally transient, and therapy was continued after nadir was passed. However, blood transfusion support might be necessary in some cases. In patients with mCRPC, myelosuppression was significantly more frequent in patients with pre-existing grade 2 cytopenia or high bone tumour burden. PHD after PRRT with ^{177}Lu-DOTATATE, defined as diagnosis of MDS, AML, MPN, MDS/MPN, or otherwise unexplained cytopenia (for >6 months), was reported in up to 5% of the patients in the literature which is in line with the pivotal trials for Lutathera and Pluvicto.

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.

Grade 3/4 renal toxicity and hepatotoxicity were rarely reported in published literature. NET patients pretreated with chemotherapy had a higher risk to develop renal toxicity. 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.

Moreover, tumour lysis syndrome has been reported following lutetium (^{177}Lu) 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.

Serious hepatotoxicity was reported in single patients only, many of whom had liver metastases. 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.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken. This is also addressed in the product information. Point-source approximation shows that the average dose rate experienced 20 hours after administration of a 7.4 GBq dose of a 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 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.

Procedural guidelines for the management of radiotherapy, including regulations on patients' discharge, have been developed and should be strictly followed to avoid unnecessary radiation exposure. Information related to occupational hazards and radiation exposure to hospital staff and to the environment is properly addressed and captured in the product information for Theralugand (see section 12 of the SmPC). Before use, packaging and radioactivity should be checked. Activity may be measured using an ionisation chamber. Lutetium (^{177}Lu) is a beta (β−)/gamma emitter. Activity measurements using an ionisation chamber are very sensitive to geometric factors and therefore should be performed only under geometric conditions which have been appropriately validated. Usual precautions regarding sterility and radioactivity should be respected. Withdrawals should be performed under aseptic conditions. The vials must not be opened before disinfecting the stopper, the radiopharmaceutical precursor solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system. If the integrity of the vial is compromised, the radiopharmaceutical precursor solution should not be used. The complexing agent and other reagents should be added to the vial with lutetium (^{177}Lu) chloride. Free lutetium (^{177}Lu) is taken up and accumulates in the bones. This could potentially result in osteosarcomas. It is recommended to add a chelating agent such as DTPA prior to intravenous administration of lutetium (^{177}Lu)-labelled radiopharmaceuticals in order to form a complex with free lutetium (^{177}Lu), if such is present, leading to its rapid renal clearance. Adequate quality control of the radiochemical purity of ready to use radiopharmaceuticals gained after radiolabelling with Theralugand should be assured. Limits for radiochemical impurities should be set recognising the radiotoxicological potential of lutetium (^{177}Lu). Free non-bound lutetium (^{177}Lu) should be consequently minimised.

There have been reports of extravasation of lutetium (^{177}Lu)-labelled ligands in the post-marketing setting. In case of extravasation, infusion of the 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.

With respect to special population it is considered that the applicant has used dose calculations through realistic anthropomorphic phantoms from software's for internal dosimetry (e.g. IDAC-Dose 2.1) and this is agreed. Also, it is agreed dosimetry extrapolation to paediatric population despite of there are currently no ^{177}Lu-labelled radiopharmaceuticals authorised for use in these populations. It is noted that IDAC-Dose 2.1 version 1.01 software is only for adults calculations and OLINDA/EXM version 1.0 has been used for the remaining populations (paediatric population).

Dosimetry is presented for both sex (male and female) and for paediatric population in two tables (see 2.6.2.2. mCRPC). In both tables, derived Effective dose according ICRP 60 is shown for each age population and sex-averaged dose derived according to ICRP Publication 103 is presented for the whole age population. This approach is considered adequate.

2.6.10. Conclusions on clinical safety

For the purpose of an application for a radiopharmaceutical for radiolabelling, the safety of Theralugand has been adequately characterised and adequate measures have been set up to manage the risks associated with Theralugand.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 25: 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 (MDS)/ Acute myeloid leukaemia (AML)
Important potential risks	• Osteosarcoma • Radiation-induced nephropathy • Radiation-induced hepatotoxicity
Missing information	• None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities. Routine pharmacovigilance activities including adverse reactions reporting and signal detection are considered sufficient.

2.7.3. Risk minimisation measures

Table 26: Part V.3 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk:		
Radiation effects on persons who are unaware of the exposure when in close vicinity of the patient	**Routine risk minimisation measures:** *SmPC sections 2, 4.1, 4.2, 4.4, 4.9, 6.4, 6.6, and 12* *Restricted user group* *Legal status* *Radiation labelling* **Additional risk minimisation measures:** *None*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *None* **Additional pharmacovigilance activities:** *None*
Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia)	**Routine risk minimisation measures:** *SmPC sections 4.4 and 4.8* *Restricted user group* *Legal status* *Radiation labelling* **Additional risk minimisation measures:** *None*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *None* **Additional pharmacovigilance activities:** *None*
Myelodysplastic syndrome (MDS)/ Acute myeloid leukaemia (AML)	**Routine risk minimisation measures**: *Restricted user group* *SmPC sections 4.4 and 4.8* *Legal status* *Radiation labelling* **Additional risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *None* **Additional pharmacovigilance activities:**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None	*None*
Important Potential Risks:		
Osteosarcoma	**Routine risk minimisation measures:** *SmPC section 4.1, 4.2, 4.4, 4.9, 5.3, 6.6, 11, 12* *Product label* *Restricted user group* *Legal status* *Radiation labelling* **Additional risk minimisation measures:** *None*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *None* **Additional pharmacovigilance activities:** *None*
Radiation-induced nephropathy	**Routine risk minimisation measures:** *SmPC section 4.4* *Restricted user group* *Legal status* *Radiation labelling* **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities:** *None*
Radiation-induced hepatotoxicity	**Routine risk minimisation measures:** *SmPC section 4.4* *Restricted user group* *Legal status* *Radiation labelling* **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities:** *None*

2.7.4. Conclusion

The CHMP considers that the risk management plan version 3.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. 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.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

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

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC have been submitted by the applicant and has been found acceptable only partly by the QRD Group for the following reasons:

1. Omission of the "name of the manufacturer" and "expiry date" on the small immediate packaging units - **Acceptable**

2. Usage of the smaller font size for the small immediate label and on the label of the acrylic insert of the lead container (outer packaging) – **Acceptable**

3. Omission of the sentence "*1 mL of solution contains 40 GBq of lutetium (177Lu) chloride at activity reference time (ART)*" on the lead container and metallic can label (outer packaging) – **Not acceptable.** This information is considered radiologically safe for healthcare professionals due to the protection offered by shielding.

4. Omission of the sentence "*Keep out of sight and reach of children*" on the lead container and metallic can label (outer packaging) - **Acceptable**

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The medicinal product Theralugand (lutetium (^{177}Lu) chloride) 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.

3.1.2. Available therapies and unmet medical need

Theralugand was developed as a radiopharmaceutical precursor developed to be clinically used for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with $^{177}LuCl_3$. The most common, best described and already established in the routine clinical practice carrier molecules available for radiolabelling with ^{177}Lu are DOTA-coupled octreotate (DOTATATE) and PSMA, indicated for treatment of SSTR-positive NETs or mCRPC, respectively.

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.

3.1.3. 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 Lutetium (^{177}Lu) chloride when is attached to appropriate carrier molecules has been provided. Two compound types most commonly used with ^{177}Lu (DOTA-coupled octreotate, DOTATATE, and PSMA) were chosen to demonstrate the clinical utility of ^{177}Lu and to serve as basis for the benefit-risk assessment of ^{177}Lu-based therapies. In both indications the applicant has thoroughly reported the available information on efficacy and safety based on the available literature.

Appropriate bibliographic data from the literature were presented to support efficacy and safety of ^{177}Lu products in already approved RLT indications (SSR-pos-NETs and mCRPC) and illustrate the clinical use of ^{177}Lu-radiolabelled compounds in general.

3.2. Favourable effects

A review of the literature has been submitted in order to document the clinical utility of ^{177}Lu, in particular in the treatment of neuroendocrine tumours (NETS) and castration resistant metastatic prostate cancer (mCRPC). Both therapeutic options are meanwhile well established in clinical practice. Additional clinical data have been presented in indication specific ^{177}Lu-products radiolabelled with specific carrier molecules (octreotide and PSMA) showing a positive benefit-risk balance in controlled Phase III trial see Lutathera (EMEA/H/C/004123) EPAR for NET-tumours and Pluvicto EPAR for mCRPC (EMEA/H/C/005483)).

3.3. Uncertainties and limitations about favourable effects

Not applicable

3.4. Unfavourable effects

Unfavourable effects will mainly depend on the intended administration of ^{177}Lu when it is added to a carrier molecule.

Safety concerns for the radiolabelling with ^{177}Lu might arise due to unstable labelling or inadvertent direct injection of Theralugand, resulting in introduction of free ^{177}Lu into the body. Since complexing with the most commonly used chelators like DOTA is claimed highly efficient and irreversible and no free ^{177}Lu is thereby administered or released from the chelate complexes (Maecke et al., 2003). In very implausible case of a direct injection, the main safety concern is radiation toxicity to the bone marrow as shown in the animal dosimetry results for direct injection.

After therapy with ^{177}Lu-labelled peptides, haematological toxicity, myelodysplastic syndrome, renal toxicity and liver toxicity have been reported. Haematotoxicity and dry mouth have been reported with ^{177}Lu-labelled PSMA-ligands in radioligand therapy for metastatic castration-resistant prostate cancer.

Specific risk associated with the use of ^{177}Lu-labelled DOTATATE and PSMA compounds should be primarily addressed in the MAs of the corresponding medicinal products.

Decreased blood cell count (anaemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia, pancytopenia) and myelodysplastic syndrome/acute myeloid leukaemia as well radiation effects on persons who are unaware of the exposure when in close vicinity of the patient are included in the RMP as important identified risks. In addition, osteosarcoma, radiation nephropathy and radiation-induced hepatotoxicity are considered as important potential risks in the RMP. Moreover, corresponding special warnings and precautions for use are included in the SmPC accordingly.

3.5. Uncertainties and limitations about unfavourable effects

Toxicity of free lutetium (^{177}Lu) due to *in vivo* release from the labelled biomolecule in the body during therapy could occur. It is unclear to what degree is *in vivo* release likely to occur or how would such *in vivo* release be measured in practice. However, this issue depends also on the carrier molecule added to ^{177}Lu and will have to be clarified in the case of a specific application for approval.

3.6. Effects table

Not applicable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor intended to be used for radiolabelling of suitable carrier molecules (peptides, antibodies) which have been specifically developed and authorised for radiolabelling with lutetium-177. 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 Theralugand 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.

^{177}Lu is broadly used as a therapeutic radionuclide for radiolabelling of specific carrier molecules which are developed for targeted radiotherapies (currently authorised or experimental) of various oncologic diseases, such as NETs and prostate cancer.

The two most important, best described in the published literature and most common therapeutic indications approved in the EU for ^{177}Lu are currently the treatment of gastroenteropancreatic NETs (GEP-NETs) and the treatment of mCRPC (as Lutathera and Pluvicto, respectively).

Unfavourable effects are mainly related to the radioactivity of ^{177}Lu. Adverse reactions following the administration of a ^{177}Lu-labelled medicinal product prepared by radiolabelling with the proposed medicinal product will be mainly dependent on the specific medicinal product being used. 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.

3.7.2. Balance of benefits and risks

Theralugand is a radiopharmaceutical precursor and is not intended to be administered on its own to patients. As a result, the benefits and risks of the intended administration of ^{177}Lu will be assessed independently when it is added to a carrier molecule. For the purpose of an application for a radiopharmaceutical for radiolabelling, the clinical utility and the safety of Theralugand has been adequately addressed. Since the precursor ^{177}Lu products are a prerequisite for this type of RLT, a positive risk benefit balance can be confirmed from a non-clinical and clinical perspective.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Theralugand is positive.

4. Recommendations

Outcome

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

Theralugand 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 (177Lu) chloride.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **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.

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

- **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.