20 July 2017
EMA/506460/2017
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## LUTATHERA

International non-proprietary name: lutetium (177lu) oxodotreotide

Procedure No. EMEA/H/C/004123/0000

## Note

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

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# List of abbreviations

| | |
|---|---|
| 5-HIAA | 5-Hydroxy indoleacetic acid |
| ASMF | Active Substance Master File |
| AE | Adverse event |
| BED | Biological effective dose |
| Bq | Becquerel (1 decay/second) |
| CGA | Chromogranin A |
| Cl | Clearance |
| CR | Complete response |
| CT | Computed tomography |
| CTCAE | Common terminology criteria for adverse events |
| CV | Coefficient of variation |
| CYP450 | Cytochromes P450 |
| DMF | Dimethyl fumararate |
| DoR | Duration of Response |
| DOTATATE | Oxodotreotide, DOTA0-Tyr3-octreotate |
| DOTATOC | Edotreotide, or DOTA-Tyr3-octreotide |
| DTPA | Diethylenetriaminepentaacetic acid |
| EANM | European Association of Nuclear Medicine |
| EC | European Commission |
| ECG | Electrocardiogram (or Electrocardiography) |
| ENETS | European Neuroendocrine Tumour Society |
| EOP | End of production |
| ESMO | European Society for Medical Oncology |
| FAS | Full analysis set |
| FT-IR | Fourrier Transform Infrared Spectroscopy |
| FTM | Fluid thioglycollate medium |
| GBq | Gigabecquerel |
| GC | Gas chromatography |
| GC-MS | Gas chromatography mass spectrometry |
| GEP-NET | Gastroentreopancreatic neuroendocrine tumour |
| GMP | Good Manufacturing Practice |
| HPGe | High Purity Germanium Detector |
| HPLC | High performance liquid chromatography |
| IAEA | International Atomic Energy Agency |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICP-AES | Inductively coupled plasma atomic emission spectroscopy |
| ICP-OES | Inductively coupled plasma-atomic emission spectrometry |
| IR | Infrared |
| ITLC | Instant thin-layer chromatography |
| ITLC-SG | Instant thin-layer chromatography silica gel |
| Lu-177 | Lutetium-177 |
| Lutathera® | $^{177}$Lu-Oxodotreotide 370 MBq/ml solution for infusion |
| MBq | Megabecquerel |
| MDS | Myelodysplastic Syndrome |
| MR | Minor response |
| MRI | Magnetic resonance imaging |
| MS | Mass spectroscopy |
| MS-MS | Tandem mass spectroscopy |
| NANETS | North American Neuroendocrine Tumour Society |
| NET | Neuroendocrine tumour |
| NIR | Near Infrared Spectroscopy |
| NMR | Nuclear Magnetic Resonance |
| NPC | Net peptide content |
| ORR | Objective response rate |
| OS | Overall survival |
| PETG | Polyethylene terephthalate glycol |
| PFS | Progression free survival |
| Ph. Eur. | European Pharmacopoeia |
| P-gp | P-glycoprotein |

| | |
|---|---|
| PK | Pharmacokinetics |
| PR | Partial response |
| PRRT | Peptide receptor radionuclide therapy |
| QoL | Quality of Life |
| RH | Relative humidity |
| RP-HPLC | Reversed-phase high-performance liquid Chromatography |
| RP-UV-HPLC | Reversed-phase ultraviolet high-performance liquid Chromatography |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SmPC | Summary of Product Characteristics |
| SNMMI | Society of Nuclear Medicine and Molecular Imaging |
| SSA | Somatostatin analogue |
| Sstr1-5 | Somatostatin receptor subtype 1 to 5 |
| Tc | Calibration time |
| TFA | Trifluoroacetic acid |
| TLC | Thin layer chromatography |
| TSB | Tryptose soya broth |
| TSE | Transmissible Spongiform Encephalopathy |
| TTP | Time to progression |
| USP | United States Pharmacopoeia |
| UV | Ultraviolet absorption spectroscopy |
| Vz | Distribution volume during the terminal phase |
| WBC | White blood cells |
| WHO | World Health Organization |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Advanced Accelerator Applications submitted on 26 April 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for LUTATHERA, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 November 2014.

LUTATHERA, was designated as an orphan medicinal product EU/3/07/523 on 31 January 2008 in the following condition: Treatment of gastro-entero-pancreatic neuroendocrine tumours.

The applicant applied for the following indication: Treatment of unresectable or metastatic, somatostatin receptor positive gastro-enteropancreatic neuroendocrine tumours (GEP-NETs) including foregut, midgut and hindgut in adults.

**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 studies and/or bibliographic literature substituting/supporting certain tests or studies.

## *Information on Paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

## *Information relating to orphan market exclusivity*

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Lutathera as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designation.

## 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.

## Applicant's request for consideration

## Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No

726/2004.

## New active Substance status

The applicant requested the radiopharmaceutical substance lutetium ($^{177}$Lu) oxodotreotide to be considered as a new active substance as it is a constituent not previously authorised in a medicinal product in the European Union and the coupling mechanism to link the ligand and the radionuclide has not been authorised previously in the European Union.

## *Protocol Assistance*

The applicant received Protocol Assistance from the CHMP on 19 February 2009 and 3 March 2011. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Robert James Hemmings Co-Rapporteur: Harald Enzmann

- The application was received by the EMA on 26 April 2016.
- Accelerated Assessment procedure was agreed-upon by CHMP on 28 April 2016. The procedure reverted to standard TT at the time of the adoption of the List of Questions.
- The procedure started on 19 May 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 3 August 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 August 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 19 August 2016.
- During the meeting on 2 September 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 15 September 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 March 2017.
- The following GCP and GMP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A routine GCP inspection at 2 clinical investigator sites between 5 - 29 July 2016.
  - A triggered GCP inspection at the CRO site between 4 - 7 October 2016. The outcome of the inspections carried out was issued on 06 December 2016.
  - A GMP inspection at two sites responsible for manufacture of the active substance and the finished product between 12-15 July 2016 and 5-8 September 2016, respectively. The outcome of the inspections carried out was issued on 29 September 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 24 April 2017.
- During the PRAC meeting on 5 May 2017, the PRAC agreed on the PRAC Assessment Overview

and Advice to CHMP.

- During the CHMP meeting on 18 May 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 June 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 July 2017.
- During the meeting on 20 July 2017, 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 LUTATHERA.

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) constitute a heterogeneous group of neoplasms arising from the diffuse neuroendocrine system. Well-differentiated carcinoid tumours over-express somatostatin subtype 2 receptors (sstr2) which is a common feature of all GEP-NETs.

### 2.1.2. Epidemiology and risk factors, screening tools/prevention

The worldwide incidence of GEP-NETs is increasing. In the US, a significant increase in the reported annual age-adjusted incidence of NETs from 10.9 per million in 1973 (Yao 2008) to 57.6 per million in 2007 (Lawrence 2011) has been documented.

The incidence of GEP-NETs can be estimated at maximally 3.5 per 100,000 inhabitants in the European population.

### 2.1.3. Biologic features

Carcinoid tumours represent the largest group of GEP-NETs (about two thirds). A long-standing classification system divides carcinoids into foregut, midgut and hindgut tumours, based on the embryonic origin of the tumours. Foregut primaries are located in the lung, thymus, stomach, duodenum, and pancreas; the midgut with primary tumours in the ileum, caecum and proximal colon; and the hindgut with the primaries in the distal colon and rectum. Note that some of these locations (e.g., lung and thymus) are outside the definition of GEP-NET (but not carcinoid), so the classification systems contribute to some confusion[1].

A more recent WHO classification system has been developed which is considered more clinically relevant. The current World Health Organization (WHO) classification specifies four subtypes

[1] Rindi G, Kloppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, Erikssson B, Falchetti A, Falconi M, Komminoth P, K, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B, participants AOFCC, S) ENTS(NET (2006). TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 449(4):395-401

(irrespective of site of origin) under two main categories (well differentiated and poorly differentiated) and is therefore relevant for all neuroendocrine tumour types:

Neuroendocrine neoplasm (well differentiated)

- grade 1 (<3% Ki67 index)
- grade 2 (3%-20% Ki67 index)

Neuroendocrine carcinoma (poorly differentiated)

- grade 3, small cell carcinoma (>20% Ki67 index)
- grade 3, large neuroendocrine carcinoma (>20% Ki67 index)

**Table 1: Histopathology of Neuroendocrine tumours[2, 3]**

| Histological Classification | Well Differentiated (Low Grade, G1) | Moderately Differentiated (Intermediate Grade, G2) | Poorly Differentiated (High Grade, G3) |
|---|---|---|---|
| Appearance | Monomorphic population of small, round cells | * | Cellular pleomorphism |
| Prognosis | Prolonged survival | Intermediate | Poor |
| Mitotic Rate | <2 | 2–20 | >20 |
| Ki-67 Index+ | <3% | 3–20% | >20% |
| Necrosis | Absent | * | Present |

*Not well defined in the medical literature.

+ Ki-67 index applies only to WHO and European Neuroendocrine Tumor Society (ENETS) classification of gastroenteropancreatic NET.

Somatostatin receptors are members of the 7-segment G-protein coupled receptor family and there are 5 known receptor subtypes. The sst2 receptor is frequently overexpressed in neuroendocrine tumours, and is central to the mode of action of a number pharmaceutical agents including somatostatin agonists for control of symptoms in GEP-NET patients, and somatostatin analogues used as targeted delivery vehicles for radionuclides useful for diagnostic imaging or therapy.

## 2.1.4. Clinical presentation, diagnosis and stage/prognosis

GEP-NETs may also be divided into functioning and non-functioning tumours. Functioning tumours clinically present with symptoms related to overproduction of biogenic amines and peptide hormones. The majority of GEP-NETs do not secrete sufficient levels of biologically active substances to induce symptoms and are therefore classified as non-functioning and consequently often present fairly late with symptoms of mass effects, or distant metastases.

[2] Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas.* 2010;39:707-712.
[3] Strosberg JR, Nasir A, Hodul P, Kvols L. Biology and treatment of metastatic gastrointestinal neuroendocrine tumors. Gastrointest Cancer Res. 2008;2:113-125.

## 2.1.5. Management

Therapeutic options

GEP-NET patients with early stage disease are often asymptomatic or present with poorly defined symptoms. Consequently, at the time of confirmed diagnosis, a significant percentage of GEP-NET patients have hepatic metastasis. Typically, the clinical management involves a multi-modal approach including surgery and other means of cytoreductive treatment, embolisation, chemo-embolisation, radiotherapy and medical treatment with chemotherapy, interferons and somatostatin analogues.

In the case of inoperable disease, neither chemotherapy nor external beam radiation therapy are considered effective. Consequently, there are few treatment options, if any, with significant efficacy for patients with advanced disease. Most of the medicinal products approved in the target indication have limited application because they are only approved for use in sub-populations of GEP-NET patients.

Like for other GEP-NETs, for patients with metastasized or locally advanced, inoperable neuroendocrine tumours of the midgut, treatment options are currently limited. Octreotide LAR (Sandostatin LAR®) is authorised in the indication "*treatment of patients with advanced neuroendocrine tumours of the midgut or of unknown primary origin where non-midgut sites of origin have been excluded*".

Somatostatin analogues like octreotide or lanreotide should be preferentially used as first-line therapy in advanced intestinal NEN (midgut) according to current recommendations of the ENETS[4] and other medical scientific societies (ESMO[5], Joint IAEA, EANM and SNMMI practical guidance[6]). These recommendations are mainly based on the PROMID trial. As also stated in the SmPC for Sandostatin LAR, in this trial, treatment naïve patients with histologically confirmed, locally inoperable or metastatic well-differentiated, functionally active or inactive neuroendocrine tumours with primary tumour located in the midgut (or unknown origin believed to be of midgut origin if a primary within the pancreas, chest, or elsewhere was excluded) were randomised to receive Sandostatin LAR 30 mg every 4 weeks (n=42) or placebo (n=43) for 18 months, or until tumour progression or death. In the conservative ITT (cITT) analysis population in which 3 patients were censored at randomization, 26 and 40 progressions or tumour-related deaths were observed in the Sandostatin LAR and placebo groups, respectively (HR=0.34; 95% CI 0.20 to 0.59; p=0.000072). Median time to tumour progression was 14.3 months (95% CI 11.0 to 28.8 months) in the Sandostatin LAR group and 6.0 months (95% CI 3.7 to 9.4 months) in the placebo group. According to a publication of the PROMID results by Rinke et al.[1], median OS could not be estimated in the Octreotide LAR group and the estimation of 73.3 months in the placebo group is not robust because of the low number of deaths. Of note, after progression most patients received a treatment with somatostatin analogue which further biases the OS results for the placebo group.

In the 2016 ENETS GL, it is discussed that even among patients with advanced loco-regional disease or distant metastasis, there could be patients with non-functional, low grade (G1) tumours with low tumour burden and stable disease which should not directly be medically treated and "watch and wait" could rather be an option in such patients. According to the ENETS guideline, in such patients, i.e. with non-functional tumours (if of moderate grade (G2) and/or high tumour burden, progressive or symptomatic) and in patients with carcinoid syndromes, Somatostatin analogues are recommended as first-line treatment.

[4] M. Pavel et al.; ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site; Neuroendocrinology 2016;103:172–185

[5] K. Öberg et al.; Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up; Annals of Oncology 23 (Supplement 7): vii124–vii130, 2012

[6] JJ Zaknun et al.; The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours; Eur J Nucl Med Mol Imaging, 2013

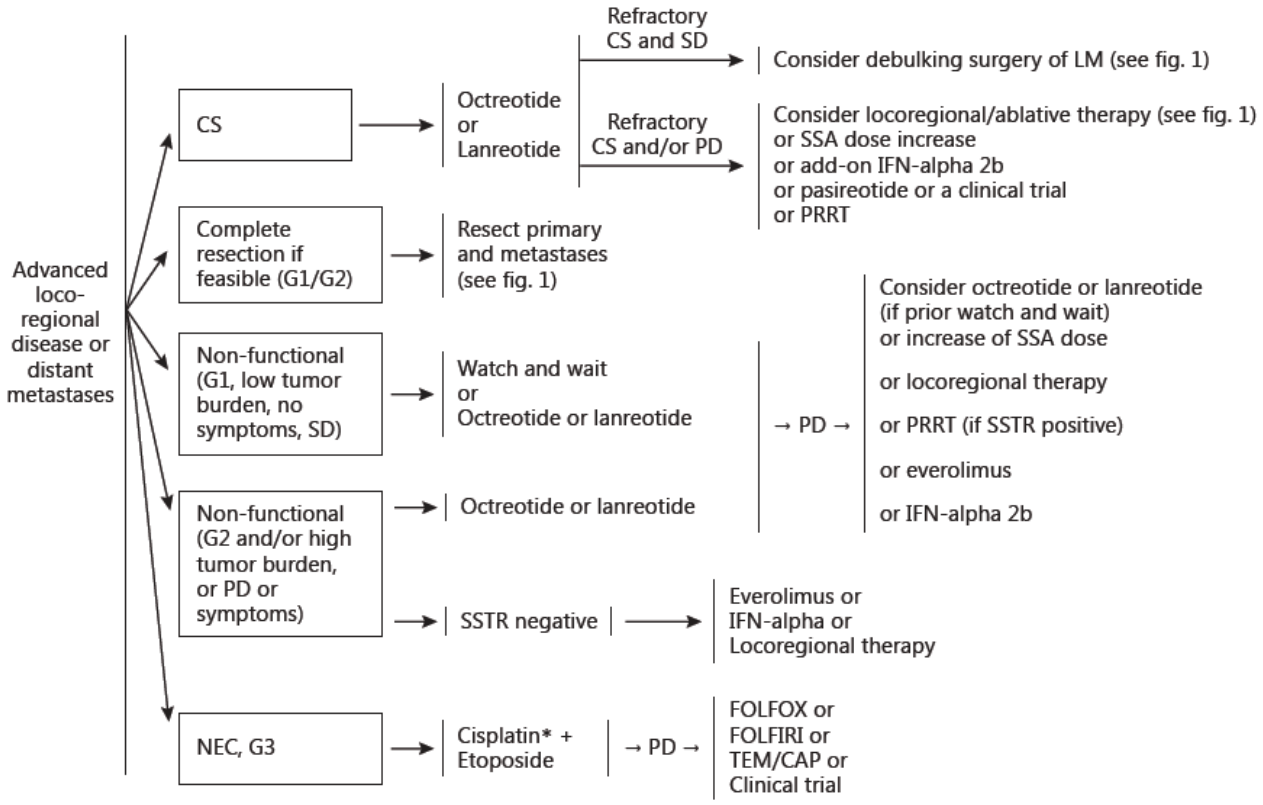



**Figure 1: ENETS therapeutic algorithm for the management of intestinal (midgut) NEN with advanced locoregional disease and/or distant metastases**

CS = Carcinoid syndrome; LM = liver metastasis; PD = progressive disease; SD = stable disease; TEM/CAP = temozolomide/capecitabine. * Cisplatin may be replaced by carboplatin

*Source: M. Pavel et al.; ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site; Neuroendocrinology 2016;103:172–185*

**Table 2: Systemic treatment available in GEP-NETs**

| Active substance | Brand Name | MAH | Type of product | Indication | Registration in the MSs |
|---|---|---|---|---|---|
| Streptozotocin | Zanosar® | KEOCYT | Chemo-therapeutic drug | Treatment of metastatic islet cell carcinoma | France |
| Everolimus | Afinitor® | Novartis Europharm Limited | Targeted therapy (mTOR inhibitor) | Treatment of unresectable or metastatic, well or moderately differentiated pNET in adults with progressive disease. | EU |
| Sunitinib | Sutent® | Pfizer Ltd | Targeted therapy (RTK inhibitor) | Treatment of unresectable or metastatic, well differentiated pNETs with disease progression in adults. | EU |
| Octreotide acetate (long-acting) | Sandostatin® LAR® and associated names (10 mg, 20 mg and 30 mg powder and solvent for suspension for injection) | Novartis | Somatostatin analogue | Treatment of patients with symptoms associated with functional GEP-NET e.g. carcinoid tumours with features of the carcinoid syndrome.<br><br>Treatment of patients with advanced GEP-NET of the midgut or of unknown primary origin where non-midgut sites of origin have been excluded. | Most of EU MSs (SmPC harmonised during referral in 2014) |
| Octreotide acetate (short-acting) | Sandostatin® 0.05 mg/1 ml; 0.1 mg/1 ml; 0.5 mg/1 ml; 0.2 mg/ml; ampoules, solution for injection (s.c.) or concentrate for solution for infusion (i.v. infusion) | Novartis | Somatostatin analogue | Relief of symptoms associated with functional GEP-NET, e.g. carcinoid tumours with features of the carcinoid syndrome. Not an anti-tumour therapy and is not curative in these patients. | Most of EU MSs (SmPC harmonised during referral in 2014) |
| Lanreotide acetate (long-acting) | Somatuline Depot Injection /Somatuline Autogel (60 mg, 90 mg and 120 mg) | Ipsen Pharma | Somatostatin analogue | The treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) GEP-NETs of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease.<br><br>The treatment of clinical symptoms, namely flushing and diarrhoea, associated with GEP-NET (carcinoid, VIPomas, gastrinomas, glucagonomas, insulinomas), which cannot be treated by surgery. | Most of EU MSs (SmPC not harmonised – detected differences highlighted in grey) |

| Active substance | Brand Name | MAH | Type of product | Indication | Registration in the MSs |
|---|---|---|---|---|---|
| Lanreotide acetate (short-acting) | Somatuline LA (30 mg) | Ipsen Pharma | Somatostatin analog | Relief of clinical symptoms, e.g., flushing and diarrhoea, associated GEP-NET (carcinoid, VIPomas, gastrinomas, glucagonomas, insulinomas) tumours, which cannot be treated by surgery. | Most of EU MSs (SmPC not harmonised detected differences highlighted in grey) |
| Meta-Iodo[131I]benzylguanidine sulphate | Meta-Iodobenzylguanidine-131I (MIBG-131I) for therapeutic use, solution for injection | Polatom or others | Radiopharma-ceutical | Treatment of GEP-NETs. | Most of EU MSs |
| Interferon alfa-2b | Intron® | Merck Sharp & Dohme Limited | Interferon | Treatment of carcinoid tumours with lymph node or liver metastases and with "carcinoid syndrome" | EU |

A brief description on efficacy data found for potential comparators in the treatment of pancreatic NETs is provided below:

- Sunitinib is authorised for the indication "*treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults"*. As stated in the current SmPC, a pivotal phase 3, multi-centre, international, randomized, double-blind placebo-controlled study of single-agent sunitinib was conducted in patients with unresectable pNET (SUTENT). These patients were required to have documented progression, based on RECIST, within the prior 12 months and were randomized (1:1) to receive either 37.5 mg sunitinib once daily without a scheduled rest period (n = 86) or placebo (n = 85). Use of somatostatin analogues was allowed in the study. Forty-nine percent of sunitinib patients had non-functioning tumours versus 52% of placebo patients and 92% patients in both arms had liver metastases. The median investigator-assessed PFS was 11.4 months (95%CI: 7.1-19.8) for the sunitinib arm compared to 5.5 months (95%CI: 3.6-6.0) for the placebo arm [hazard ratio: 0.418 (95% CI: 0.263, 0.662), p-value = 0.0001]. A blinded independent central review of scans was performed and showed similar results (12.6 vs. 5.8 months). Median OS observed after 5 years follow-up in an unblinded extension study (which was biased by crossed over to open-label sunitinib following disease progression or after unblinding) was 38.6 months (95%CI : 25.6-56.4) in the sunitinib group versus 29.1 months (95%CI : 16.4-36.8) in the placebo group, (HR 0.730; 95% CI: 0.504, 1.0507; p=0.0940).
- Afinitor is, beside others, authorised for the treatment of "*unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease"*. The pNET indication is based on the results of the RADIANT-3 study, a phase III, multicentre, randomised, double-blind study of Afinitor plus best supportive care (BSC) versus placebo plus BSC in patients with advanced pNET. As stated in the SmPC, patients with well- and moderately-differentiated advanced pNET whose disease had progressed within the prior 12 months were included and treatment with somatostatin analogues was allowed as part of BSC. Median progression-free-survival (PFS) based upon investigator radiological review was 11.0 months (95%CI : 8.4-13.9) in the everolimus + BSC group versus 4.6 months (95%CI : 3.1-5.4) in the placebo + BSC group, (HR 0.35; 95% CI: 0.27, 0.45; p<0.0001). Median OS, which was biased by crossed over to open-label Afinitor following disease progression or after unblinding was 44.02 months (95%CI: 35.6-51.8) in the

everolimus + BSC group versus 37.7 months (95%CI: 29.1-45.8) in the placebo + BSC group, (HR 0.35; 95% CI: 0.27, 0.45; p<0.0001).

Based on the results of the RADIANT-4 study, Afinitor was recently approved for the treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease. In the RADIANT-4 trial, a total of 302 patients were randomised in a 2:1 ratio to receive either everolimus (10 mg daily) (n=205) or placebo (n=97). Median progression-free-survival (PFS) based upon independent radiological review was 11.0 months (95%CI: 9.2-13.3) in the everolimus + BSC group versus 3.9 months (95%CI: 3.6-7.4) in the placebo arm. The pre-planned OS interim analysis after 101 deaths (out of 191 required for final analysis) and 33 months follow-up favoured the everolimus arm; however, no statistically significant difference in OS was noted (HR= 0.73 [95% CI: 0.48 to 1.11; p=0.071]).

- Somatuline Autogel is also authorised for treatment of pNETs, the indication states: "*The treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease".* Details of the CLARINET trial are reported in the SmPC. This phase III, 96-week, fixed duration, randomized, double-blind, multi-centre, placebo-controlled trial of Somatuline Autogel was conducted in patients with gastroenteropancreatic neuroendocrine tumours to assess the antiproliferative effect of lanreotide. Patients were randomized 1:1 to receive either Somatuline Autogel 120 mg every 28 days (n=101) or placebo (n=103). According to the main publication of the study results by Caplin et al in 2014, almost all patients had stable disease at baseline. Median progression-free-survival (PFS) based upon independent centrally-reviewed radiological assessment was not reached but estimated to be ≥22 months (95%CI: not estimated) in the lanreotide-depot group versus 18 months (95%CI: 12-24) in the placebo + BSC group, (HR 0.47; 95% CI: 0.304, 0.729; p=0.0002).

The ENETS 2016 treatment algorithm for pancreatic NETs is cited below:

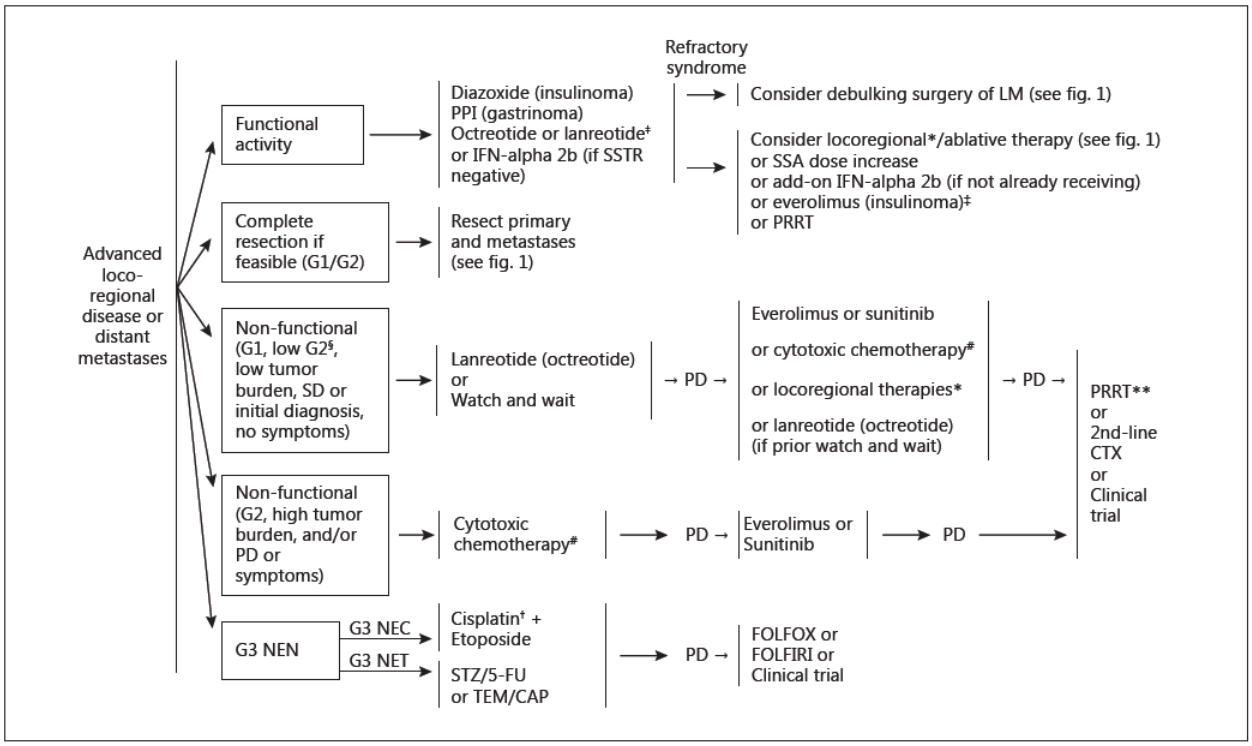


**Figure 2: ENETS therapeutic algorithm for the management of pancreatic NEN with advanced locoregional disease and/or distant metastases.**

§ Ki-67 <5–10%; * locoregional therapies are contraindicated after Whipple procedure; # recommended chemotherapy includes STZ/5-FU or STZ/doxorubicin; TEM/CAP is an alternative chemotherapy regimen if STZ-based chemotherapy is not available; * * if SSTR imaging is positive; ‡ patients should be closely monitored for paradoxical reaction (increasing hypoglycemia); † cisplatin may be replaced by carboplatin; G3 NET is coined for tumours with Ki-67 >20% but well- or moderately differentiated morphology.

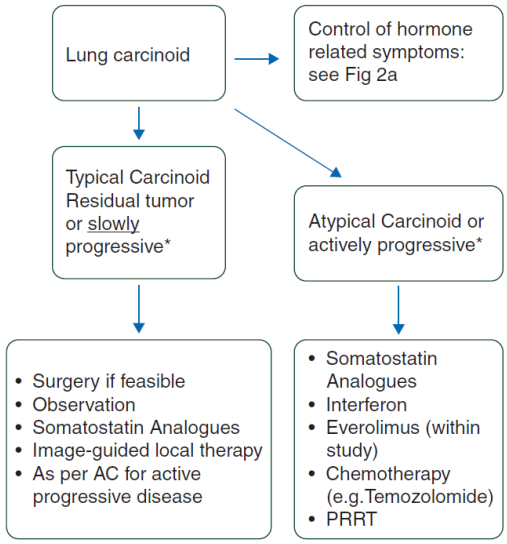
The term 'or' indicates that the use of the other options at further progression should be considered, e.g. patients with G1 or low-grade G2 NET and/ or low tumour burden who received everolimus may be treated with standard cytotoxic chemotherapy upon progression before unapproved drugs, second-line chemotherapy or a clinical trial is considered.

5-FU = 5-Fluorouracil; CS = carcinoid syndrome; CTX = chemotherapy; LM = liver metastasis; PD = progressive disease; SD = stable disease; TEM/CAP = temozolomide/capecitabine.

*Source: M. Pavel et al.; ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site; Neuroendocrinology 2016;103:172–185*

As seen in the treatment logarithm above and comparable to GI NETs, according to the ENETS, at initial diagnosis, watch and wait could be an option in patients with non-functional pNETs (G1, low G2), low tumour burden and no symptoms.

According to the current ENETS guideline on bronchial NETs[7], there are several significant parameters that differ from GI NETs which need to be highlighted. Mentioned differences include but are not limited to: a higher diversity of hormone-related symptoms, a bronchial-specific carcinoid syndrome that may exist even in patients free of liver metastases, low number of patients with distant metastases at diagnosis, higher prevalence of bone, cutaneous and brain metastases, and lower frequency of MEN1 syndrome. According to the ENETS guideline, current treatment recommendations for bronchial NETs differentiated between typical and atypical lung carcinoids:




Progression is defined according to RECIST criteria PRRT: peptide radiolabeled receptor radiotherapy

**Figure 3**: **ENETS 2015 recommendations for the control of hormone-related symptoms and tumour growth**

[7] ME Caplin et al.; Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids; Annals of Oncology 26: 1604–1620, 2015

*Source: ME Caplin et al.; Pulmonary neuroendocrine (carcinoid) tumours: European Neuroendocrine Tumour Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids; Annals of Oncology 26: 1604–1620, 2015*

As illustrated in the figure above, in typical carcinoids (in case of residual tumours or slowly progressive disease), one of the treatment options in some patients might be "watch and wait".

Therapeutic options in nuclear medicine Peptide Receptor Radionuclide Therapy

The biological basis for peptide receptor targeted radionuclide therapy (PRRT) is the receptor-mediated internalization and intracellular retention of radiolabelled somatostatin analogues. For neuroendocrine tumours, the sst2 receptor is regarded to be the most important subtype, as the receptor density is higher on tumour than on non-tumour tissue, and because sst2 receptors internalize into cells after ligand (agonist or analogue) binding. Consequently, radioactivity delivered by the radiolabelled peptide is captured in the target cell after binding to the sst2 receptor.

The first application for peptide receptor targeted radionuclide therapy (PRRT) of somatostatin receptor positive tumours involved the investigational use of $^{111}$In-pentetreotide (Octreoscan®). $^{111}$In decays by electron capture, and emits gamma rays and Auger electrons which can destroy cells after internalisation.

## *About the product*

The mechanism of action of 177Lu-Oxodotreotide is through the combination of site-specific uptake (receptor specific binding) mediated by the peptide portion of the molecule, and the (tumour) cell killing properties of the radionuclide chelated to the DOTA portion of the molecule.

$^{177}$Lu-Oxodotreotide (Lutathera), is a $^{177}$Lu-labelled somatostatin tumour-targeted peptide receptor radionuclide therapy (PRRT) agent for the treatment of patients with somatostatin receptor positive, gastroenteropancreatic neuroendocrine tumours (GEP-NETs). Lutathera being a radiolabelled somatostatin analogue has a high affinity for somatostatin subtype 2 (sst2) receptors. Oxodotreotide is comprised of the somatostatin peptide analogue Octreotate, coupled to the metal-ion chelating moiety DOTA radiolabelled with the beta-emitting radionuclide, Lutetium-177 ($^{177}$Lu). Lutetium-177 ($^{177}$Lu) is a $\beta^-$ emitting radionuclide with a maximum penetration range in tissue of 2.2 mm (mean penetration range of 0.67 mm), which is sufficient to kill targeted tumour cells with a limited effect on neighbouring normal cells.

## *Type of Application and Aspects on Development*

The applicant applied for the following indication:

- Lutathera is a radiopharmaceutical product indicated for the treatment of unresectable or metastatic, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) including foregut, midgut and hindgut in adults.

The agreed indication is as follows:

- Lutathera is a indicated for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP NETs) in adults.

Lutathera should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings (see section 6.6) and after evaluation of the patient by a qualified physician.

*Posology*

Before starting treatment with Lutathera, somatostatin receptor imaging (scintigraphy or positron emission tomography [PET]) must confirm the overexpression of these receptors in the tumour tissue with the tumour uptake at least as high as normal liver uptake (tumour uptake score ≥ 2).

The recommended treatment regimen in adults consists of 4 infusions of 7,400 MBq each. The recommended interval between each administration is 8 weeks which could be extended up to 16 weeks in case of dose modifying toxicity (DMT) (see Table 5 of the SmPC).

For renal protection purpose, a 4-hour infusion of an intravenous amino acid solution must be started 30 minutes prior to start of lutetium ($^{177}$Lu) oxodotreotide infusion and maintained for at least 3 hours after administration**.**

Treatment monitoring

Before each administration and during the treatment, biological tests are required to re-assess the patient's condition and adapt the therapeutic protocol if necessary (dose, infusion interval, number of infusions).

The minimum laboratory tests needed before each infusion are:

- Liver function (alanine aminotransferase [ALAT], aspartate aminotransferase [ASAT], albumin, bilirubin)
- Kidney function (creatinine and creatinine clearance)
- Haematology (Haemoglobin [Hb], white blood count, platelet count)

These tests should be performed at least once within 2 to 4 weeks prior to administration and shortly before the administration. It is also recommended to perform these tests every 4 weeks for at least 3 months after the last infusion of Lutathera and every 6 months thereof, in order to be able to detect possible delayed adverse reactions (see section 4.8). Dosing may need to be modified based on the tests results.

For information on the method of administration, please see SmPC section 4.2.

For information of the preparation of the radiopharmaceutical, please see SmPC section 12.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as a solution for infusion. One ml of solution contains 370 MBq of lutetium ($^{177}$Lu) oxodotreotide at the date and time of calibration as active substance.

The total amount of radioactivity per single dose vial is 7,400 MBq at the date and time of infusion. Given the fixed volumetric activity of 370 MBq/ml at the date and time of calibration, the volume of the solution is adjusted between 20.5 ml and 25.0 ml in order to provide the required amount of radioactivity at the date and time of infusion.

Lutetium ($^{177}$Lu) has a half-life of 6.647 days. Lutetium ($^{177}$Lu) decays by β-emission to stable Hafnium ($^{177}$Hf) with the most abundant β- (79.3%) having a maximum energy of 0.497 MeV. The average beta energy is approximately 0.13 MeV. Low gamma energy is also emitted, for instance at 113 keV (6.2%) and 208 keV (11%).

Other ingredients are: acetic acid, sodium acetate, gentisic acid, ascorbic acid, pentetic acid, sodium chloride, sodium hydroxide, and water for injections.

The product is available in clear colourless type I glass vial, closed with a bromobutyl rubber stopper and aluminium seal as described in section 6.5 of the SmPC.

## 2.2.2. Active Substance

The active ingredient in Lutathera is lutetium ($^{177}$Lu) oxodotreotide, a chemical entity containing the radionuclide $^{177}$Lu, a gamma-ray and beta-ray emitting radionuclide.

The manufacture of the active substance involves a chemical precursor oxodotreotide (DOTA-TATE) and a radioactive precursor, $^{177}$Lutetium chloride.

In line with the Guideline on Radiopharmaceuticals, a separate module 3.2.S is presented for the non-radioactive chemical precursor. The ASMF procedure is used to provide the quality information for the chemical precursor.

Two suppliers of the radioactive precursor, $^{177}$Lutetium chloride, are proposed. A complete module 3.2.S is provided for each supplier.

A separate module 3.2.S for the active substance has also been submitted. Due to its radioactive nature, the active substance is not isolated. The synthesis of the active substance and its formulation into the finished product are part of an automated continuous process which does not allow isolation and testing of the pure active substance.

**Non-radioactive chemical precursor**

***General information***

The chemical name of oxodotreotide (also called DOTA-TATE) is 2,2',2''-(10-(2-((*R*)-1-((4*R*,7*S*,10*S*,13*R*,16*S*,19*R*)-13-((1*H*-indol-3-yl)methyl)-10-(4-aminobutyl)-4-((1*S*,2*R*)-1-carboxy-2-hydroxypropylcarbamoyl)-16-(4-hydroxybenzyl)-7-((*R*)-1-hydroxyethyl)-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentaazacycloicosan-9-ylamino)-1-oxo-3-phenylpropan-2-ylamino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid corresponding to the molecular formula $C_{65}H_{90}N_{14}O_{19}S_2$ x $C_2HF_3O_2$.It has a relative molecular weight of 1,435.6 g/mol and the following structure:

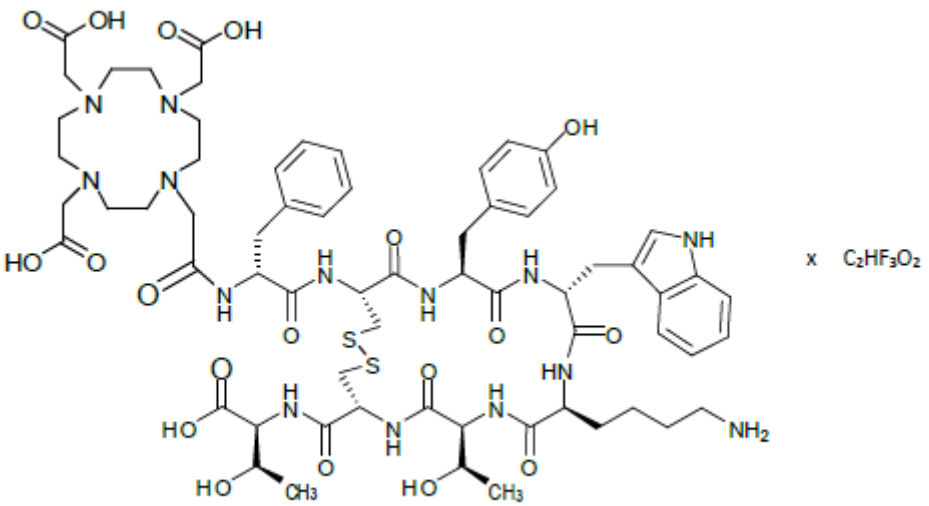


**Figure 4: Structure of oxodotreotide**

Oxodotreotide (TFA salt) is a peptide. The molecule is cyclised through a disulfide bridge between the SH groups of the cysteines. The counter ion of the molecule is trifluoroacetic acid (TFA).

The structure of oxodotreotide was confirmed by performing suitable tests and they have been adequately described.

Oxodotreotide is a white to off white powder freely soluble in water. It is not hygroscopic.

The precursor exhibits stereoisomerism due to the presence of ten chiral centres. Enantiomeric purity is controlled routinely by GC-MS (Ph. Eur.) in the specifications. Polymorphism is not considered relevant since it is dissolved prior to incorporation into the finished product.

***Manufacture, characterisation and process controls***

Detailed information on the manufacture of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Oxodotreotide is manufactured by one manufacturer.

Oxodotreotide is synthesized in seven main steps: solid phase peptide synthesis including DOTA ligand coupling and acetylation, cleavage, precipitation, isolation and freeze drying, purification 1 (linear peptide), cyclisation, disulfide bridge formation, purification 2 (cyclised peptide), lyophilisation of the bulk material, and bulk aliquotation, using well defined starting materials with acceptable specification.

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

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

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

***Specification***

The active substance specification includes tests for appearance (visual), identification (MS-MS sequencing, molecular mass (MS), identity (IR), amino acid analysis (GC), enantiomeric purity (GC-MS), peptide content by amino acid analysis (GC), net peptide content (GC), assay (RP-HPLC), purity (RP-HPLC), impurities (RP-HPLC), residual solvents (GC), counter ion content (ion chromatography, GC), water content (GC), bacterial endotoxins (Ph. Eur.), and microbial contamination (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. A justification for specific impurities was presented and it is in accordance to the guideline on genotoxic impurities. The generic justification for any other potential genotoxic impurity based on the exposure is according to the ICH M7 and it was considered satisfactory.

The analytical methods used have been adequately described appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis data from 4 commercial batches of the precursor were provided. The results are within the specifications and consistent from batch to batch.

***Stability***

To evaluate the stability of the bulk after liquid aliquotation, stability studies were carried out on 4 batches stored in borosilicate glass vials for up 24 months under long term conditions (-20 °C ± 5 °C). A 12 month accelerated stability study of aliquots at 5 °C ± 3 °C was also performed on one batch. Data was also collected from 1 batch stored in glass vials for up to 14 days at 25 ºC / 60% RH. Bulk aliquots were stored in upright and inverted positions. The following parameters were tested: appearance, mass spectrometry, counter ion content, water content, net peptide content, peptide purity, impurities, bacterial endotoxins, and microbial contamination.

The stability data showed that no significant changes were detected under long term conditions. Under accelerated conditions, the aliquoted chemical precursor is stable in all types of tested containers for 14 days, and it is stable under storage conditions at 5 °C ± 3 °C up to 12 months.

Stability data from 1 bulk production scale batch of the precursor from the proposed manufacturer stored in polypropylene cryovials for 36 months under long term conditions (-20 °C ± 5 °C) and 4 bulk production scale batches from the proposed manufacturer stored in PETG bottles, borosilicate glass vials and polypropylene cryovials for up to 14 days under accelerated conditions (25 °C ± 2 °C) according to the ICH guidelines were provided. The following parameters were tested: peptide purity and impurities.

No significant changes in the quality of the bulk chemical precursor were detected under the conditions investigated.

Photostability testing following the ICH guideline Q1B was performed on one batch. Based on the results of the study, the peptide purity of the chemical precursor decreased after overexposure to light, indicating that it is photolabile.

A stress test study using acidic, basic, oxidizing and oxidizing/basic solvents was performed on one batch. Results of the study showed that the chemical precursor remained stable in solution under strong acidic conditions, but is instable under all other investigated conditions.

The stability results indicate that the precursor (bulk or bulk aliquots) manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months stored at -20 ºC ± -5 ºC in the proposed containers. The results of the accelerated studies show there is no issue should short term temperature excursions occur during shipping.

**Radioactive chemical precursor $^{177}$Lutetium chloride**

***General information***

The chemical name of the radioactive chemical precursor is lutetium ($^{177}$Lu) chloride corresponding to the molecular formula $^{177}LuCl_3$.It has a relative molecular of 283.258 g/mol and the following structure:

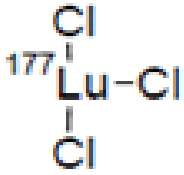



**Figure 5: Structure of lutetium (177Lu) chloride**

The chemical characterisation or elucidation of the structure is not necessary as it is a salt of lutetium, a chemical element.

Lutetium chloride is a colourless or white monoclinic crystal soluble in water and has a non-chiral molecular structure. Polymorphism has not been observed.

The radioactive material for the active substance is the salt $^{177}LuCl_3$. It is presented as no-carrier-added solution with advantages to handling the solution and decreasing the effect of radiolysis, although the latter is not to be expected in a salt solution.

Lutetium ($^{177}$Lu) is a radiopharmaceutical precursor solution. It is not isolated during the manufacturing process. The lutetium ($^{177}$Lu) manufacturing process involves dissolving irradiated lutetium nitrate in dilute hydrochloric acid to afford an intermediate bulk solution. The general properties of the bulk solution directly relate to the (further diluted) lutetium ($^{177}$Lu) chloride in hydrochloric acid solution (0.05N).

The relevant decay scheme for $^{177}$Lu and $^{177m}$Lu is presented in Figure 4.

Both nuclides are produced during the bombardment of enriched $^{176}$Lu (defined as starting material):

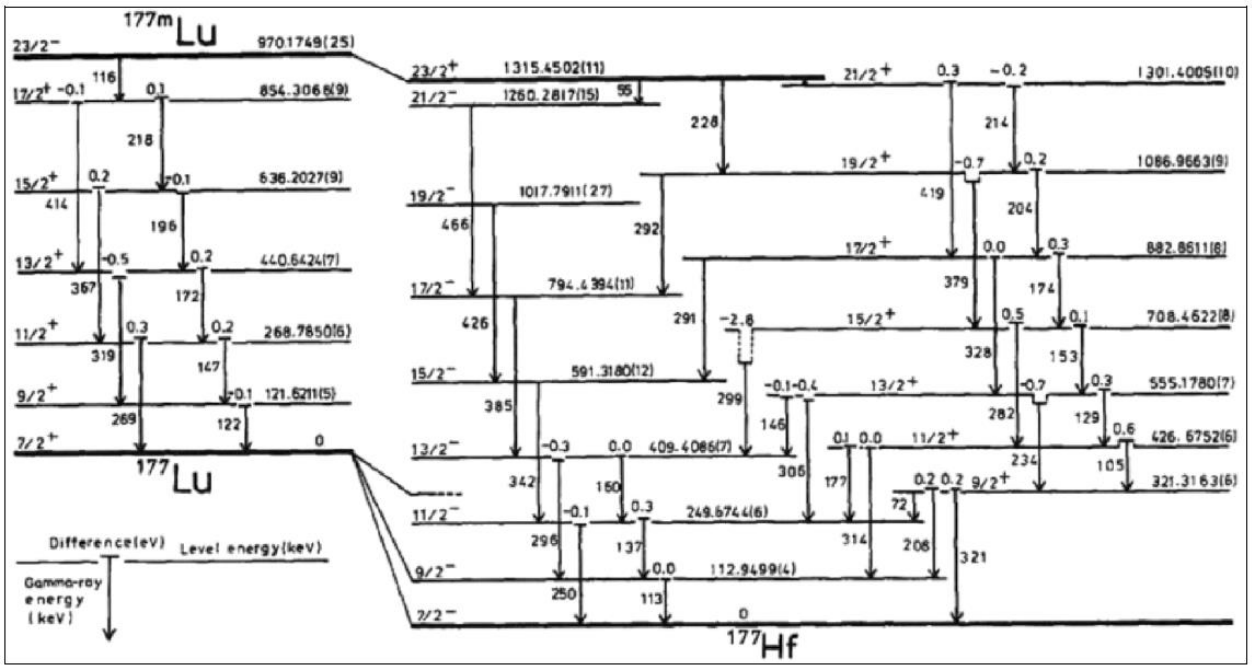



**Figure 6: Decay scheme of 177mLu and 177Lu. Shown are the level energies, spins, and level differences that created the released gamma energies**

The maximum beta energy for the decay of $^{177}$Lu to $^{177}$Hf is 0,497 MeV. The average beta energy is approximately 0,13 MeV. $^{177}$Lu also emits several gamma rays useful for imaging.

***Manufacture, characterisation and process controls***

$^{177}LuCl_3$ is manufactured by two manufacturers.

$^{177}LuCl_3$ is synthesized in 8 main steps: control of starting material, preparation of the stock solution, preparation of the $^{176}Lu\ (NO_3)_3$ target, irradiation of the target, dissolving of $^{177}Lu\ (NO_3)_3$ targets in 0.05M HCl, formulation and dispending, sterilization, and packaging using commercially available well defined starting materials with acceptable specifications.

Being a sterile medicinal product, each batch is subject to a sterility test according to Ph. Eur. The testing is performed after appropriate decay of the radioactivity. Such late sterility testing, however, is commonly applied to radiopharmaceuticals.

The active substance is packaged in type I glass vials which comply with the Ph. Eur. requirements.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The $^{177}$Lutetium chloride radiopharmaceutical precursor formulation process is based on the dissolution of neutron bombarded lutetium nitrate targets with 0.05N hydrochloric acid. The lutetium nitrate-sourced radiochemical has been manufactured for more than five years prior to process validation using this basic formulation methodology.

Process validation was performed in accordance with the approved protocols..

***Specification***

The active substance specification for one of the manufacturers includes for the following components:

Specification for the bulk solution of active substance $^{177}$Lu: radioactive concentration bulk solution (dose calibrator measurement).

Pre-release tests: appearance (visual), labelling (visual), volumetric activity (activity measurement), specific activity (activity measurement), pH (potentiometric), chloride test (silver nitrate test), radionuclidic identification (identity $^{177}$Lu) (gamma spectroscopy, Ge detector), radionuclidic impurities (gamma spectroscopy, Ge detector), radionuclidic purity (gamma spectroscopy, Ge detector), radiochemical identification (identity iconic form $^{177}$Lu) (TLC-Plastic Scintillator/NMT detector), radiochemical purity (TLC-Plastic Scintillator/NMT detector), endotoxins (LAL).

Post-release test: sterility (direct incubation in FTM and TSB).

Test performed on annual base: metallic impurities (ICP-AES-MS).

The active substance specification for the other manufacturer includes tests for: radionuclide identification (Ph. Eur.), radiochemical purity (ITLC-SG), radionuclidic purity (HPGe gamma spectroscopy detector), pH, specific activity (ICP-OES), chemical purity (ICP-OES), endotoxin (Ph. Eur.), and sterility (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data (20 and 24 commercial scale batches respectively) of the precursor were provided. The results were within the specifications and consistent from batch to batch.

***Stability***

Following the Guideline on Radiopharmaceuticals, the general stability guidelines are not applicable due to the very high radioactive nature of this solution. Any stress testing is not feasible.

Stability data on 3 commercial scale batches of active substance from each of the proposed manufacturers stored in the intended commercial packages for 14 days under long term conditions at 30 °C were provided.

Considering stability data is available throughout the proposed shelf-life, accelerated stability data is not applicable.

The following parameters were tested*:* appearance, pH, chloride test, radiochemical identity, radiochemical purity, radionuclidic identity, radionuclidic impurities, endotoxins, sterility and metallic impurities. The analytical methods used were the same as for release and were stability indicating.

Considering the lead container in which the product is stored, photostability testing is not applicable.

Furthermore, inverted vials were also included in the stability study.

No formal statistical analysis is performed because the data show very little degradation and little variability with the exception of the $^{177m}$Lu impurity. Test results also show no significant difference between vials stored inverted and vials stored upright.

The stability results indicate that the radioactive chemical precursor manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 11 days in the proposed container.

**Active substance (lutetium ($^{177}$Lu) oxodotreotide)**

***General information***

The chemical name of lutetium ($^{177}$Lu) oxodotreotide is lutetium($^{177}$Lu)-*N*-[(4,7,10-tricarboxymethyl-1,4,7,10-tetraazacyclododec-1-yl)acetyl]-*D*-phenylalanyl-*L*-cysteinyl-*L*-tyrosyl-*D*-tryptophanyl-*L*-lysyl-*L*-threoninyl-*L*-cysteinyl-*L*-threonine-cyclic(2-7)disulfide (synonyms: DOTATATE or DOTA$^{0}$-Tyr$^{3}$-Octreotate) corresponding to the molecular formula $C_{65}H_{87}N_{14}O_{19}S_2{}^{177}Lu$. It has a relative molecular mass of 1609.6 g/mol and the following structure:

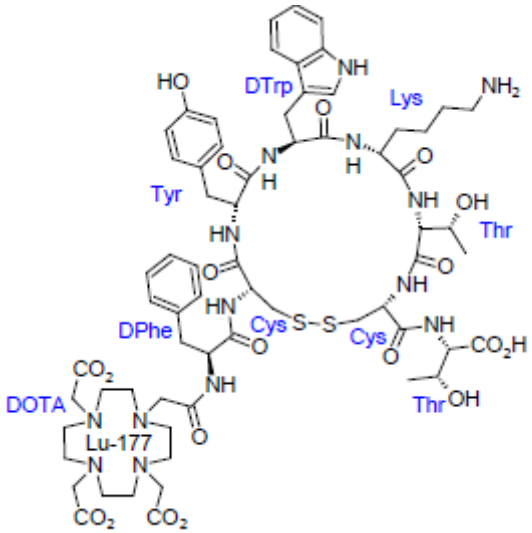



**Figure 7: Structure of lutetium (177Lu) oxodotreotide**

The structure of the active substance has been elucidated by suitable tests and have been adequately described.

The radioactive active substance is produced as an aqueous concentrated solution (mother solution). Due to its radioactive nature, the active substance is not isolated. The synthesis of the active substance and its formulation into the finished product are part of an automated continuous process which does not allow isolation and testing of the pure active substance. For this reason, all the general properties described in this section refer to the mother solution.

The active substance is an aqueous yellow solution free of particles.

The synthesis of the active substance is a complexation reaction between $^{177}$Lu chloride and oxodotreotide. This reaction does not have any impact on the chiral centres of the peptide. The characterization of the chiral centres is performed by the supplier of the chemical precursor oxodotreotide. Polymorphism is not considered relevant since it is dissolved prior to incorporation into the finished product.

***Manufacture, characterisation and process controls***

The active substance is manufactured at three manufacturing sites. The radioactive active substance is produced as a sterile, aqueous concentrated solution. The active substance synthesis steps are performed in the self-contained closed-system synthesis module which is automated and remotely

controlled by GMP compliant software with automated monitoring and recording of the process parameters. The synthesis of the active substance and its formulation into the finished product are part of an automated continuous process which does not allow for isolation and testing of the active substance due to its radioactive decay. Therefore, validation of the manufacturing process of the pure active substance is not possible.

The active substance process consists of combining the carrier ligand and the radiolabelled precursor followed by sterile filtration.

The active substance is produced in a shielded closed-system; manufacturing, purification and formulation process of the active substance are part of a continuous process. The decay of the radionuclide does not allow enough time for any interruption.

At the end of synthesis, the active substance is collected in a sterile recovery type I vial in the dispensing isolator.

***Specification***

The synthesis of the active substance and its formulation into the finished product are part of an automated continuous process which does not allow for isolation and testing of the pure active substance. Therefore, specifications, associated analytical procedures, relevant method validation, batch analyses data and justification of specifications are available only for the finished product.

***Stability***

As already mentioned, the active substance is not isolated as it is part of an automated continuous process which does not allow for isolation and testing of the pure active substance. Therefore, stability is only available for the finished product.

## 2.2.3. Finished Medicinal Product

***Description of the product and Pharmaceutical development***

The finished product is a sterile ready-to-use solution for infusion with a volumetric activity of 370 MBq/ml at reference date and time (calibration time (Tc)).

Calibration time (Tc) corresponds to the End of Production (EOP = $t_0$).

The finished product is presented as a single dose vial, containing suitable amount of solution that allows delivery of 7.4 GBq of radioactivity at injection time.

Considering the variable injection time and constant decay of the radionuclide, the filling volume needed for an activity of 7.4 GBq at injection time is calculated and can range from 20.5 and 25.0 ml.

The composition of the finished product:

- The active substance is lutetium ($^{177}$Lu) oxodotreotide.
- The other ingredients are: acetic acid, sodium acetate, gentisic acid, ascorbic acid, pentetic acid, sodium chloride, sodium hydroxide, water for injections.

Natural decay of the radionuclide is a property of any radiopharmaceutical, whether it is produced industrially or in-house. Consequently, specific activity, total radioactivity, and radio concentration (volumetric activity) of the finished product change over time.

The applicant developed the finished product as a ready to use radiopharmaceutical solution for infusion. Overall manufacturing of the finished product involves an automated continuous process, where the synthesis of the active substance is also part of this process.

The applicant started the finished product development from an already existing formulation initially produced in the hospital radiopharmacies. The formulation was the subject of an investigator sponsored phase I/II clinical study and the data of the formulation of this study are used by the applicant to support the present marketing authorization application. The applicant continued to optimize the formulation by implementing some minor changes and designing the quality specifications and its manufacturing process, that consistently deliver the intended performance of the product. The final formulation has been used by the applicant in a Phase III clinical study which successfully demonstrated the performance of the finished product.

The selection of the excipients was directly impacted by the already existing composition of the finished product used in phase I/II clinical trials. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards or in-house specifications. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The primary packaging is clear colourless type I glass vial, closed with a rubber stopper and aluminium seal. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

***Manufacture of the product and process controls***

The finished product is manufactured at three manufacturing sites. The manufacturing process of the finished product starts with recovery of the active substance from the synthesis cell into the dispensing isolator, where it is diluted to reach the pre-defined radioactive concentration, sterilized and dispens*ed* into primary packaging.

The manufacturing process of the active substance and finished product has been satisfactory validated to demonstrate that a robust and reproducible manufacturing process has been set up successfully in the facilities and that the manufacturing procedures described allow production and dispensing of the finished product according to the release and shelf-life specification.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible mannerThe in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

***Product specification***

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (RP-γβ-HPLC), pH (Ph. Eur.), assay of gentisic acid (RP-UV-HPLC), assay of ascorbic acid (RP-UV-HPLC), chemical purity (RP-UV-HPLC), radiochemical purity (RP-γβ-HPLC, ITLC), specific activity (dose calibrator/HPLC), filter integrity test (Ph. Eur.), microbiological tests (Ph. Eur.), volumetric activity (dose calibrator/balance), radionuclidic purity (γ-spectroscopy) identification (Ph. Eur.).

In addition, specifications have been defined for the finished product to be performed after injection (microbiological test, Ph. Eur.).

Free [$^{177}$Lu] Lutetium ions may cause serve radiotoxic effects which is the reason why DTPA is used to chelate them in order to facilitate renal excretion. Considering the important role of DTPA for the safe use of Lutathera, i.e. minimising radiotoxic effects of free [$^{177}$Lu] Lutetium ions, the DTPA content should be specified and the content tested during finished product release. Therefore, the CHMP requested that the determination of the DTPA content (sum of complexed and free DTPA) be added to the release specification of the finished product and it was agreed by the applicant. Because a test on DTPA was not intended by the applicant in the initial finished product specification the further development and implementation of the analytical method will be necessary in a two-step action. The CHMP recommended that:

As immediate action:

• The developed analytical method will be validated in all sites by end of November 2017 using the existing analytical equipment available on each site.

• DTPA test will be implemented and performed on each batch starting from January 2018.

• The test will be performed post-injection within 7 days after the end of the manufacturing process.

In a second step, as intermediate action, the use of an additional HPLC system by his manufacturers for the determination of DTPA:

• All manufacturing sites will purchase new HPLC analytical equipment and validate the DTPA content test method on the new specific equipment by the end of January 2018.

• DTPA test will be implemented and performed on each batch starting from March 2018.

• This test will be performed as release test and result will be available before dose injection.The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis results were provided for 250 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

***Stability of the product***

Stability data from 18 commercial scale batches of finished product stored for up 72 hours under long term conditions (25 ± 2 ºC) and under refrigerated conditions (5 ± 3) ºC and for up to 48 hours under accelerated conditions (32 ± 2 ºC) were provided. Stability studies for radiopharmaceuticals do not need to be in compliance with ICH guidelines. The batches of medicinal product were identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

A variable temperature stability (12 h at 32 °C and 60 h at 25 °C) study was carried out on 3 batches (one per synthesis module/batch size). The objective of this study was to evaluate the effect of a higher than normal temperature for a short period of time. The design of this study was performed based on the results of the stability studies at 25 °C and 32 °C. Vials were stored at 32 ± 2 °C for 12 h and then moved to 25 °C ± 2°C for 60 hours. Test results after 72 hrs were compared with those at release.

The container closure stability was evaluated on 3 batches (one per synthesis module/batch size). The objective of this study was to evaluate the interaction between the finished product and the rubber

stopper to guarantee an adequate closure of the vial. In this study, a vial was stored in upright and inverted position for 72 h at 25 ± 2 °C. Results were compared with those at release.

Samples were tested for the same specifications as for releaseThe analytical procedures used are stability indicating.

Independent of synthesis module, batch size and vial filling volume, the finished product did not show any significant changes whilst stored in any of the storage conditions tested for 72 hours.

Based on available stability data, the proposed shelf-life of 72 hours from the date and time of calibration stored below 25 °C in the original package to protect from ionizing radiation (lead shielding) as stated in the SmPC (section 6.3) is acceptable.

***Adventitious agents***

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

## 2.2.4. 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.

## 2.2.5. 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.

## 2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- Because a test on DTPA was not intended by the applicant in the initial finished product specification the further development and implementation of the analytical method will be necessary in a two-step action.

As immediate action:

• The developed analytical method will be validated in all sites by end of November 2017 using the existing analytical equipment available on each site.

• DTPA test will be implemented and performed on each batch starting from January 2018.

• The test will be performed post-injection within 7 days after the end of the manufacturing process.

In a second step, as intermediate action, the use of an additional HPLC system by his manufacturers for the determination of DTPA:

• All manufacturing sites will purchase new HPLC analytical equipment and validate the DTPA content test method on the new specific equipment by the end of January 2018.

• DTPA test will be implemented and performed on each batch starting from March 2018.

• This test will be performed as release test and result will be available before dose injection.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

Pharmacokinetic (PK) properties of octreotide were investigated in nonclinical PK studies in mice and cynomolgus monkeys after single iv administration. Multiple dose pharmacokinetic/toxicokinetic (TK) data were obtained during the course of repeat-dose toxicity studies in mice, rats, and cynomolgus monkeys.

Safety pharmacology studies were performed using the non-radioactive compound $^{175}$Lu-Oxodotreotide. The studies were designed according to the ICH S7A Guideline and were in compliance with GLP regulations. All pivotal nonclinical toxicity studies were conducted consistent with International Conference on Harmonisation (ICH) Nonclinical Testing Guidelines and in compliance with the Good Laboratory Practice (GLP) Regulations. Single and repeat dose toxicity studies were performed in rats and dogs.

### 2.3.2. Pharmacology

#### *Primary pharmacodynamic studies*

**In vitro pharmacology**

***Somatostatin Receptor Affinity Studies – In Vitro Studies; Human Tumour Tissue***

There are five known human somatostatin receptor subtypes, hsst1-hsst5. According to cited literature (Table 3) octreotide compounds have been shown to bind to hsst2, hsst3, and hsst5 receptors. Based on the affinity profiles, octreotate derivatives have shown to have a higher selectivity for hsst2.

**Table 3: Affinity profiles of human $sst_{1-5}$ receptors for somastatin analogues[8] (Reubi et al., 2000)**

| | $IC_{50}$ (nM) | | | | |
|---|---|---|---|---|---|
| **Peptide** | **$hsst_1$** | **$hsst_2$** | **$hsst_3$** | **$hsst_4$** | **$hsst_5$** |
| Somatostatin-28 | 5.2 ± 0.3 | 2.7 ± 0.3 | 7.7 ± 0.9 | 5.6 ± 0.4 | 4.0 ± 0.3 |
| Octreotide | >10000 | 2.0 ± 0.7 | 187 ± 55 | >1000 | 22 ± 6 |
| $DTPA^0$-Octreotide | >10000 | 12 ± 2 | 376 ± 84 | >1000 | 299 ± 50 |
| In-$DTPA^0$-Octreotide | >10000 | 22 ± 3.6 | 182 ± 13 | >1000 | 237 ± 52 |
| $DOTA^0$-$Tyr^3$-Octreotide | >10000 | 14 ± 2.6 | 880 ± 324 | >1000 | 393 ± 84 |
| Y-$DOTA^0$-$Tyr^3$-Octreotide | >10000 | 11 ± 1.7 | 389 ± 135 | >10000 | 114 ± 29 |
| $DTPA^0$-$Tyr^3$-Octreotate | >10000 | 3.9 ± 1 | >10000 | >1000 | >1000 |
| In-$DTPA^0$-$Tyr^3$-Octreotate | >10000 | 1.3 ± 0.2 | >10000 | 433 ± 16 | >1000 |
| $DOTA^0$-$Tyr^3$-Octreotate | >10000 | 1.5 ± 0.4 | >1000 | 453 ± 176 | 547 ± 160 |
| Y-$DOTA^0$-$Tyr^3$-Octreotate | >10000 | 1.6 ± 0.4 | >1000 | 523 ± 239 | 187 ± 50 |

[8] Reubi JC, Schär JC, Waser B, Wenger S, Heppeler A, Schmitt JS, Mäcke HR (2000). Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med 27(3):273-282

***Cell Internalization – In Vitro Studies; Rodent Tumour Tissue***

Internalisation and retention of $^{177}$Lu-Oxodotreotide into sst2 positive AR42J cancer cells has been shown to occur in vitro (Study No. 20000420). In this assay 27.2% of the initial, decay-corrected, $^{177}$Lu activity was internalised, a value quite similar to the positive control, $^{111}$In-DTPA$^{0}$-Tyr$^{3}$-Octreotate (21.1%).

***In Vitro Efficacy in Rat Tumour Cell Lines***

Anti-tumour activity in rat tumour cell lines is derived from the literature. Capello et al.[9] compared tumour activity of a number of somatostatin analogues using an *in vitro* cell survival assay with the rat pancreatic cell line CA20948. Literature cited data shown that cold Oxodotreotide, $^{177}$Lu-Oxodotreotide, and $^{177}$Lu-DOTA were compared for tumour activity in an in vitro cell survival assay. The unlabelled peptide was shown to have almost no effect on cell survival, whereas $^{177}$Lu-DOTA (chelate without peptide), showed measurable cell killing activity, but was much less active than $^{177}$Lu-Oxodotreotide. $^{177}$Lu-Oxodotreotide was compared to $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotide and $^{177}$Lu-Oxodotreotide was found to be significantly more potent at all concentrations tested (at equivalent specific activities), and of the two, only $^{177}$Lu-Oxodotreotide was able to reach a 100% cell kill rate.

***In vivo studies $^{177}$Lu-Oxodotreotide***

CA20948 tumour-bearing male Lewis rats were administered a single intravenous dose of either 1.0, 2.5, or 5.0 mCi/rat (4 to 20 mCi/kg) of $^{177}$Lu-Oxodotreotide or received multiple intravenous doses of $^{177}$Lu-Oxodotreotide at 30-day intervals (3 repeat doses of 2.5 or 5 mCi/dose). Tumour regression was observed in both cases.

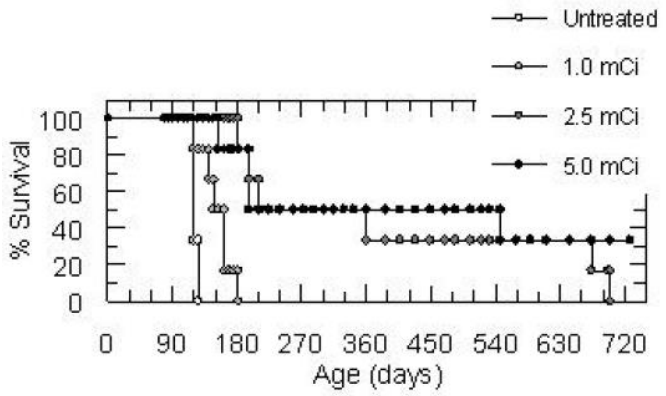



**Figure 8: Survival of tumour implanted Lewis rats treated with single doses of $^{177}$Lu-Oxodotreotide**

[9] Capello, A., Krenning, E. P., Breeman, W. A., Bernard, B. F., Konijnenberg, M. W. and de Jong, M. (2003). Tyr3-octreotide and Tyr3-octreotate radiolabeled with 177Lu or 90Y: peptide receptor radionuclide therapy results in vitro. Cancer Biother. Radiopharm. 18, 761-768.

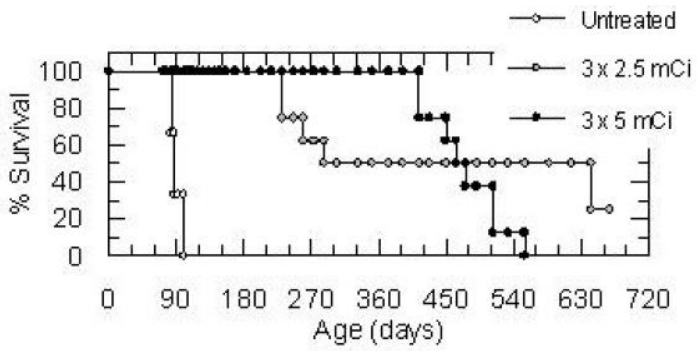



**Figure 9: Survival of tumour implanted Lewis rats treated with multiple doses of $^{177}$Lu-Oxodotreotide**

In another study by De Jong (de Jong et al., 2001), efficacy and biodistribution of Oxodotreotide radiolabelled with 177Lu, 88Y, or 111In was investigated in male Lewis rats implanted with the somatostatin receptor positive rat pancreatic tumour line, CA20948. 177Lu-Oxodotreotide showed a higher uptake in the tumour and sstr2-positive organs (adrenals, pituitary and pancreas) when compared to the 88Y- and 111In -labelled peptide. A 100% complete response was achieved in the groups of rats bearing small (≤ 1 cm2) CA20948 tumours after 2 doses of 7.5 mCi (277.5 MBq) or after a single dose of 15 mCi (555 MBq) 177Lu-Oxodotreotide. A complete response rate of 75% was achieved after a single administration of 7.5 mCi (see Figure 3 A). In rats bearing larger (> 1 cm2) tumours, 40% and 50% complete response rates were achieved in the groups that received 1 or 2 x 7.5 mCi injections of 177Lu-Oxodotreotide, respectively. A 60% complete response rate was achieved after 2 repeated injections (see Figure 3 B).

It is important to notice that in this study a 40% reduction of 177Lu-Oxodotreotide kidney uptake was observed when animals received a co-injection of 400 mg/kg D-Lysine.

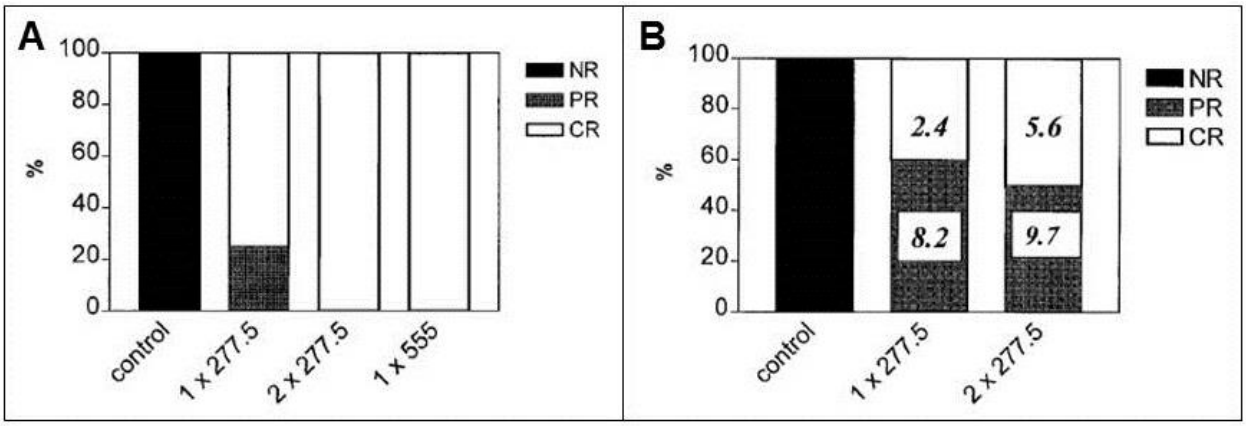



**Figure 10: Tumour size responses found in groups of rats (n ≥ 6) bearing the CA20948 tumours smaller (A) or larger (B) than 1 cm2 after the indicated doses in MBq of 177Lu-Oxodotreotide. NR, no response; PR, partial response; CR, complete response. In B, the figures in the bars indicate the size of tumours in cm2 at the beginning of therapy**

## *Secondary pharmacodynamic studies*

The applicant did not submit secondary pharmacodynamic studies (see non-clinical discussion).

## *Safety pharmacology programme*

### *$^{175}$Lu-Oxodotreotide: Behavioural Irwin tests and effect on body temperature following single intravenous administration in the rat*

In a GLP-complaint study, the effects of $^{175}$Lu-Oxodotreotide on neurobehavioral parameters and body temperature were assessed in male Wistar rats (8/group) for up to 24 hours after a single IV bolus administration at 0, 1250, 5000 and 20000 µg/kg (which is claimed to be approximately 40, 170 and 700-fold the intended human dose, scaled to rat based on the body surface area).

$^{175}$Lu-Oxodotreotide had no effect either on behaviour or on body temperature at any dose level. The NOEL of $^{175}$Lutetium-Oxodotreotide was considered to be ≥20000 µg/kg.

### Evaluation of effects of $^{175}$Lu-Oxodotreotide on hERG current in stably transfected HEK-293 cells

The effects of $^{175}$Lu-Oxodotreotide on hERG tail current were evaluated in HEK-293 cells stably transfected with hERG-1 cDNA, using the patch clamp technique (Study 20100184PEHPPB). The vehicle alone (acetate buffer) induced a decrease of 12% in the hERG tail current while $^{175}$Lu-Oxodotreotide at $10^{-4}$ M induced a decrease of 19% ± 2% in hERG tail current.

### Evaluation of $^{175}$Lu-Oxodotreotide effect on blood pressure, heart rate, electrocardiogram and body temperature after single intravenous administration to conscious dog

The effect of $^{175}$Lu-Oxodotreotide on blood pressure (mean, systolic and diastolic), heart rate, body temperature and electrocardiogram (duration of PR, PQ, QT and QRS) was assessed in conscious beagle dogs via a single IV administration.

Telemetric measurements were performed on animals dosed at 0, 80 µg/kg, 250 µg/kg and 800 µg/kg of $^{175}$Lu-Oxodotreotide. No effects on body temperature or cardiac conduction times (i.e. PR and PQ interval duration, QRS complex duration and QT interval duration as well as QTc interval duration and QT shift using the probabilistic method) were observed at any dose tested. No arrhythmias attributable to $^{175}$Lu-Oxodotreotide was noted at any dose level.

Following administration via a slow infusion (1.2 mL/min) at 80 and 40 µg/kg, $^{175}$Lu-Oxodotreotide induced an increase in mean, systolic and diastolic arterial pressure up to 6 h (at 80 µg/kg) or up to 4 h (at 40 µg/kg). A reflex-mediated decrease in heart rate was also noted during this time. No arrhythmias and no effects on body temperature or cardiac conduction times (i.e. PR and PQ interval duration, QRS complex duration and QT interval duration as well as QTc interval duration and QT shift using the probabilistic method) were observed at any dose tested.

In the second part of the study, beagle dogs (3/sex) were given a single IV bolus dose of $^{175}$Lu-Oxodotreotide at 80 µg/kg for the determination of toxicokinetics and clinical signs. Two male animals (males) displayed diarrhoea between 3 and 4 hours post-dosing. No other clinical signs were observed.

### *Evaluation of $^{175}$Lu-Oxodotreotide effect on respiration in the unrestrained conscious rat following single intravenous administration*

In a GLP compliant study, male Wistar (CHS DM) rats (8/group) were given single IV bolus doses of 0, 1250, 5000 and 20000 µg/kg $^{175}$Lu-Oxodotreotide. The positive control was carbamylcholine chloride at 0.3 mg/kg, administered by the IV route over 15 minutes via an infusion pump.

At 20000 µg/kg, a respiratory stimulant effect was observed on most of the evaluated respiratory parameters up to 30 or 60 minutes post-dosing: respiratory rate, peak inspiratory and peak expiratory flows and minute volume were all increased; inspiration and expiration times were decreased. At 5000 µg/kg, less pronounced effects were recorded on peak inspiratory flow (increased) and inspiration time (decreased). No changes, compared to the controls, were observed in animals of the low dose group (1250 µg/kg). Therefore, the NOEL on respiratory parameters in conscious rats corresponded to 1250 µg/kg when administered by the intravenous route.

### *Pharmacodynamic drug interactions*

The applicant did not submit studies on pharmacodynamic drug interactions.

## 2.3.3. Pharmacokinetics

#### *Biodistribution of $^{177}$Lu-Oxodotreotide in normal rats*

Following i.v. injection in normal Sprague Dawley rats, $^{177}$Lu-Oxodotreotide was excreted rapidly through the renal system (Study 19990213). A biphasic decrease of radioactivity in blood was observed: the first, steeper phase had a half-life of approximately 15 min. In the slowly decreasing phase, the half-life was approximately 10.5 h (only a very small fraction of the injected dose was still present). The only organs with notable uptake and longer retention compared to other organs were the kidney (the compound is almost exclusively eliminated by the renal system) and the pancreas (which is known in rats to have high levels of sst2 receptors). The % Injected Dose/ gram (ID/g) of tissue at 5 min after injection was 3.8 in the kidneys and 7.8 in the pancreas (and 1.6 % in the kidneys and 10.6 % in the pancreas at 4 h after injection):

**Table 4: Biodistribution of $^{177}$Lu radiolabelled Oxodotreotide in normal Sprague Dawley rats**

| Tissue | %ID/gram of organ | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 5 min | 10 min | 15 min | 30 min | 45 min | 60 min | 120 min | 240 min |
| Blood | 0.729 ± 0.028 | 0.593 ± 0.091 | 0.485 ± 0.053 | 0.190 ± 0.023 | 0.126 ± 0.018 | 0.057 ± 0.010 | 0.015 ± 0.002 | 0.003 ± 0.001 |
| Kidneys | 3.771 ± 0.874 | 3.838 ± 1.091 | 2.889 ± 0.283 | 1.986 ± 0.150 | 1.955 ± 0.049 | 1.670 ± 0.248 | 1.742 ± 0.133 | 1.619 ± 0.161 |
| Skeletal muscle | 0.142 ± 0.021 | 0.117 ± 0.015 | 0.098 ± 0.009 | 0.048 ± 0.04 | 0.031 ± 0.003 | 0.017 ± 0.004 | 0.008 ± 0.002 | 0.005 ± 0.001 |
| Pancreas | 7.847 ± 1.234 | 9.265 ± 1.245 | 7.426 ± 0.347 | 12.054 ± 0.896 | 11.901 ± 3.009 | 12.901 ± 0.718 | 12.679 ± 0.836 | 10.611 ± 0.778 |

#### *Biodistribution of $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotide and $^{177}$Lu-Oxodotreotide in tumour bearing rats*

Octreotate and Octreotide derivatives have been studied in rodent tumour models (CA20948 and AR42J tumour implanted Lewis rats) using both $^{111}$In and $^{177}$Lu labelled compounds, derivatised with either DOTA or DTPA linked chelates. The biodistribution properties of $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotide (1, 4 and 24 h study) and $^{177}$Lu-Oxodotreotide (1, 4, 12, 24, 48, 72 h study) were assessed in CA20948 tumour-bearing Lewis rats (studies 19980909 and 20000701) and are shown in Table 5 .

**Table 5: Biodistribution of $^{177}$Lu radiolabelled DOTA$^{0}$-Tyr$^{3}$-Octreotide and Oxodotreotide in CA20948 tumour-bearing Lewis rats**

| Tissue | $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotide (%ID/gram of organ ± SE) | | $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotate (%ID/gram of organ ± SE) | |
|---|---|---|---|---|
| | 4 hours | 24 hours | 4 hours | 24 hours |
| Blood | 0.004 ± 0.001 | 0.001 ± 0.000 | 0.005 ± 0.000 | 0.002 ± 0.000 |
| Kidneys | 2.324 ± 0.049 | 2.186 ± 0.115 | 1.424 ± 0.062 | 1.293 ± 0.063 |
| Liver | 0.065 ± 0.005 | 0.054 ± 0.007 | 0.039 ± 0.001 | 0.032 ± 0.001 |
| Pancreas | 2.400 ± 0.152 | 1.463 ± 0.072 | 7.591 ± 0.010 | 2.779 ± 0.136 |
| Tumour | 1.307 ± 0.063 | 0.862 ± 0.050 | 4.367 ± 0.090 | 2.521 ± 0.052 |
| Urine* | NA | 78.620 ± 1.721 | NA | 66.608 ± 0.445 |
| Faeces* | NA | 7.217 ± 1.689 | NA | 6.225 ± 0.758 |
| Total Excreted | NA | 85.837 ± 2.113 | NA | 72.833 ± 1.007 |

**Total amount excreted over 24 h. NA: Not applicable.*

***Excretion***

CA20948 pancreatic tumour bearing Lewis rats were given $^{177}$Lu-Oxodotreotide (40 microCi [1.3 MBq]; 0.67 mg) by the intravenous route showed a similar biodistribution profile to the one observed in humans, except for the high uptake in pancreas and relatively high uptake in the bone. Total cumulative activity excreted in the urine by 24 h was about 62.5 % (20.91% + 15.46% + 26.13%), and the total cumulative fecal excretion was about 6.1% (0.004% + 0.004% + 6.12%), indicating a fast elimination.

**Table 6: Excretion of $^{177}$Lu-Oxodotreotide in CA20948 tumor-bearing Lewis rats (n=5) at selected timepoints (Lewis et al., 2001).**

| Sample | % Injected Dose ± SD | | | | |
|---|---|---|---|---|---|
| | 1 hour | 1-3 hours | 3-24 hours | 24-48 hours | 1-72 hours |
| Urine | 20.91 ± 18.56 | 15.46 ± 19.15 | 26.13 ± 17.95 | 2.54 ± 0.64 | 68.74 ± 2.37 |
| Feces | 0.004 ± 0.012 | 0.004 | 6.12 ± 1.79 | 3.17 ± 0.94 | 15.84 ± 3.11 |

The only tissues besides tumour that have total uptake greater than 1% are the kidney, pancreas and bone, which account for most of the remaining uptake.

***$^{177}$Lu-Radiolablled DOTA-peptides and Free $^{177}$Lu***

Radiolabelling of Oxodotreotide with $^{177}$Lu is very efficient but there is the potential that a small amount of free $^{177}Lu^{3+}$ could be present at the end of the labelling reaction and has the potential to accumulate in bone with resultant undesirable irradiation of bone marrow. However, $^{177}$Lu complexed with DTPA is reported to be stable in serum *in vitro* and to have rapid renal excretion in vivo and therefore chelation of free $Lu^{3+}$ with DTPA would prevent accumulation in bone and facilitate renal elimination. Breeman et al.[10] showed free $^{177}LuCl_3$ had high skeletal uptake in the femur (primarily in the epiphyseal pates), with signi ficant retention in other tissues. At 24 h total whole body retention was found to be 80% of the ID, whereas it was 19% of the ID for $^{177}$Lu-Oxodotreotide. A small uptake of $^{177}$Lu-Oxodotreotide into bone (0.28% ID/g at 24 h could be blocked (to 0.02% ID/g at 24 h) by

[10] Breeman, W. A., van der Wansem, K., Bernard, B. F., van Gameren, A., Erion, J. L., Visser, T. J., Krenning, E. P. and de Jong, M. (2003). The addition of DTPA to [177Lu-DOTA0,Tyr3]octreotate prior to administration reduces rat skeleton uptake of radioactivity. European journal of nuclear medicine and molecular imaging 30, 312-315.

pre-treatment with cold Octreotide) and was therefore thought to be somatostatin receptor mediated. $^{177}$Lu complexed with DTPA was found to be rapidly eliminated through the kidneys with only 4% whole body retention of ID at 24 h. Additionally, free $^{177}Lu^{3+}$ added to a preparation of $^{177}$Lu-Oxodotreotide could be readily complexed to DTPA *in vitro* and excess accumulation of $^{177}$Lu in femur, blood, liver and spleen was dependant on the amount of free $^{177}Lu^{3+}$ present in the injected sample. The accumulations could be negated by the addition of DTPA to the sample before injection.

***Plasma protein binding***

The estimation of the unbound fraction of $^{175}$Lu-Oxodotreotide in rat, dog and human plasma by equilibrium dialysis method, at 300 and 1000 ng/mL were assessed in a protein binding study (Study BAN1116A27).

**Table 7: $^{175}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotide percent unbound fraction in Rat, Dog and Human plasma (Mean Percentage ± SD)**

| Test Concentration | Rat | Dog | Human |
|---|---|---|---|
| 300 ng/mL | 9.8 ± 5.4 | 5.3 ± 1.6 | 25.0 ± 3.0 |
| 1000 ng/mL | 26.8 ± 3.3 | 6.4 ± 0.6 | 9.4 ± 1.5 |

## *Metabolism*

In vitro metabolism studies have been performed with the non-radioactive $^{175}$Lu-Oxodotreotide formulation (containing $^{175}$Lu-Oxodotreotide and Oxodotreotide).

***Comparative in vitro metabolism studies of $^{175}$Lu-Oxodotreotide with freshly isolated rat, dog and human hepatocytes***

$^{175}$Lu-Oxodotreotide formulation was incubated at 1 and 10 µM with freshly isolated rat, dog and human hepatocytes for up to 4 hours at 37°C and analysed by LC-MS/MS in order to assess intrinsic clearance (1 µM) and metabolic profiling (10 µM) (Study AAA/01). Metabolite profiling analysis of the 10 µM incubation samples did not detect the presence of any predicted or expected metabolites.

***Comparative in vitro metabolism studies of $^{175}$Lu-Oxodotreotide with rat, dog and human kidney homogenate***

$^{175}$Lu-Oxodotreotide formulation was incubated at 1 and 10 µM with rat, dog and human kidney homogenate for up to 4 hours at 37°C and analysed by LC-MS/MS in order to assess intrinsic clearance (1 µM) and metabolic profiling (10 µM) (Study AAA/05).

**Table 8: Summary of metabolites identified by LC-MS in the 10 µM incubation samples of $^{175}$Lu-Oxodotreotide + Oxodotreotide in rat, dog and human kidney homogenate**

| | Metabolites | Rat | Dog | Human | Ctrl |
|---|---|---|---|---|---|
| M1 | LuDOTA-Phe-Cys-Tyr-Trp-Lys-Thr-COOH | - | √ | √ | - |
| M2 | DOTA-Phe-Cys-Tyr-Trp-Lys-Thr-COOH | - | √ | √ | - |
| M3 | Hydroxylated (LuDOTA-Phe-Cys-Tyr-Trp-Lys-Thr-Cys-COOH (no cysteine bridge)) | √ | √ | √ | - |
| M4 | Asn-Tyr-NH-$CH_2$-CH=N | √ | √ | √ | - |
| M5 | Hydroxylated (DOTA-Phe-Cys-Tyr-Trp-Lys-Thr-Cys-COOH (no cysteine bridge)) | √ | √ | √ | - |
| M6 | Asn-Tyr | √ | √ | √ | - |
| M7 | Asn-[Tyr]-Hydroxylation | √ | √ | √ | - |
| M8 | DOTA-Phe-Cys-Tyr-Trp-Lys-Thr-Cys-COOH | - | √ | - | - |
| - | DOTA$^0$-Tyr$^3$-Octreotate | - | √ | - | √ |
| - | $^{175}$Lu-DOTA$^0$-Tyr$^3$-Octreotate | - | √ | - | √ |

***Assessment of the potential for $^{175}$Lu-Oxodotreotide to inhibit human CYP450 enzymes in vitro***

The effect of $^{175}$Lu-Oxodotreotide on the activities of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 in pooled human liver microsomes was assessed at concentrations of 0, 0.001, 0.01, 0.1, 1, 3 and 10 µM (Study AAA/02). The inhibition profile of $^{175}$Lu-Oxodotreotide was assessed using both a 0 and 30 minute pre-incubation period to ascertain whether any inhibition observed was reversible or time-dependent.

Direct inhibition (0 minute pre-incubation): Less than 10% inhibition was observed with all CYP450 isoforms except CYP2C9, where the maximal inhibition was approximately 33% at 10 µM. All $IC_{50}$ values were greater than 10 µM.

Time-dependent inhibition (30 minute pre-incubation): There was no decrease in $IC_{50}$ values for all CYP450 assays tested (all remained >10 µM).

At 10 µM, an increase CYP1A2 inhibition was observed, from approximately 5% to 22% inhibition between 0 and 30 minutes pre-incubation.

***Assessment of the potential for $^{175}$Lu-Oxodotreotide to induce human hepatic CYP450 enzymes using human hepatocytes in culture***

The potential of $^{175}$Lu-Oxodotreotide to induce the major human cytochrome P450 (CYP450) enzymes involved in drug metabolism was assessed in human hepatocytes (Study AAA/03).

No cytotoxicity was observed at concentrations in the range of 7 to 700 nM. Human hepatocytes were then exposed to concentrations of 7, 70 and 700 nM to achieve the expected human plasma concentration (70 nM) with a 10-fold lower and 10-fold higher concentration. In addition, hepatocytes were also exposed to multiple doses of omeprazole, phenobarbital and rifampicin (positive controls) and then assayed for various cytochrome P450 enzyme activities (CYP1A2, CYP2B6 and CYP3A4) using CYP450-selective chemical substrates and UPLC-MS/MS as the analytical technique. qRT-PCR analysis was also used to investigate CYP450-specific mRNA levels.

## 2.3.4. Toxicology

### *Single dose toxicity*

**Table 9: Summary of single dose toxicity studies with $^{175}$Lu-Oxodotreotide**

| Study ID | Species/ Sex/Number/ Group | Dose/Route | Approx. lethal dose / observed max non-lethal dose | Major findings |
|---|---|---|---|---|
| 20100179TRP | Rats (SD) 3F/group | 1150, 4845, 20455 µg/kg i.v. | Max non-lethal dose = 20455 µg/kg | None |
| 20100181TRP | Dog (Beagle)<br><br>Phase 1:<br>Gp 1 – 2M + 2F<br>Gp 2 – 1M + 1F<br><br>Phase 2:<br>Gp 1 – 1M + 1F<br>Gp 2 – 1M + 1F | Phase 1:<br>0 (Gp 1), 400, 800, 1600 and 3200 µg/kg (Gp 2)<br><br>Phase 2:<br>6400 (Gp 1) and 10000 µg/kg (Gp 2<br><br>i.v. | Max non-lethal dose = 10000 µg/kg | Soft to liquid faeces (all doses)<br><br>Jejunum, duodenum or rectum: Spread red areas (400 - 3200 µg/kg) or dark red areas (6400 and 10000 µg/kg). |

### *Repeat dose toxicity*

**Table 10: Repeat-dose toxicity studies with $^{175}$Lu-DOTA$^{0}$-Tyr$^{3}$- Octreotate**

| Study ID | Species/Sex/ Number/Group | Dose (µg/kg)/ Route | Duration | NO(A)EL (µg/kg) | Major findings |
|---|---|---|---|---|---|
| 20100180 TRP GLP | Rat<br><br>Sprague-Dawley<br><br>M+F/10 – Main study<br><br>M+F/5 (Recovery)<br><br>M+F/6 (TK) | 0, 1250, 5000, 20000 - once every two weeks<br><br>Intravenous | 42 days<br><br>Recovery period 3 months | NOEL (proposed): 1250 | ≥1250: BW and FC ↓ (M) – minimal.<br>≥5000: Pancreatic acinar apoptosis minimal to moderate. |
| 20100182 TCP GLP | Dog<br><br>Beagle<br><br>M+F/4<br><br>M+F/2 (Recovery) | 0, 80, 500, 3200<br><br>Intravenous | 43 days<br><br>Recovery period 3 months | NOAEL (proposed): 3200 | 3200: Salivation, soft to liquid faeces and/or vocalisation – all marked severity.<br><br>≥80: Pancreatic acinar apoptosis minimal to moderate. |

### *Genotoxicity*

A total of two pivotal in vitro GLP genotoxicity studies were conducted with $^{175}$Lu-Oxodotreotide.

**Table 11: Genotoxicity studies with $^{175}$Lu-Oxodotreotide**

| Study | GLP | Species | Dose | Treatment Duration / Recovery Period | Noteworthy findings |
|---|---|---|---|---|---|
| **1 AMES test**<br>81900 | Yes | Bacteria *S.typhimurium* | Up to 902 µg/plate | 72 hours | Negative |
| **1 mammalian cell gene mutation study**<br>81910 | Yes | Mouse lymphoma L5178Y cells | 12.3–395 µg/mL + and -S9 | 3 or 24 hours | Negative |

## *Carcinogenicity*

The applicant did not submit carcinogenicity studies (see non-clinical studies).

## *Reproduction Toxicity*

The applicant did not submit reproductive and developmental toxicity studies (see non-clinical discussion).

## *Toxicokinetic data*

Sprague-Dawley rats were given $^{175}$Lu-Oxodotreotide at 0, 1250, 5000 or 20000 µg/kg, once every two weeks for 42 days (i.e four administrations in total), via the intravenous route followed by a 3-month treatment-free period to assess recovery. Results are shown in Table 12.

**Table 12: Mean Toxicokinetic parameters of $^{175}$Lu-Oxodotreotide after i.v. administration in rats at 1250, 5000 and 20000 µg/kg**

| | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| | | Group 2 | Group 3 | Group 4 | Group 2 | Group 3 | Group 4 |
| **Dose** | *ug/kg* | 1250 | 5000 | 20000 | 1250 | 5000 | 20000 |
| **DAY 1** | | | | | | | |
| $C_{max}$ | *ng/mL* | 1580.8 | 7028.6 | 27237.7 | 1359.3 | 6931.2 | 28434.8 |
| $t_{max}$ | *min* | 5 | 5 | 5 | 5 | 5 | 5 |
| $AUC_{all}$ | *ng/mL*min* | 45109.6 | 175137.1 | 588731.7 | 40170.0 | 189918.9 | 670288.5 |
| $C_{max}/D$ | *(ng/mL)/(ug/kg)* | 1.26 | 1.42 | 1.36 | 1.09 | 1.36 | 1.42 |
| $AUC_{all}/D$ | *(ng/mL*min)/(ug/kg)* | 36.1 | 35.4 | 29.4 | 32.1 | 38.1 | 33.5 |

| | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| **DAY 42** | | | | | | | |
| **$C_{max}$** | *ng/mL* | 2149.2 | 6975.0 | 26257.9 | 1863.6 | 6299.2 | 26631.7 |
| **$t_{max}$** | *min* | 5 | 5 | 5 | 5 | 5 | 5 |
| **$AUC_{all}$** | *ng/mL*min* | 59575.7 | 184100.1 | 687521.1 | 47260.2 | 164711.6 | 719279.4 |
| **$C_{max}$/D** | *(ng/mL)/(ug/kg)* | 1.72 | 1.40 | 1.31 | 1.49 | 1.26 | 1.33 |
| **$AUC_{all}$/D** | *(ng/mL*min)/(ug/kg)* | 47.7 | 36.8 | 34.4 | 37.8 | 32.9 | 36.0 |

*BLLOQ = Below the Lower Limit of Quantification (156.2 ng/mL)*

The No-Observed Effect Level (NOEL) in the repeat dose toxicity study in rats corresponds to 1250 µg/kg, which is 40 times the human dose.

$^{175}$Lu-Oxodotreotide was administered to Beagle dogs once every two weeks for 43 days (i.e. four administrations in total) at 0, 80, 500 or 3200 µg/kg via the intravenous route, followed by a 3-month treatment-free period to assess recovery.

Toxicokinetic measures showed exposure to $^{175}$Lu-Oxodotreotide ($AUC_{all}$) increased less than dose proportionally in males , but was dose proportional in females on Day 1. By Day 43, exposure was proportional to dose in males but less than dose proportional in females. No relevant accumulation was observed.

**Table 13: Toxicokinetic parameters (mean ± SD) of 175Lu-Oxodotreotide after i.v. administration in dogs at 80, 500 and 3200 µg/kg**

| | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| **Dose** | *ug/kg* | 80 | 500 | 3200 | 80 | 500 | 3200 |
| **DAY 1** | | | | | | | |
| **$C_{max}$** | *ng/mL* | 109.4 ± 6.0 | 590.3 ± 76.9 | 4245.1 ± 169.1 | 99.7 ± 6.8 | 681.1 ± 65.4 | 4340.3 ± 416.6 |
| **$t_{max}$** | *min* | 5 ± 0 | 5 ± 0 | 5 ± 0 | 5 ± 0 | 5 ± 0 | 5 ± 0 |
| **$AUC_{all}$** | *ng/mL*min* | 8026.5 ± 549.4 | 32129.1 ± 2094.0 | 253960.0 ± 19696.9 | 6346.9 ± 269.5 | 40981.3 ± 3065.9 | 240018.1 ± 14656.1 |
| **$C_{max}$/D** | *(ng/mL)/(ug/kg)* | 1.37 ± 0.08 | 1.18 ± 0.15 | 1.33 ± 0.05 | 1.25 ± 0.09 | 1.36 ± 0.13 | 1.36 ± 0.13 |
| **$AUC_{all}$/D** | *(ng/mL*min)/(ug/kg)* | 100 ± 7 | 64 ± 4 | 79 ± 6 | 79 ± 3 | 82 ± 6 | 75 ± 5 |
| **DAY 43** | | | | | | | |

| | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| **$C_{max}$** | *ng/mL* | 153.8 ± 10.5 | 798.7 ± 105.9 | 4308.6 ± 313.0 | 142.0 ± 7.6 | 648.9 ± 95.5 | 4642.9 ± 396.2 |
| **$t_{max}$** | *min* | 5 ± 0 | 9 ± 4 | 5 ± 0 | 5 ± 0 | 5 ± 0 | 5 ± 0 |
| **$AUC_{all}$** | *ng/mL*min* | 6428.1 ± 647.7 | 41714.3 ± 4043.3 | 234593.4 ± 7281.8 | 7817.2 ± 607.6 | 35323.9 ± 4243.4 | 228920.7 ± 10396.2 |
| **$C_{max}$/D** | *(ng/mL)/(ug/kg)* | 1.92 ± 0.13 | 1.60 ± 0.21 | 1.35 ± 0.10 | 1.77 ± 0.10 | 1.30 ± 0.19 | 1.45 ± 0.12 |
| **$AUC_{all}$/D** | *(ng/mL*min)/(ug/kg)* | 80 ± 8 | 84 ± 8 | 73 ± 2 | 98 ± 7 | 71 ± 8 | 72 ± 3 |

### *Local Tolerance*

The applicant did not submit specific local tolerance studies (see non-clinical discussion).

### *Other toxicity studies*

The applicant did not provide other toxicity studies (see non-clinical discussion).

## 2.3.5. Ecotoxicity/environmental risk assessment

**Table 14: Summary of main study results**

| **Substance (INN/Invented Name): Lutathera 370 MBq/mL solution for infusion** | | | |
|---|---|---|---|
| **CAS-number (if available):** | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | Schottelius et al. (2015), | -3.16 (LogP) | Potential PBT (N) |
| ***PBT-assessment*** | | | |
| **PBT-statement :** | The log P value is < 4.5 and therefore screening for PBT is not required as this does not meet the criteria for classification as a PBT compound. | | |
| ***Phase I*** | | | |
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| PEC $_{surfacewater}$ , default (e.g. prevalence, literature) | 0.00131 | µg/L | > 0.01 threshold (N) |
| Other concerns (e.g. chemical class) | None | | |
| **Outcome of Phase I :** | **The PECsw value is < 0.01 µg/L action limit and therefore a Phase II environmental fate and effect analysis is not required.** | | |
| ***Phase II Physical-chemical properties and fate*** | | | |
| **Not Applicable** | | | |

## 2.3.6. Discussion on non-clinical aspects

Pharmacology studies have shown internalisation and retention of $^{177}$Lu- Oxodotreotide in vitro. $^{177}$Lu-Oxodotreotide had a high affinity and selectivity for the sst2 receptor in the rat and in the dog animal models. The compound was specifically taken up by sstr2 expressing tumours as shown by Lewis et al.[11]. The uptake of $^{177}$Lu-Oxodotreotide lead to a significant tumour-free period in treated rats up to 5 months after single dose administration and up to 26 months after multiple dose administration of $^{177}$Lu-Oxodotreotide. Given the known biological activity targets of SSAs, no further secondary pharmacodynamics of $^{177}$Lu-Oxodotreotide are required.

Safety studies of the cold compound ($^{175}$Lu-Oxodotreotide) indicated no particular potential for the compound to cause prolongation of the cardiac action potential or increase of QT interval since no relevant effects of $^{175}$Lu-Oxodotreotide on the hERG tail current was observed. Furthermore, in beagle dogs treated with $^{175}$Lu-Oxodotreotide no effects on blood pressure, heart rate, body temperature and electrocardiogram (duration of PR, PQ, QT and QRS) after single i.v. administration of 80 up to 800 µg/kg (that is 10 to 100 fold the intended human dose, scaled to dog based on body surface area) was observed. However, $^{175}$Lu-Oxodotreotide showed to have a hypertensive effect associated with a reflex mediated bradycardia when administered intravenously, either as bolus (80, 250 and 800 µg/kg) or

[11] Lewis, J. S., Wang, M., Laforest, R., Wang, F., Erion, J. L., Bugaj, J. E., Srinivasan, A. and Anderson, C. J. (2001). Toxicity and dosimetry of (177)Lu-DOTA-Y3-octreotate in a rat model. International journal of cancer. Journal international du cancer 94, 873-877.

slow infusion (40 µg/kg and 80 µg/kg). No neurobehavioral effects or effects on body temperature were observed at any dose tested (1250, 5000 and 20000 µg/kg) after a single i.v. administration in rats. A respiratory stimulant effect was observed on several respiratory parameters (respiratory rate, peak inspiratory and peak expiratory flows, inspiration and expiration times and minute volume) at 20000 µg/kg (approximately 700-fold the intended human dose, scaled to rat based on body surface area) and some effects were also noted at 5000 µg/kg (approximately 170-fold higher than the intended human dose).

Biodistribution of $^{177}$Lu-Oxodotreotide in normal rats showed that organs with notable uptake were the kidneys and the pancreas. Tumor bearing rats showed a similar distribution pattern compared to humans with the exception of the pancreas. Since rodents have high levels of sst2 receptors as compared to humans, a significantly higher uptake of $^{177}$Lu-Oxodotreotide was observed in the rat. There is relatively low plasma protein binding of $^{175}$Lu-Oxodotreotide.

The pharmacokinetic studies showed that $^{177}$Lu-Oxodotreotide had a moderately short half-life in rats of ~10.5 hours. Tumour tissue showed high uptake and there was also notable distribution into the pancreas, a tissue known in rats to have high levels of sst2 receptors. Metabolic profiling detected the presence of five rat, eight dog and seven human metabolites. No human specific metabolites were observed. Excretion was mostly by the renal system and *in vitro* studies did not indicate any liver-dependent metabolism although there was evidence of metabolism by kidney tissue. There are no drug-drug interactions that are anticipated. The proposed levels of the chelating agent DTPA in the final drug product are acceptable.

Toxicological studies with rats have demonstrated that a single intravenous injection of up to 4,550 MBq/kg was well tolerated and no deaths were observed. When testing the cold compound (non-radioactive lutetium ($^{175}$Lu) oxodotreotide) as a single intravenous injection in rats and dogs at doses up to 20,000 µg/kg (rats) and 3,200 µg/kg (dogs), the compound was well tolerated in both species and no deaths were observed. Toxicity with four repeated administrations, once every 2 weeks, of 1,250 µg/kg of the cold compound in rats and 80 µg/kg in dogs was not observed. This medicinal product is not intended for regular or continuous administration. Renal toxicity was detected following a single 15 mCi (555 MBq) dose (~75 mCi/kg), or with two 7.5 mCi (278 MBq) of the radiolabelled product. Potential renal toxicity has been discussed in the product literature and renal protection is also addressed by the administration of an amino acid solution 30 minutes prior to administration of Lutathera, which is acceptable (SmPC section 4.2).

Mutagenicity studies and long-term carcinogenicity studies have not been carried out, which is acceptable according to the relevant guidelines (ICH Topic S1A) where carcinogenicity testing can be waived, considering the short term use, the life threatening indication, and the use of radioactively labelled product in the clinic.. Non-clinical data on the cold compound (non-radioactive lutetium ($^{175}$Lu) oxodotreotide) reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity. At the concentration used (about 10 µg/mL in total, for both free and radiolabeled forms), the peptide oxodotreotide does not exert any clinically relevant pharmacodynamic effect.

As the product acts by delivering a dose of radiation to tumour cells, genotoxicity is likely where there is internalisation of the molecule. Substantial harm to a foetus is expected from radioactivity. , however, the product has been contraindicated in established or suspected pregnancy or when pregnancy has not been excluded (SmPC section 4.3 and 4.6). Both male and female patients also have to apply contraceptive measures during treatment with $^{177}$Lu-Oxodotreotide and for 6 months afterwards (SmPC section 4.6).

No animal studies have been performed to determine the effects of lutetium (177Lu) oxodotreotide on the fertility of either gender. Ionizing radiations of lutetium (177Lu) oxodotreotide may potentially

have temporary toxic effects on female and male gonads. Genetic consultation is recommended if the patient wishes to have children after treatment. Cryopreservation of sperm can be discussed as an option to male patients before the treatment.

An environmental risk assessment has been performed to evaluate the potential environmental risk resulting from the use of Lutathera. $^{177}$Lu-Oxodotreotide's $PEC_{SURFACEWATER}$ value (0.00131 μg/L) is below the action limit of 0.01 μg/L and it is not a PBT substance as log $K_{ow}$ does not exceed 4.5. A Phase II analysis of the physical-chemical properties and fate is therefore not required. Any unused medicinal product or waste material should be disposed according to local requirements (SmPC section 6.4 and 6.6). As a result, 177Lu DOTA0 Tyr3 Octreotate is not expected to pose a risk to the environment.

### 2.3.7. Conclusion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic, and toxicological characteristics of Lutathera have been well characterised in the non-clinical aspects. The non-clinical aspects are considered to be appropriately addressed.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

### *GCP*

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

**Table 15: Information on the Erasmus MC Phase I/II clinical study**

| Study ID | Study Status, No Pts Enrolled/ Enrollment Goal | Design, Control Type | Study and Control Drugs/ Dose/ Route/ Regimen | Primary/ Secondary Objective | Duration of follow-up | Diagnosis Inclusion Criteria |
|---|---|---|---|---|---|---|
| MEC 127.545/1993/84 | 1,214 patients enrolled between January 2000 – December 2012 | Open label Phase I/II | Treatment - cumulative administered dose 29.6 GBq (800 mCi, 4 x 200 mCi) $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotate / Drug infused i.v. Treatment interval, 6 to 13 weeks. | Primary Objectives<br>- Determine the efficacy of treatment with $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotate<br>- Evaluate safety of treatment with $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotate in patients with somatostatin receptor positive tumors as measured by rate of serious adverse events and monitoring of selected laboratory evaluations.<br><br>Other Objectives<br>- Evaluate the effect of the treatment with $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotate in patients with somatostatin receptor positive tumors on Quality of Life as measured by the EORTC QLQ-C30 questionnaire.<br>- Evaluate Time To Progression, Progression-Free Survival, Disease-Specific and Overall Survival after treatment with $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotate in patients with somatostatin receptor positive GEPNETs.<br>- Analysis of PK/biodistribution and dosimetry data and correlation with toxicity | Upon conclusion of the treatment phase, patients enter the follow-up period which, extends up to the moment of documented disease progression or death. | - Safety evaluated in patients with somatostatin receptor positive tumors as measured by the rate of serious adverse events and the monitoring of selected laboratory evaluations.<br>- Efficacy evaluated in patients with somatostatin receptor positive GEPNETs who meet the inclusion criteria for GEPNET patients, as measured by tumor response rate |

**Table 16: Information on the NETTER-1 Phase III clinical study**

| Study ID | Study Status, No Pts Enrolled/ Enrollment Goal | Design, Control Type | Study and Control Drugs/ Dose/ Route/ Regimen | Primary/ Secondary Objective | Duration of follow-up | Diagnosis Inclusion Criteria |
|---|---|---|---|---|---|---|
| | The enrolment was completed on 14 January 2016, with 231 patients randomized in 41 active centers in EU and USA (27 EU sites and 14 USA sites). At the time of the cut-off date for the primary end-point analysis, 229 patients were randomized | Multicenter, stratified, open, randomized, comparator-controlled, parallel-group Phase III study | Treatment - cumulative administered dose 29.6 GBq (4 x 7.4 GBq) $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotate / Drug infused i.v. Treatment interval: 8 weeks. | **Primary objective:**<br>- To compare Progression Free Survival (PFS) after treatment with $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotate plus best supportive care (30 mg Octreotide LAR) to treatment with high dose (60 mg) Octreotide LAR in patients with inoperable, progressive (as determined by RECIST Criteria), somatostatin receptor positive, well-differentiated neuroendocrine tumors of the small bowel (midgut carcinoid tumors).<br>**Secondary objectives:**<br>- To compare the Objective Response Rate (ORR) between the two study arms;<br>- To compare the Overall Survival (OS) between the two study arms;<br>- To compare the Time to Tumor Progression (TTP) between the two study arms;<br>- To evaluate the safety and tolerability of $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotate;<br>- To evaluate the health related quality of life (QoL) as measured by the EORTC QLQ-G.I.NET21 questionnaire;<br>**Exploratory objectives:**<br>- To explore the correlation of toxicity outcomes and administered radioactivity corrected for body weight and body surface area;<br>- To explore the correlation of clinical efficacy outcomes with the levels of the biomarkers Chromogranin-A (CgA) in the serum and 5-Hydroxyindoleacetic acid (5-HIAA) in the urine;<br>- To evaluate dosimetry, pharmacokinetics (PK) and ECG in a subset of 20 patients;<br>- To explore the correlation of clinical efficacy outcomes with OctreoScan® tumor uptake score;<br>- To explore the correlation of clinical outcomes with serum levels of Alkaline Phosphatase (AP):<br>- To evaluate the Duration of Response (DoR) in the two study arms;<br>- To evaluate the Time to Second Progression (PFS2) in the two study arms | Long term follow-up: 5-years from the date of randomization of the last randomized patient. | |

## 2.4.2. Pharmacokinetics

With the purpose of confirming and further substantiating the safety, pharmacokinetic and dosimetry findings of the Erasmus MC Phase I/II Clinical study, a centrally assessed dosimetry, pharmacokinetics and ECG substudy has been conducted in a subset of 20 patients enrolled in the Phase III NETTER-1 substudy ($^{177}$Lu-Oxodotreotide treatment arm) in order to define the pharmacokinetic profile of $^{177}$Lu-Oxodotreotide.

### *Absorption*

Biodistribution and excretion of $^{177}$Lu-Oxodotreotide was also studied in 26 patients with high tumour burden (7 in Group-2 and 19 in Group-3). Group-2 patients received 3.7 GBq (100 mCi), while Group-3 patients received 7.4 GBq (200 mCi) of 177Lu-Oxodotreotide. All patients received amino acid co-infusion. The %IA of $^{177}$Lu-Oxodotreotide in the plasma after administration follows an exponential curve over time: 91% of the IA is cleared from the plasma with a half-life (Tα)of 24 min. In the subsequent phases the plasma half-lives are 4.6 h (Tβ) and 168 h (Tγ) corresponding to 7.7% and 0.29% of the IA, respectively. The combined data (from Group-2 and -3) can be fitted with an exponential curve with a correlation coefficient (R2) of 0.993.

The biodistribution of $^{177}$Lu-Oxodotreotide has been determined by a number of methods in the NETTER-1 sub-study. Using image analyses, the majority of the enrolled subjects show the typical biodistribution pattern observed in patients treated with PRRT, namely a high uptake in the tumors, as well as uptake in the spleen and the kidneys (particularly evident in the posterior views), and, to a lesser extent, in the liver. Time activity curves were also determined in the kidney, liver, spleen, rest of the body and in tumour tissues. Residence times were calculated in the organs and were highest in the liver (14.6h) and rest of the body (21h). Calculations were also made for the absorbed dose per

unit of injected activity (IA) (Gy/GBq) in the kidneys, the liver, the spleen, the urinary bladder wall, the total body and the red marrow.

The %IA of $^{177}$Lu-Oxodotreotide as measured in the total body (minus the abdominal radioactivity) in Group-3 after administration follows an exponential curve over time: in the alpha phase there is uptake in the abdomen: 20%IA with Tα=1.9 h. In the subsequent phases the abdominal clearance half-lives are 38 h (T1/2) and 134 h (Tγ)corresponding to 24% and 1.8% of the IA, respectively. The %IA of 177Lu-Oxodotreotide as measured in the abdominal region (liver, kidneys, spleen and tumour) in Group-3 after administration follows an exponential curve over time: 53% of the IA with T1/2=1.9 h and 30% IA with T1/2=150h.

The co-administration of amino acid was found to reduce the kidney absorbed dose by 47%.

## *Distribution and Dosimetry*

To calculate whole body and organ radiation dosimetry of $^{177}$Lu-Oxodotreotide and to determine the dose to critical organs (e.g., kidney and bone marrow) in the substudy, full body (planar) and 3D SPECT scans were performed on the day of the $^{177}$Lu-Oxodotreotide administration, at different time points up to 72 h (or 168 h in case one or more images were skipped or not performed at the correct time).

Biodistribution and dosimetry studies were initially performed in 3 groups of patients with increasing doses of $^{177}$Lu-Oxodotreotide: 1.85, 3.7 and 7.4 GBq. The effect of amino acid co-infusion on biodistribution were studied in 6 patients following the initial dose of 1.85 GBq. The low dose of 1.85 GBq was initially studied in patients with a low tumour burden. The percentage of infused radioactivity (%IA) of $^{177}$Lu-Oxodotreotide in the plasma after administration over time follows an exponential curve. Without amino acid co-infusion, 75% of the IA was cleared from the plasma with a half-life (Tα) of 4.2 min. In the subsequent phases the plasma half-lives were 0.88 h and 7.95 h corresponding to 19.1% and 5.03% of the IA cleared from the plasma, respectively. With amino acid co-infusion, 78% of the IA was cleared from the plasma with a half-life of 5.8 min. In the subsequent phases the plasma half-lives were 2.72 h and 55.1 h corresponding to 16.0% and 0.80% of the IA cleared from the plasma, respectively.

All patients who were enrolled in the Erasmus MC I/II study underwent planar imaging to determine kidney dosimetry. Dosimetry was performed minimally after the first treatment to determine if the 4th treatment with 7.4 GBq of 177Lu-Oxodotreotide would result in a kidney radiation dose that would not exceed the 23 Gy threshold limit. 408 of the 615 enrolled patients had quantifiable kidney uptake, which enabled kidney dosimetry. Whenever possible, dosimetry was performed at first treatment, but dosimetry at treatment 2 or 3 was also performed in a few cases. In the same treatment, blood and urine samples were collected at different intervals after $^{177}$Lu-Oxodotreotide administration, and radioactivity measured at the investigational site. Urine samples were additionally characterized at a central laboratory by HPLC analysis according to validated procedures in order to examine the chemical status of the radionuclide in urine. Overall, the results of the dosimetric analysis performed in the NETTER-1 dosimetry/PK substudy are in agreement with the findings from Erasmus Phase I/II study and indicate that the standard protocol for $^{177}$Lu-Oxodotreotide administration is safe. Moreover, the generally high and prolonged uptake of the radiolabelled compound in the tumor lesions observed in the NETTER-1 study, confirms $^{177}$Lu-Oxodotreotide tumor uptake data reported in literature, reinforcing the basis for Lutathera therapeutic efficacy in sstr2-expressing tumors. To allow comparison with published dosimetry and toxicity data from various radiation sources (PRRT with 90Y and external beam radiation) and different dosing schemes, the biologically effective dose for the kidney parenchyma cells were calculated. The effective half-life (Teff) of the radioactivity to the kidneys for the 408 ´dosimetry´ patients after treatment with the actual cumulative administered radioactivity of

up to 29.6 GBq (800 mCi; 4 times 7.4 GBq (200 mCi)) 177Lu-Oxodotreotide was 61±12 h (range: 27-135 h) and the mean BED to the kidneys 20.6±6.0 Gy (range: 5-38 Gy). If all 408 patients would have received the full treatment with a cumulative radioactivity of 29.6 GBq, then the mean BED would have been 23.3±8.3 Gy

The concentration of radioactivity in a bone marrow aspirate from 14 subjects was compared with the concentration of radioactivity in a blood sample that was obtained at the same time. The mean radioactivity in the bone marrow was 2.2±0.9 kBq/mL (range: 0.85-4.47 kBq/mL) and in the blood samples: 2.4±1.3 kBq/mL (range: 1.08-6.45 kBq/mL). The mean of the red marrow over blood ratio was 0.88 and therefore the radioactivity in blood can be considered as an indicator of radioactivity present in the bone marrow. The bone marrow radiation dose was calculated based on total body distribution (from whole body images and urinary excretion data). The mean dose per administered radioactivity to the bone marrow for the 5 out of 6 patients following the lowest dose is 0.070±0.009 mGy/MBq (range: 0.054-0.078 mGy/MBq. The mean dose per administered radioactivity to the bone marrow for the 7 patients dosed with 3.7 GBq is 0.082±0.036 mGy/MBq. The interpatient variation in the radiation dose to the bone marrow was large, especially in terms of the contribution of the remainder of the body to the dose. The median bone marrow dose per IA was 0.022 mGy/MBq (range: 0.011-0.126 mGy/MBq), with the largest contribution from the remainder of the body: 50% (range: 31-92%). The data from all Groups allowed the calculation of the mean bone marrow dose, as the Kolmogorov-Smirnov test showed the combination of group data to be normally distributed; the mean dose per administered activity in the total of 29 evaluable patients in these groups is 0.049±0.036 mGy/MBq. At an activity administration schedule of 4 times 7.4 GBq this would lead to a bone marrow dose of 4 x 0.36 Gy, in total: 1.5±1.1 Gy.

Liver dosimetry based on planar image acquisition is hampered by the presence of (extensive) liver metastases, which are inherent to the clinical status of the enrolled patients. The consequence of taking the whole liver as region of interest, leads to an overestimation of the liver radiation dose. Therefore, the radiation dose to the liver was established from dosimetry measurements performed for patients with low tumour burden. The mean radiation dose to the liver in 5 patients for whom dosimetry data is available is 0.21±0.5 mGy/MBq. In patients dosed with 3.7 GBq and higher tumour burden, liver dosimetry was also determined using a ROI which encompassed only apparently normal liver tissue. The median dose in the 7 patients in Group-2 was 0.0163 mGy/MBq (range:0.012-0.12 mGy/MBq). When the abdominal uptake measured in Group-3 (dosed 7.4 GBq) is assumed to distribute proportionally to the organ masses, according to normal man (liver: 1.9 kg, spleen: 180 g and kidneys 300 g) an additional radiation dose estimate can be obtained. The mean dose per administered activity of 2.0±1.4 mGy/MBq reflects the high dose resulting from the tumour metastases in the liver.
The following conclusions on treatment with lutetium ($^{177}$Lu) oxodotreotide were determined from radiation dosimetry evaluations performed in clinical studies:

- The critical organ is the bone marrow, however, with the recommended Lutathera cumulative dose of 29,600 MBq (4 administrations of 7,400 MBq), no correlation between hematologic toxicity and the total radioactivity administered or bone marrow absorbed dose has been observed either in Erasmus phase I/II or in NETTER-1 phase III study.
- Kidney is not a critical organ if a co-infusion of an appropriate amino acids solution is performed.

Overall, the results of the dosimetric analysis performed in the NETTER-1 phase III dosimetry substudy and in the Erasmus phase I/II study are in agreement and indicate that lutetium ($^{177}$Lu) oxodotreotide dose regimen (4 administrations of 7,400 MBq) is safe.

**Table 17: Absorbed dose estimates for lutetium ($^{177}$Lu) oxodotreotide from NETTER-1 phase III study (Olinda output)**

| **Organ** | **Organ absorbed dose (mGy/MBq) (n = 20)** | |
|---|---|---|
| | **Mean** | **SD** |
| Adrenals | 0.04 | 0.02 |
| Brain | 0.03 | 0.02 |
| Breasts | 0.03 | 0.01 |
| Gallbladder Wall | 0.04 | 0.02 |
| Lower Large Intestine Wall | 0.03 | 0.02 |
| Small Intestine | 0.03 | 0.02 |
| Stomach Wall | 0.03 | 0.02 |
| Upper Large Intestine Wall | 0.03 | 0.02 |
| Heart Wall | 0.03 | 0.02 |
| Kidneys | 0.65 | 0.29 |
| Liver | 0.49 | 0.62 |
| Lungs | 0.03 | 0.01 |
| Muscle | 0.03 | 0.02 |
| Ovaries** | 0.03 | 0.01 |
| Pancreas | 0.04 | 0.02 |
| Red Marrow | 0.03 | 0.03 |
| Osteogenic Cells | 0.15 | 0.27 |
| Skin | 0.03 | 0.01 |
| Spleen | 0.85 | 0.80 |
| Testes* | 0.03 | 0.02 |
| Thymus | 0.03 | 0.02 |
| Thyroid | 0.03 | 0.02 |
| Urinary Bladder Wall | 0.45 | 0.18 |
| Uterus** | 0.03 | 0.01 |
| Total Body | 0.05 | 0.03 |

*n=11 (male patients only)
**n=9 (female patients only)

Radiation dose to specific organs, which may not be the target organ of therapy, can be influenced significantly by pathophysiological changes induced by the disease process. This should be taken into consideration when using the following information.

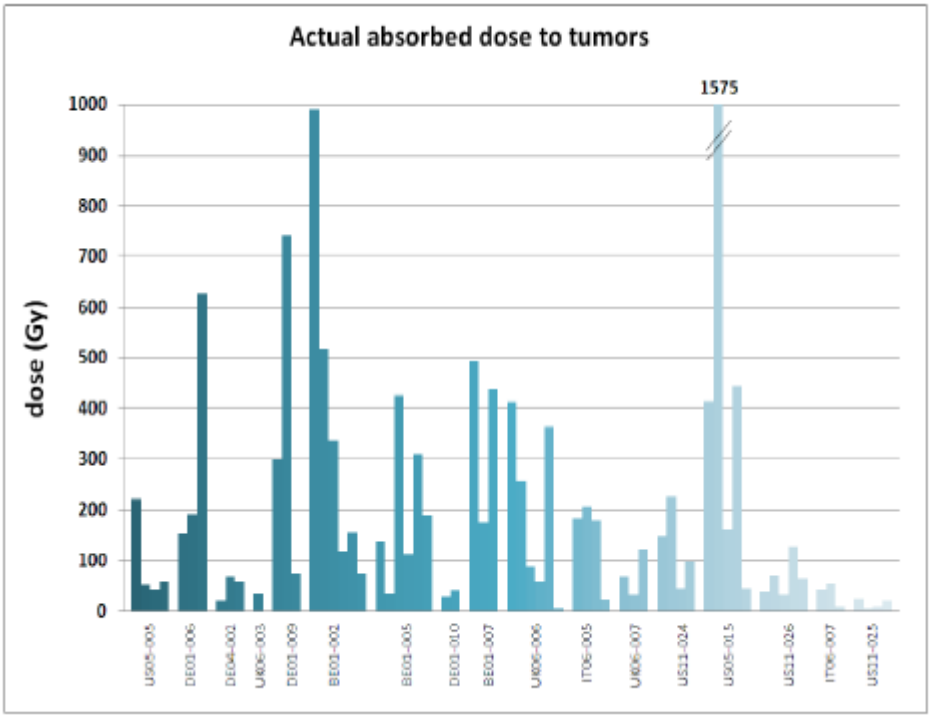



**Figure 11: Cumulative absorbed doses to specific tumour masses based on actual administered activity for all patients with evaluable lesions**

## *Elimination*

The primary route of excretion is through the kidneys following an exponential curve with 70-80% of the IA eliminated in the urine within 48 h. Without amino acid co-infusion: 30.5% IA with Tα=50.0 min, 62.4% IA with Tβ=7.5 h and 9.2% IA with Tγ=150 h. Concordant with the reduced kidney radioactivity residence time with amino acid coinfusion, the urinary excretion appears to be faster: 45.4% IA with Tα=89 min and 52.6% IA with Tβ=51.2 h. Calculated doses to the kidneys were reduced by a mean of 47% (range: 34%-59%) by the co-administration of amino acids.

With amino acid co-infusion, the kidney uptake is reduced and the kinetics of the radioactivity decrease in the kidney is faster: 31% IA with Tα=26 min, 13% IA with Tβ=2.7 h and 2.9% IA with Tγ=131 h. The mean reduction in kidney residence time by amino acid co-infusion is 26% (range: 3-42%).

The $^{177}$Lu-Oxodotreotide that is not taken up in the tumours or organs is rapidly excreted in the urine with 67% of the IA within 24 hours. 70% is eliminated within 3 days with the remainder attributed to slow elimination post day 3. There is evidence of some persistence of drug in the body which may have safety implications however the current safety profile is reassuring.

The aim of the NETTER-1 substudy was to verify that the dosimetry evaluations of patients receiving four, 7.4 GBq (200 mCi) treatments of $^{177}$Lu-Oxodotreotide are consistent with the dosimetric findings of Erasmus MC Phase I/II study. Additionally, the study examined the impact and clinical significance of reaching dosimetry limits to critical organs considered in the Erasmus MC Phase I/II study, namely the kidney BED of 38 Gy and the red marrow absorbed dose of 3.7 Gy.

The 3 effective half-lives fitting the median values of the blood experimental data are: Teff1= 0.9 h, Teff2 = 3.2 h; Teff3=34.3 h. Peak plasma concentrations are reported as 9.32 ng/ml. AUC is 33.96 ng.h/ml. Plasma clearance is 4.53L/h.

Renal excretion is variable with values as low as 30% in some subjects and 90% in others, the majority occurs in the first 24 hours. Clearance values suggest the value is lower than GFR. Metabolite characterisation of urine samples appears to show minimal concentrations of metabolites.

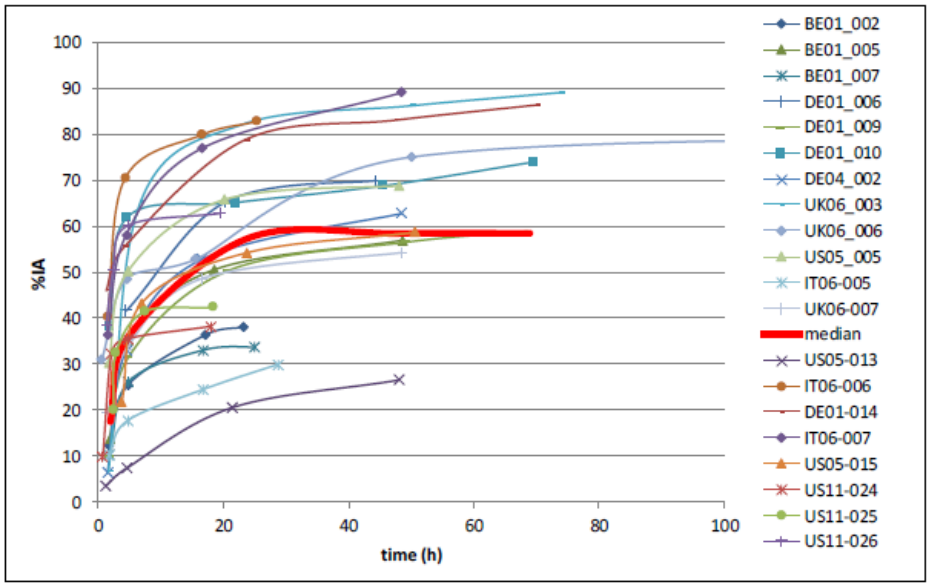



**Figure 12: Cumulative injected activity eliminated versus time in the urine**

Patients enrolled in the NETTER-1 dosimetry substudy were found to have a mean radiation doses to kidneys of 0.65 ± 0.29 Gy/GBq of $^{177}$Lu-Oxodotreotide, and a mean radiation dose to bone marrow of 0.04 ± 0.03 Gy/GBq. Mean total absorbed doses for these two organs were determined to be 19.4 ± 8.7 Gy, and 1.0 ± 0.8 Gy after 4 administrations with a total activity of 29.6 GBq. Median doses and ranges of variability were 19 (5-35) Gy and 0.7 (0.3-4.1) Gy, for kidneys and red marrow, respectively, which are similar to those determined for patients enrolled in the Erasmus MC Phase I/II study.

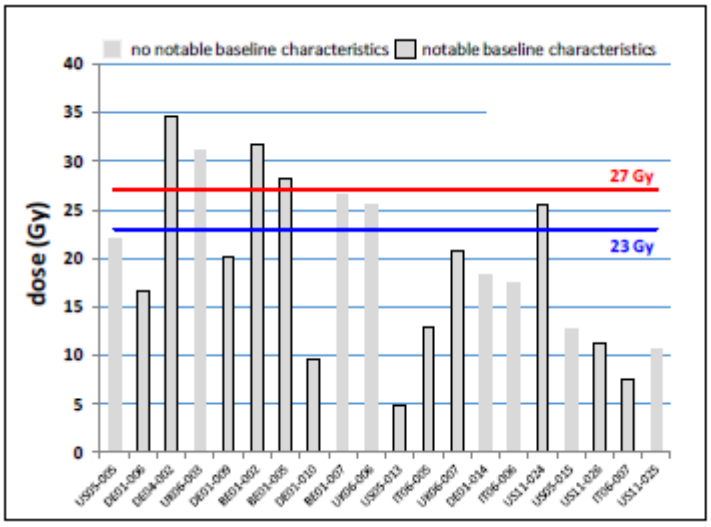



**Figure 13: Kidney absorbed dose assuming 4 administration of 7.4 GBq of $^{177}$Lu-Oxodotreotide**

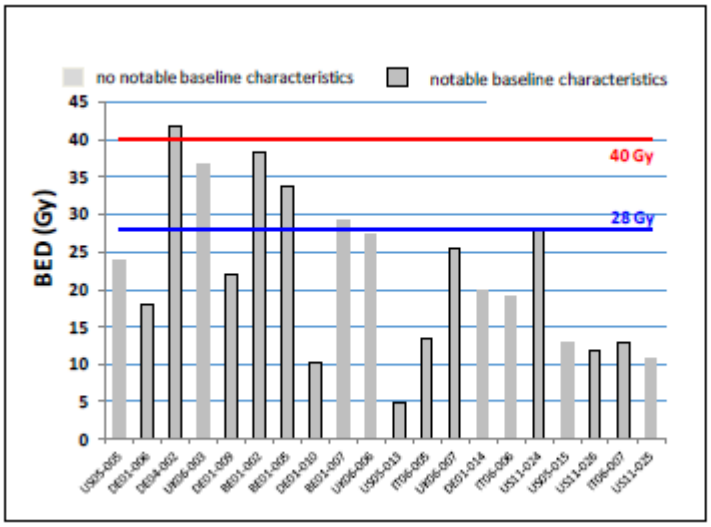



**Figure 14: Kidney BED values assuming 4 administrations of 7.4 GBq of $^{177}$Lu-Oxodotreotide**

Moreover, the mean and median renal and red marrow doses obtained in this group of patients are within the recognized limits described in literature, and are comparable with the findings from published studies[12, 13, 14, 15, 16, 17].

## *Dose proportionality and time dependencies*

Biodistribution and PK data available on 5 patients with limited tumour burden, treated with 1.85 GBq (Erasmus MC Phase I/II study, group 1), 3.7 GBq and 7.4 GBq (Erasmus MC Phase I/II study, Group 2 and 3 respectively) is shown in the figures below. In all patients the radioactivity cleared from plasma very rapidly, the percentage of injected activity decreasing to around 20% (in most of patients below 10%) in the first hour after treatment. In all three groups the elimination profile in urine is also similar, with 65%-70% of injected radioactivity excreted in the first 24 hours (as shown in Figure B below).

[12] Wehrmann C, Senftleben S, Zachert C, M, Baum RP (2007). Results of individual patient dosimetry in peptide receptor radionuclide therapy with 177Lu DOTA-TATE and 177Lu DOTA-NOC. Cancer Biother Radiopharm 22(3):406-416
[13] Bodei L, Cremonesi M, Ferrari M, Pacifici M, Grana CM, Bartolomei M, Baio SM, Sansovini M, Paganelli G (2008). Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with 90Y-DOTATOC and 177Lu-DOTATATE: the role of associated risk factors. Eur J Nucl Med Mol Imaging 35(10):1847-1856
[14] Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, Feelders RA, van Aken MO, Krenning EP (2008). Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol 26(13):2124-2130
[15] Garkavij M, Nickel M, Sj, Ljungberg M, Ohlsson T, Wingårdh K, Strand SE, Tennvall J (2010). 177Lu-[DOTA0,Tyr3] octreotate therapy in patients with disseminated neuroendocrine tumors: Analysis of dosimetry with impact on future therapeutic strategy. Cancer 116(4 Suppl):1084-1092
[16] Larsson G, Sjoden PO, Oberg K, Eriksson B, von Essen L (2001). Health-related quality of life, anxiety and depression in patients with midgut carcinoid tumours. Acta Oncol 40(7):825-831
[17] Sandström M, Garske-Román U, Granberg D, Johansson S, Widstr, Eriksson B, Sundin A, Lundqvist H, Lubberink M (2013). Individualized dosimetry of kidney and bone marrow in patients undergoing 177Lu-DOTA-octreotate treatment. J Nucl Med 54(1):33-41

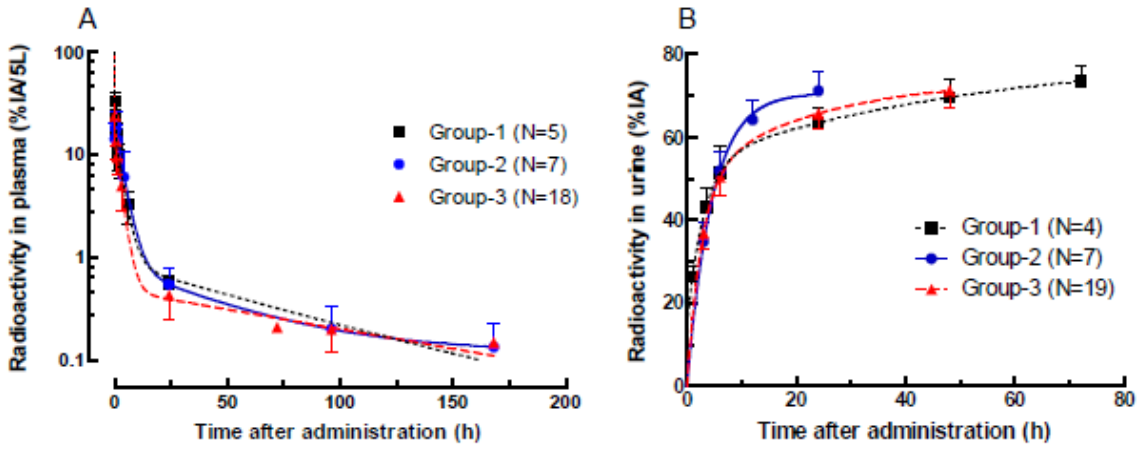



**Figure 15: Mean radioactivity in plasma (Figure A) and in urine (Figure B) for Group 1 (1.85 GBq) , Group 2 (3.7 GBq), and Group 3 (7.4 GBq) of treated patients**

Moreover, comparing the dosimetry data available for the few patients with limited tumour burden treated with 1.85 GBq (Group 1) with those from patients with higher tumour burden, treated with 3.7 GBq and 7.4 GBq (Group 2 and 3), it appears that the kidney absorbed dose per GBq administered is quite similar for the two groups: 0.81 ± 0.19 Gy/GBq in Group 1, 0.78 ± 0.26 Gy/GBq in Group 2 and 3.

## *Special populations*

There were no patients over 75 years of age

The applicant did not submit studies on renal or hepatic impaired patients (see pharmacology discussions). The applicant proposes a 50% reduction of the proposed dose for patients with renal toxicity. The drug is contra-indicated in patients with GFR <30 ml/min and not recommended in patients with GFR <50 ml/min.

## *Pharmacokinetic interaction studies*

Plasma protein binding studies indicate that at the expected plasma levels in humans, $^{175}$Lu-Oxodotreotide is not very highly-protein bound compound, the bound fraction being 57%.

$^{175}$Lu-Oxodotreotide is not an inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1.

$^{175}$Lu-Oxodotreotide is not an inducer of CYPs 1A2, 2B6 or 3A4.

$^{175}$Lu-Oxodotreotide is not an inhibitor of Pgp, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, OCT1, and BCRP at relevant maximal plasma concentrations.

There is evidence from *in vitro* and *in vivo* studies that concomitant use of glucocorticosteroids could induce SSTR2 down-regulation and there was a trend towards more PFS events in patients concomitantly treated with glucocorticosteroids. Therefore, as a matter of cautiousness, in line with the study protocol for the NETTER-1 study (version 3.0; pg. 50), section 4.5 of the SmPC should be amended to state that glucocorticosteroids should be avoided as preventive anti-emetic treatment because of potential receptor down-regulation.

### *Pharmacokinetics using human biomaterials*

The applicant did not submit studies in pharmacokinetics using human biomaterials (see clinical pharmacology discussion).

## 2.4.3. Pharmacodynamics

### *Mechanism of action*

The applicant did not submit studies on the mechanism of action (see non-clinical aspects).

### *Primary and Secondary pharmacology*

The applicant did not submit secondary pharmacodynamic studies ( see clinical pharmacology discussion).

## 2.4.4. Discussion on clinical pharmacology

The medicinal product is administered intravenously and is immediately and completely bioavailable. The recommended treatment regimen in adults consists of 4 infusions of 7,400 MBq each. The recommended interval between each administration is 8 weeks which could be extended up to 16 weeks in case of dose modifying toxicity (DMT) (see Table 5 of the SmPC). The proposed dose is given at 8- 16 week intervals therefore accumulation is not expected.

At 4 hours after administration, the distribution pattern of lutetium ($^{177}$Lu) oxodotreotide shows a rapid uptake in kidneys, tumour lesions, liver and spleen, and in some patients in the pituitary gland and in the thyroid. The co-administration of amino acid solution decreases the kidney uptake, enhancing the elimination of radioactivity (see section 4.4). Biodistribution studies show that lutetium ($^{177}$Lu) oxodotreotide is rapidly cleared from the blood. For renal protection purpose, a 4 hour infusion of an intravenous amino acid solution must be started 30 minutes prior to start of lutetium (177Lu) oxodotreotide infusion and maintained for at least 3 hours after administration (section 4.2 of the SmPC).

An analysis performed with human plasma to determine the extent of plasma protein binding of non-radioactive compound (lutetium ($^{175}$Lu) oxodotreotide) showed that about 50% of the compound is bound to plasmatic proteins.

Transchelation of lutetium from lutetium ($^{175}$Lu) oxodotreotide into serum proteins has not been observed.

There is evidence, from the analysis of urine samples of 20 patients included in the NETTER-1 phase III Dosimetry, pharmacokinetic and ECG substudy, that lutetium ($^{177}$Lu) oxodotreotide is poorly metabolized and is excreted mainly as intact compound by renal route.

The high performance liquid chromatography (HPLC) analyses performed on urine samples collected up to 48 hours post infusion showed a lutetium ($^{177}$Lu) oxodotreotide radiochemical purity close to 100% in most of the analysed samples (with lowest radiochemical purity value being greater than 92%), indicating that the compound is eliminated in urine mainly as intact compound.

This evidence confirms what has been previously observed in the Erasmus phase I/II study, in which HPLC analysis of a urine specimen collected 1 hour post administration of lutetium ($^{177}$Lu)

oxodotreotide from one patient receiving 1.85 MBq of lutetium ($^{177}$Lu) oxodotreotide indicated that the main portion (91%) was excreted unchanged.

These finding are supported by *in vitro* metabolism data in human hepatocytes, in which no metabolic degradation of lutetium ($^{175}$Lu) oxodotreotide was observed.

Based on the data collected during the Erasmus phase I/II and NETTER-1 phase III studies, lutetium ($^{177}$Lu) oxodotreotide is primarily eliminated by renal excretion: about 60% of the medicinal product is eliminated in the urine within 24 hours, and about 65% within 48 hours following the administration.

Overall the density of somatostatin receptors in SSTR2-expressing tumour tissues is known to be far higher than in the other organs of the body. The highest expression of the receptor was found in the cerebellum.. Patients scanned with radiolabelled DOTA0-Tyr3-Octreotide for peripheral tumours without brain pathology had no visualization of their CNS. Clinical practice shows that the main critical organs for possible Lutathera radiotoxicity are kidneys with a non-SSTR2 specific uptake (via the megalin-cubilin mechanism in the kidney) and bone marrow due to radioactivity circulating in blood. Renal uptake and resulting kidney toxicity of the compound however is largely prevented by co-infusion of amino acid solution. However, it is contraindicated in patients with kidney failure with creatinine clearance < 30 mL/min. Bone marrow toxicity is characterized by reversible/transient reductions in blood counts, and lymphocytopenia. There is no particular uptake in normal tissues unless they are affected by athero-inflammatory diseases. With regard to endocrine function, no clinically apparent relevant effect was observed on pituitary-adrenal function.

Somatostatin and its analogues competitively bind to somatostatin receptors. Therefore, administration of long acting somatostatin analogues should be avoided within 30 days prior to the administration of this medicinal product. If necessary, patients may be treated with short acting somatostatin analogues during the 4 weeks until 24 hours preceding Lutathera administration.

There is some evidence that corticosteroids can induce down-regulation of SST2 receptors. Therefore, as a matter of cautiousness, repeated administration of high-doses of glucocorticosteroids should be avoided during Lutathera treatment. Patients with a history of chronic use of glucocorticosteroids should be carefully evaluated for sufficient somatostatin receptor expression. It is not known if there is of interaction between glucocorticosteroids used intermittently for the prevention of nausea and vomiting during Lutathera administration. Therefore, glucocorticosteroids should be avoided as preventive anti-emetic treatment. In the case where the treatments previously provided for nausea and vomiting are insufficient, a single dose of corticosteroids can be used, as long as it is not given before initiating or within one hour after the end of Lutathera infusion.

The absence of inhibition or significant induction of the human CYP450 enzymes, the absence of specific interaction with P-glycoprotein (efflux transporter) as well as OAT1, OAT3, OCT2, OATP1B1, OATP1B3, OCT1 and BCRP transporters in pre-clinical studies suggest that Lutathera has a low probability of causing significant other drug-drug interactions.

The pharmacokinetics profile in elderly patients (≥ 75 years) has not been established. No data are available.

The following conclusions on treatment with Lutathera were determined from radiation dosimetry evaluations performed in clinical studies:

- The critical organ is the bone marrow, however, with the recommended Lutathera cumulative dose of 29,600 MBq (4 administrations of 7,400 MBq), no correlation between hematologic toxicity and the total radioactivity administered or bone marrow absorbed dose has been observed either in Erasmus phase I/II or in NETTER-1 phase III study.

- Kidney is not a critical organ if a co-infusion of an appropriate amino acids solution is performed.

### 2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology for Lutathera has overall been adequately characterised.

## *2.5. Clinical efficacy*

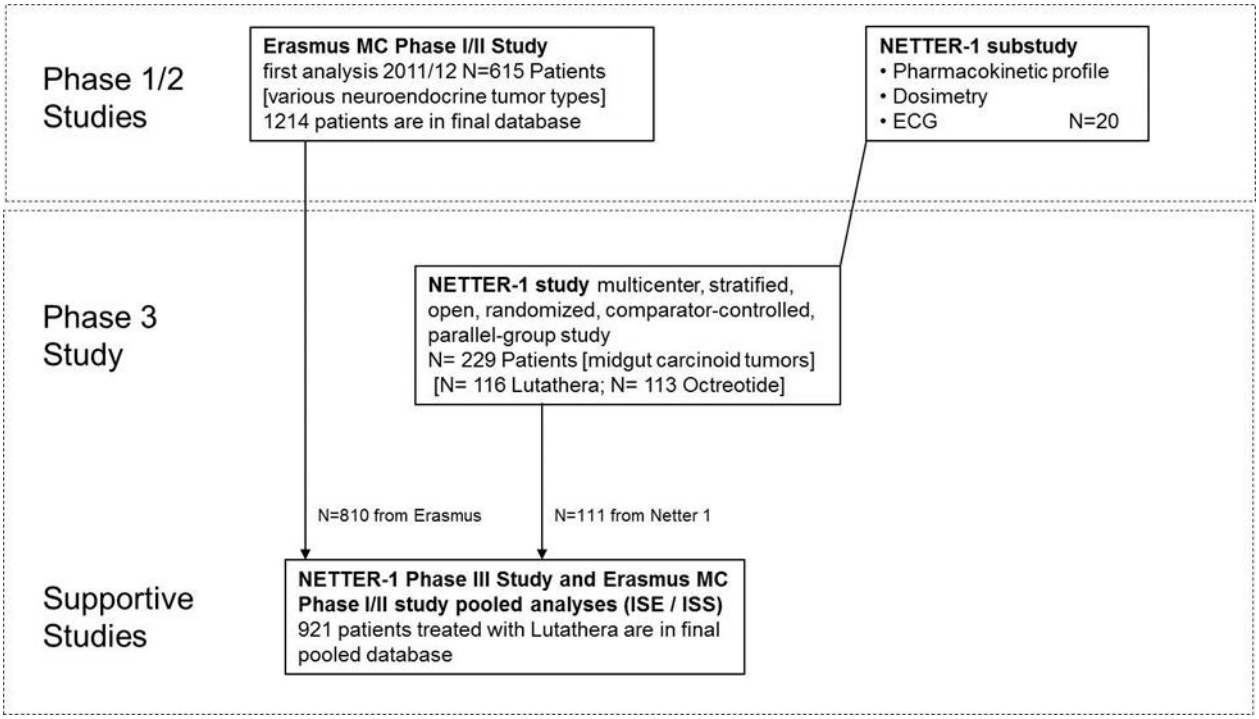



**Figure 16: Overview Clinical Studies**

### 2.5.1. Dose response study(ies)

The applicant did not submit dose-response studies.

In 2000, the Erasmus Medical Center (EMC) phase I/II study allowed treatment of a heterogenous group of patients with somatostatin receptor positive tumours with $^{177}$Lu-Oxodotreotide on a compassionate use basis. 1,214 patients with various somatostatin receptor-positive tumour types (the majority GEP-NETs) were enrolled between January 2000 and December 2012. The EMC study enrolled national (Dutch, 60%) and non-national (40%) patients.

In 2012, there was an independent assessment conducted for study EMC phase I/II study. Initial estimates of the maximum safe dose of the $^{177}$Lu-Oxodotreotide were derived from initial biodistribution and dosimetry studies in the EMC phase I/II trial. The dose was discussed during a CHMP SA (2008) and the applicant was advised to explore dose-finding further. The proposed dosing regimen and dose modification protocol was agreed with in the CHMP scientific advice in December 2010.

## 2.5.2. Main study

### NETTER-1: A multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with $^{177}$Lu-Oxodotreotide to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours

### *Methods*

### *Study Participants*

The target population comprised of adult patients with inoperable, progressive, OctreoScan positive, well-differentiated neuroendocrine tumours of the small bowel (midgut carcinoid tumours), who were treated with 20 mg or 30 mg Octreotide LAR every 3-4 weeks at a fixed dose for at least 12 weeks prior to randomization in the study.

Main key inclusion criteria:

- Presence of metastasized or locally advanced, inoperable (curative intent) at randomization time, histologically proven, midgut carcinoid tumour (to be centrally confirmed).
- Ki67 index ≤ 20% (to be centrally confirmed).
- Patients on Octreotide LAR at a fixed dose of 20 mg or 30 mg at 3-4 weeks intervals for at least 12 weeks prior to randomization in the study.
- Patients ≥18 years of age.
- Patients had to have progressive disease based on RECIST Criteria, Version 1.1 while receiving an uninterrupted fixed dose of Octreotide LAR (20-30 mg/3-4 weeks). Disease progression had to be centrally confirmed. In order to make the assessment, two CT (or MRI) scans were required. The oldest scan must not be older than 3 years from the date of randomization. The most recent scan must not be older than 4 weeks from the date of randomization. Both scans must have been obtained while the patient was receiving the same fixed dose of Octreotide LAR
  (20-30 mg/3-4 weeks) with the following exceptions; 1) it was acceptable if the oldest scan was obtained within 12 weeks of the patient receiving a fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks); AND 2) it was acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan, provided that the Octreotide LAR fixed dose resumed after the OctreoScan.
- Confirmed presence of somatostatin receptors on all target lesions (RECIST Criteria, Version 1.1) documented by CT/MRI scans, based on positive OctreoScan imaging within 24 weeks prior to randomization in the study (to be centrally confirmed). The OctreoScan should be one that was performed while the patient was on a fixed dose of Octreotide LAR. If a patient has had an OctreoScan performed while Octreotide LAR treatment-naïve, the patient must have a repeat OctreoScan performed after 3 months of Octreotide LAR treatments before entering the clinical study to prove that the index lesions or new lesions still meet the criteria for inclusion. It is acceptable to have patients temporarily switched from Octreotide LAR to Octreotide s.c.

(up to 6 weeks) in order to obtain an OctreoScan, provided they return to the same fixed dose of Sandostatin LAR prior to the scan.

- The tumour uptake observed in each target lesion using OctreoScan should be ≥ normal liver uptake observed on planar imaging (to be centrally confirmed).
- Karnofsky Performance Score (KPS) ≥60.
- Presence of at least 1 measurable site of disease.

Main key exclusion criteria:

- Either serum creatinine >150 µmol/L (>1.7 mg/dL), or creatinine clearance <50 mL/min calculated by the Cockcroft Gault method, eventually confirmed by measured creatinine clearance (or measured glomerular filtration rate (GFR) using plasma clearance methods, not gamma camera-based) <50 mL/min (the measured creatinine clearance / GFR is required only as confirmatory exam).
- Hb concentration <5.0 mmol/L (<8.0 g/dL); WBC <$2x10^9$/L (2000/$mm^3$); platelets <$75x10^9$/L ($75x10^3$/$mm^3$).
- Total bilirubin >3 x ULN.
- Serum albumin <3.0 g/dL unless prothrombin time is within the normal range.
- Pregnancy or lactation.
- For female patients of childbearing potential (defined as < 2 years after last menstruation and not surgically sterile) and male patients, who are not surgically sterile or with female partners of childbearing potential: absence of effective, non-hormonal means of contraception (intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal gel).
- Treatment with >30 mg Octreotide LAR at 3-4 weeks intervals within 12 weeks prior to randomization in the study.
- Peptide receptor radionuclide therapy (PRRT) at any time prior to randomization in the study.
- Any surgery, radioembolization, chemoembolization, chemotherapy and radiofrequency ablation within 12 weeks prior to randomization in the study.
- Interferons, Everolimus (mTOR-inhibitors) or other systemic therapies within 4 weeks prior to randomization in the study.
- Known brain metastases, unless these metastases have been treated and stabilized for at least 24 weeks, prior to randomization in the study. Patients with a history of brain metastases must have a head CT with contrast to document stable disease prior to enrolment in the study.
- Uncontrolled congestive heart failure (NYHA II, III, IV).
- Uncontrolled diabetes mellitus as defined by a fasting blood glucose >2 ULN.
- Any patient receiving treatment with short-acting Octreotide, which cannot be interrupted for 24 h before and 24 h after the administration of $^{177}$Lu-Oxodotreotide, or any patient receiving treatment with Octreotide LAR, which cannot be interrupted for at least 6 weeks before the administration of $^{177}$Lu-Oxodotreotide, unless the tumour uptake observed on target and non-

target but measurable lesions by OctreoScan imaging during continued Octreotide LAR treatment is at least as high as normal liver uptake observed by planar imaging.

- Patients with any other significant medical, psychiatric, or surgical condition, currently uncontrolled by treatment, which may interfere with completion of the study.
- Prior external beam radiation therapy to more than 25% of the bone marrow.
- Current spontaneous urinary incontinence.
- Other known co-existing malignancies except non-melanoma skin cancer and carcinoma in situ of the uterine cervix, unless definitively treated and proven no evidence of recurrence for 5 years.
- Patients who have not provided a signed informed consent form to participate in the study, obtained prior to the start of any protocol related activities.
- Patient with known incompatibility to CT Scans with I.V. contrast due to allergic reaction or renal insufficiency. If such patients can be imaged without the use of CT contrast material (i.e., can tolerate MRI scans), such patients would not be excluded.

## *Treatments*

After the screening period, patients randomised were randomly assigned to treatment with $^{177}$Lu-Oxodotreotide (Lutathera) arm or the Octreotide LAR arm.

**Lutathera Arm:**

Treatment with $^{177}$Lu-Oxodotreotide (Lutathera) consisted of 4 administrations of $^{177}$Lu-Oxodotreotide 7.4 GBq at 8±1-week intervals or up to 16 weeks to accommodate resolving acute toxicity (total cumulative radioactivity of 29.6 GBq (800 mCi)). For kidney protection, an amino acid solution was administered concomitantly.

In addition, patients received supportive care with 30 mg Octreotide LAR every 4 weeks ± 3 days until the PFS primary end-point, then until Week 72 from randomisation after the PFS primary end-point, or early termination, unless the patient progressed or died.

The scheme for dose modification after toxicity in the $^{177}$Lu-Oxodotreotide treatment arm is presented in the figure below.

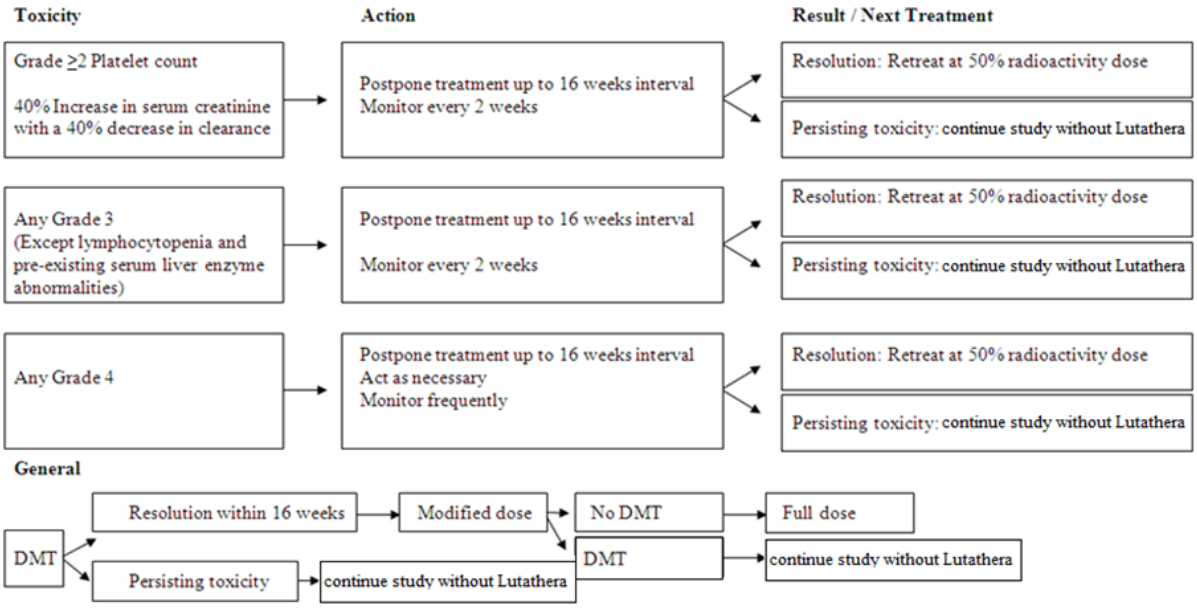



**Figure 17: Dose Modifying Schemes for 177Lu-Oxodotreotide Treatment Arm**

**Comparator Arm:**

Patients in the comparator arm received 60 mg Octreotide LAR every 4 weeks (i.m. injections) ± 3 days until the final overall analysis of PFS, unless the patient progressed or died. After the final PFS analysis, the treatment/assessment period for each patient became fixed and all patients received 60 mg for a maximum of 72 weeks and then proceeded to the long-term follow-up assessment phase for evaluation of survival.

**Concomitant and Rescue Medication**

- In the Lutathera arm only: 30 mg Octreotide LAR treatment for symptoms control administered until the final overall analysis of, unless the patient progressed or died. After the final PFS analysis, the treatment/assessment period became fixed and all patients received 30 mg for a maximum of 72 weeks and then proceeded to the long-term follow-up assessment phase for evaluation of survival and long term toxicities.
- In the Lutathera arm only: amino acid infusion (Vamin 18 in Europe and Aminosyn II 10% in USA) was given concomitantly with each administration of Lutathera for kidney protection.
- In both arms: in case patients experienced clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, Octreotide s.c. rescue injections were allowed.

## *Objectives*

**Primary objective:**

To compare Progression Free Survival (PFS) after treatment with 177Lu-Oxodotreotide plus best supportive care (30 mg Octreotide LAR) to treatment with high dose (60 mg) Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, well-differentiated neuroendocrine tumours of the small bowel (midgut carcinoid tumours).

**Secondary objectives were:**

- To compare the Objective Response Rate (ORR) between the two study arms;
- To compare the Overall Survival (OS) between the two study arms;

- To compare the Time to Tumour Progression (TTP) between the two study arms;
- To evaluate the safety and tolerability of $^{177}$Lu-Oxodotreotide;
- To evaluate the health related quality of life (QoL) as measured by the EORTC QLQ-30 and G.I.NET21 questionnaire;

## *Outcomes/endpoints*

The primary efficacy end-point was PFS as measured by objective tumour response, which was determined by RECIST Criteria, Version 1.1.

PFS is defined as the time from start of study treatment to documented progression according to RECIST Criteria or death due to any cause, as evaluated by the Independent Review Committee, within 76 weeks of start of study treatment. Patients, who drop out due to toxicity and who therefore cannot receive the full treatment are included as having disease progression. If a patient has no progression and has not died, the patient will be regarded as censored in the context of a time to event analysis at the date of last adequate tumour assessment. An Independent Image Reading Center (IRC) was to carry out centralised confirmation of disease progression. In case of discrepancies on the evaluation of the progressive status between investigator and central assessor, a third evaluator performed adjudication. The adjudicator did not have access to the local evaluation, only to the first central assessment. The censoring rules are defined below.

**Table 18: Censoring rules definition for evaluation of PFS**

| Situation | Date of Progression or Censoring | Outcome |
|---|---|---|
| No baseline tumour assessments | Date of randomization | Censored |
| Progression documented between scheduled assessment visits | Date of radiological assessment showing progression, if centrally confirmed | Event (Progressed) |
| No progression | Date of last adequate radiological assessment (date of the scan) of measured lesions | Censored |
| Treatment discontinuation for undocumented progression and no additional scans are collected | Date of last adequate radiological assessment (date of the scan) of measured lesions | Censored |
| Treatment discontinuation for toxicity or other reason with no additional scans | Date of last adequate radiological assessment (date of the scan) of measured lesions | Censored |
| Treatment discontinuation for toxicity, but with continued scanning and subsequently documented progression | Date of radiological assessment (date of the scan) showing progression, if centrally confirmed | Event (Progressed) |
| New anti-cancer treatment started | Date of last adequate radiological assessment (date of the scan) of measured lesions | Censored |
| Death before first progression assessment | Date of death | Event (Death) |
| Death between adequate assessment visits | Date of death | Event (Death) |
| Death or progression after more than one missed assessment visit during the treatment phase* | Date of last adequate radiological assessment (date of the scan) of measured lesions | Censored |

(*) In this trial, more than one missed assessment visit is defined as an assessment visit not occurring within 2.5 times the length between two assessment visits (i.e. 210 days following the last visit).

The secondary efficacy variables were:

- Objective Response Rate (ORR): Objective Response Rate (ORR) will be calculated as the proportion of patients with tumour size reduction of a predefined amount (the sum of partial responses (PR) plus complete responses (CR)) and for a minimum time period. Response duration will be calculated from the time of initial response until documented tumour progression.
- Overall Survival (OS): Overall Survival (OS) will be calculated from start of study treatment until the day of death due to any cause; OS will not be censored if a patient receives other anti-tumour treatments after study medication. Survival data will be collected at the End of Study and up to 3 years after the End of Study.

- Time to Tumour Progression (TTP): TTP is defined as the time (number of days) from start of study treatment to objective tumour progression. It includes patients who drop out due to toxicity, but omits patients who die without measured progression (censored to last follow-up date or death date).
- Duration of Response (DoR): The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.
- QoL: The impact of treatment on health related QoL was assessed using the EORTC QLQ-C30 and the EORTC QLQ-G.I.NET21 questionnaires, which was filled in by the patient prior to knowing the CT scan/MRI result. Changes from baseline were assessed every 12±1 week from the first treatment date until the PFS primary end-point, then until week 72 after randomization, unless the patient progressed or died. The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. The EORTC QLQ-G.I.NET21 questionnaire is a supplemental module for carcinoid/neuroendocrine tumours. This module comprises questions assessing disease symptoms, side effects of treatment, body image, disease related worries, social functioning, communication and sexuality.

Outcomes for both study arms were collected and evaluated in relation to objective tumour response, KPS, and other parameters of clinical relevance.

Safety was assessed on the basis of adverse events (AEs), adverse events of special interest (AESIs), laboratory results for haematology, blood chemistry and urinalysis, physical examinations, vital signs, electrocardiogram (ECG), Karnofsky performance score (KPS).

Safety assessment in both arms was performed every 12±1 weeks from the randomization date. All adverse events (AEs), whether or not spontaneously reported by the patient, were recorded starting from the signing of the ICF until the last study-related visit. Furthermore, a DSMB evaluated patient's safety throughout the study. Please be referred to section 4 on clinical safety for a detailed assessment.

***Handling of missing data***

Missing values were not replaced for the main calculation of the primary variable and secondary parameters (including key secondary parameters [OS, TTP and ORR]).

If relevant (e.g. the number of missing values is found to be substantial during the blind review), an investigation was performed to determine how sensitive the results were to the method of handling missing values, at least for the primary variable and key secondary parameters. No replacement was applied to any descriptive analysis or listings.

## *Sample size*

Sample size was calculated using the POWER Procedure Log-Rank Test for Two Survival Curves (SAS 9.2) based on the following assumptions:

- Median PFS for control arm: 14 months
- Median PFS for 177Lu-Oxodotreotide arm: 30 months

- Nominal Power: 90%
- Alpha: 0.05
- Pre-defined accrual period: 18 months
- Follow-up period: 18 months

A sample size of 124 patients with a number of 74 events (disease progression centrally confirmed or death due to any cause) was needed.

However, the sample size was also adjusted for overall survival (secondary end-point) with the following assumptions:

- Median OS for control arm: 32 months
- Median OS for 177Lu-Oxodotreotide arm: 50 months
- Nominal power: 80%
- Alpha: 0.05
- Pre-defined accrual period: 18 months
- Long term follow-up: 60 months

Based on these criteria, the study would need to randomize 124 patients (62 per arm), and would observe 74 PFS events during the course of the study. Therefore, the PFS primary analysis point occurs when there are 74 evaluable and centrally confirmed disease progressions or death events in the study. Sample size was adjusted to allow for a 20% drop-out rate and to allow detection of a statistically significant and clinically relevant difference in OS between the two treatment arms (80% power).

## *Randomisation*

After the screening period, patients were randomly assigned to the 177Lu-Oxodotreotide arm or the Octreotide LAR arm. Patient randomisation has been performed according to a centralized permuted block randomisation scheme with a balanced ratio (1:1) between the two treatment arms, stratified by OctreoScan tumour uptake score (Grade 2, 3 and 4) and by the length of time that a patient has been on constant dose of Octreotide (≤ 6 and > 6 months). Randomisation was implemented via the Interactive Web-based Response System (IWRS).

## *Blinding (masking)*

The study was designed as open-label.

## *Statistical methods*

The following analysis populations were defined for the study analyses:

*Full Analysis Set (FAS):* The Full Analysis Set consisted of all patients randomised. Following the intent-to-treat principle, patients were analysed according to the treatment they were assigned at randomisation.

*Per Protocol Set (PPS):* The Per Protocol Set (PPS) consisted of all randomised patients, who had no major protocol violations.

*Safety Set (SAF):* The Safety Set (SAF) consisted of all randomised patients, who received at least one dose of study drug. Patients were analysed according to treatment received.

The FAS was used for all analyses of efficacy, demographics and baseline characteristics. The PPS was used for the per-protocol analyses of primary objective and key secondary variables. The safety set was for all safety analyses.

Analysis methods

Primary analysis

- The final primary analysis on the PFS was performed after the planned number of 74 evaluable and centrally confirmed PFS events or deaths was achieved. The unstratified log-rank test was used to compare the PFS between the two treatment groups. The median point estimate and 95% Confidence Interval (CI) for the PFS was provided using the Kaplan-Meier method. The primary efficacy analysis was conducted on the FAS and additionally for the PPS.
- The impact of selected covariates on the estimated hazard ratio for PFS was assessed by means of a cox proportional hazards model. The model was first fitted with a binary indicator for randomized treatment and all covariates that may potentially influence PFS. A step-down procedure was used to eliminate covariates (other than treatment) that do not reach a significance level of 0.05.

Secondary analyses

- Response rates and 95% CIs was calculated for the ORR by treatment group. Frequencies in the two treatment groups were compared by Fisher's exact test.
- The median and 95% Confidence Interval (CI) for OS was estimated using the KM method. The unstratified log-rank test was used to compare OS between the two groups.

Inferential statistics were only performed for the primary variable (PFS) and selected key secondary variables (i.e. ORR and OS).

All inferential statistics were interpreted at the 5% 2-sided level, with the exception of OS where the significance level was set to 0.0085% at the interim analysis of survival done at the time of the final PFS analysis. A method to control the family-wise type I error rate for the ORR and OS end-points was used: The hypotheses for ORR and OS were tested using a fixed sequence procedure approach to control for the family-wise error. ORR was tested first at the 5% significance level at the time of the final PFS analysis. If the ORR null hypothesis was rejected, then the OS hypothesis was tested. OS analyses were adjusted using O'Brien-Fleming spending function strategy with a 0.0085% significance level at the interim analysis (PFS final analysis). Final OS analysis is planned after 158 deaths have occurred, or 5 years from the date of randomisation of the last randomized patient, whichever occurs first.

All other efficacy variables were evaluated with an exploratory intent only.
Sensitivity analyses were conducted, including (but not limited to):

- Impact of subsequent antitumor treatments after progression,

- Impact of the presence and number of distant metastases,

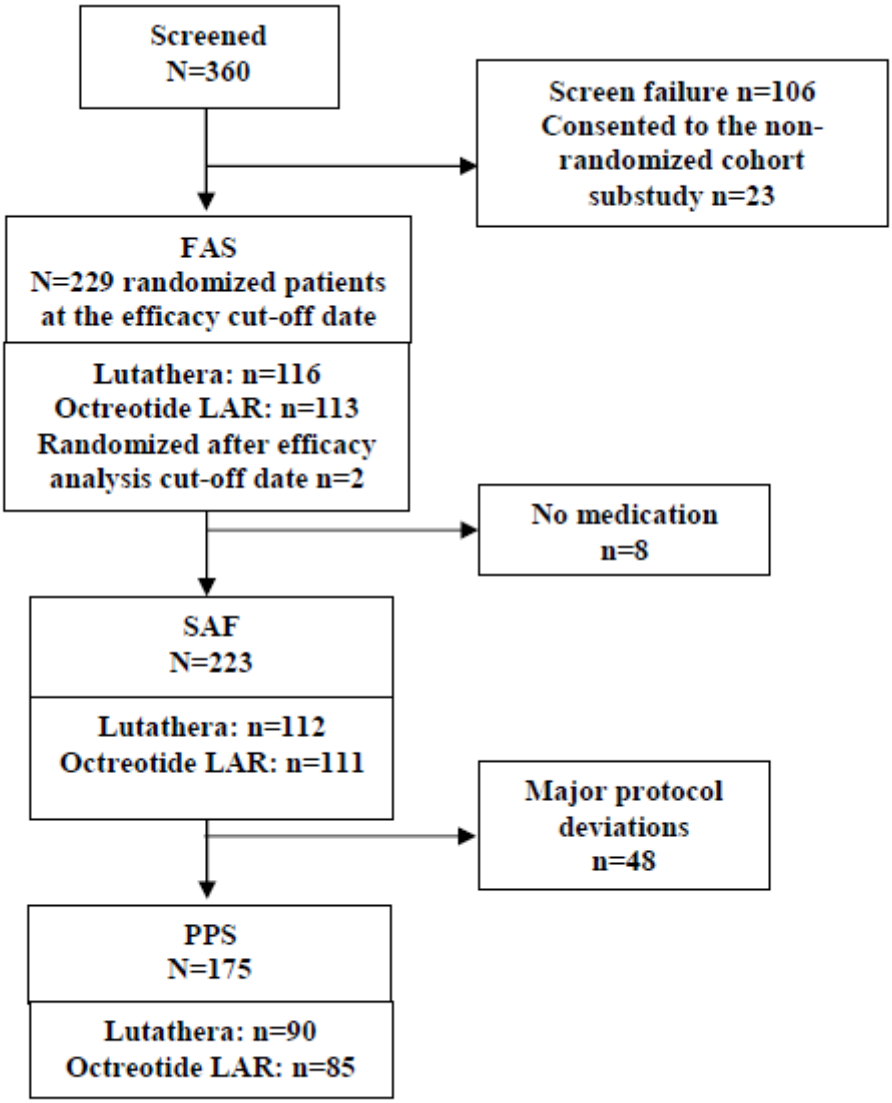
- Impact of the extent of tumour burden / tumour mass (centrally assessed),

- Impact of treatment compliance.

Duration of Response (DoR) and Time to Second Progression (PFS2) were analysed descriptively. Both local and central assessment were considered in exploratory analyses.

## *Results*

### Participant flow




### Recruitment

Countries and number of centres: 41 active centres in EU and USA (27 EU sites and 14 USA sites)

First patient in: 10 July 2012

First patient randomised: 06 September 2012

Last patient in: 08 June 2015

Primary end-point database lock: 14 September 2015

At the cut-off date for the primary end-point analysis (July 24, 2015), 341 patients were screened in 41 centres in the EU and the USA. 87 patients failed screening and were not randomised; these patients were excluded from the FAS.

All patients who consented to Amendment 4.1, i.e. to participate in the non-randomised sub-study cohort (n=25), were also excluded from the FAS since by definition they were not randomised.

Eight of the randomised patients (5 patients of the Lutathera group; 3 patients of the Octreotide LAR group) did not receive or take any trial medication. For 39 patients, protocol violations were detected and considered to be major, leading to the exclusion of these patients. Therefore, the PPS comprised 182 patients in total.

Updated analyses for PFS and OS: 30 June 2016

At the cut-off date for database lock ((30 June 2016), 360 patients had been screened in the 41 active centres in the EU and the USA. As 106 patients failed screening and were not randomized, these patients were excluded from the FAS.

## Conduct of the study

The first patient was randomised in September 2012.

The cut-off date for the primary end-point analysis was 24 July 2015 and the final amendment was on 05th June 2014 (protocol version 4.1). Overall, 139 patients (60.7%) of the FAS stopped the treatment phase due to disease progression or other reasons (52 patients [44.8%] of the Lutathera group and 87 patients [77.0%] of the Octreotide LAR group). The most frequent primary reason for stopping the treatment phase was 'disease progression centrally confirmed (16.4% of patients of the Lutathera group and 51.3% of patients of the Octreotide LAR group).

At the cut-off date of the 30 June 2016, 225 patients (97.4%) of the SAF stopped the treatment phase due to disease progression or other reasons (113 patients [96.6%] of the Lutathera group and 112 patients [98.2%] of the Octreotide LAR group). The most frequent primary reason for stopping the treatment phase was 'disease progression centrally confirmed' (16.2% of patients of the Lutathera group and 56.1% of patients of the Octreotide LAR group).

**Table 19: Incidences and reasons for premature study termination at the end of treatment period and end of long-term follow-up (randomised, N=231)**

| | | Treatment | | |
|---|---|---|---|---|
| | | Lutathera n=117 | Octreotide LAR n=114 | All N=231 |
| | | n (%) | n (%) | n (%) |
| | **Primary reason for end of treatment phase** | | | |
| Did the patient stop the treatment phase due to disease progression or other reasons? | Yes | 113 (96.6) | 112 (98.2) | 225 (97.4) |
| | No | 4 (3.4) | 2 (1.8) | 6 (2.6) |
| End of treatment phase - primary reason | Disease progression centrally confirmed | 19 (16.2) | 64 (56.1) | 83 (35.9) |
| | Best subject's interest in the investigator's opinion | 17 (14.5) | 17 (14.9) | 34 (14.7) |
| | Adverse event (including criteria from subsequent treatment) | 13 (11.1) | 10 (8.8) | 23 (10.0) |
| | Non-compliance | 2 (1.7) | (0.0) | 2 (0.9) |
| | Withdrawal by subject | 10 (8.5) | 10 (8.8) | 20 (8.7) |
| | Lost to follow-up | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Completed | 46 (39.3) | 11 (9.6) | 57 (24.7) |
| | Other | 6 (5.1) | (0.0) | 6 (2.6) |
| | Missing* | 4 (3.4) | 2 (1.8) | 6 (2.6) |
| | **Reasons for not entering or stopping the long-term follow-up** | | | |
| Did the patient enter in the long-term follow-up phase?*** | Yes | 95 (84.1) | 97 (86.6) | 192 (85.3) |
| | No | 18 (15.9) | 15 (13.4) | 33 (14.7) |
| If No, specify reason | Death during the treatment phase | 4 (3.5) | 5 (4.5) | 9 (4.0) |
| | Consent withdrawal | 7 (6.2) | 9 (8.0) | 16 (7.1) |
| | Lost to follow-up | 2 (1.8) | 1 (0.9) | 3 (1.3) |
| | Other | 5 (4.4) | 0 (0.0) | 5 (2.2) |
| Did the patient stop the long term follow-up? | Yes | 26 (27.4) | 44 (45.4) | 70 (36.5) |
| | No | 57 (60.0) | 44 (45.4) | 101 (52.6) |
| | Missing** | 12 (12.6) | 9 (9.3) | 21 (10.9) |
| Reason for interruption | Death | 24 (25.3) | 38 (39.2) | 62 (32.3) |
| | Study ended (5 years from randomization of the last subject or achievement of 158 deaths in the study) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Early study termination by the sponsor for other reasons | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Consent withdrawal | 0 (0.0) | 2 (2.1) | 2 (1.0) |
| | Lost to follow-up | 2 (2.1) | 4 (4.1) | 6 (3.1) |
| | Other | 0 (0.0) | 0 (0.0) | 0 (0.0) |

After randomisation, 8 patients did not take any study medication and were therefore excluded from the safety set (SAF). From the SAF population, there were 39 patients (17.6%) with major protocol deviations identified that led to exclusion from the per-protocol set (PPS) (17 in Lutathera arm, 22 in Octreotide LAR arm). These were confirmed at a blind data review meeting prior to data analysis.

**Table 20: Overview on major protocol deviations (FAS, N=229)**

| Type of major protocol deviation | Treatment | |
|---|---|---|
| | Lutathera (n=116) n (%) | Octreotide LAR (n=113) n (%) |
| Inclusion/Exclusion criteria not met | 9 (7.8) | 8 (7.1) |
| Incorrect procedure | 7 (6.0) | 13 (11.5) |
| Out of window | 14 (12.1) | 8 (7.1) |

N: number of patients in treatment group; n: number of patients Source data: Table 14.1.1.4

## Baseline data

The baseline and disease characteristics are presented in Table 21.

**Table 21: Demographic summary by treatment group (all populations)**

| | | Treatment | | | | | |
|---|---|---|---|---|---|---|---|
| | | Lutathera | | | Octreotide LAR | | |
| Population | | FAS | SAF | PPS | FAS | SAF | PPS |
| Age [years] | Median | 64.0 | 63.5 | 63.0 | 65.0 | 65.0 | 65.0 |
| | Mean (SD) | 63.4 ±9.4 | 63.3 ±9.3 | 62.8 ±9.77 | 64.1 ±9.7 | 64.1 ±9.9 | 64.6 ±9.3 |
| | N (Nmiss) | 116 (0) | 112 (0) | 90 (0) | 113 (0) | 111 (0) | 85 (0) |
| Height [cm] | Mean (SD) | 169.7 ±10.0 | 169.7 ±10.0 | 169.9 ±9.7 | 169.2 ±8.9 | 169.1 ±8.7 | 169.4 ±8.3 |
| | N (Nmiss) | 103 (13) | 100 (12) | 82 (8) | 106 (7) | 104 (7) | 79 (6) |
| Weight [kg] | Mean (SD) | 73.2 ±15.5 | 73.3 ±15.6 | 74.2 ±15.2 | 75.1 ±21.4 | 75.3 ±21.5 | 75.8 ±19.5 |
| | N (Nmiss) | 116 (0) | 112 (0) | 90 (0) | 113 (0) | 111 (0) | 85 (0) |
| BMI [kg/m²] | Mean (SD) | 25.6 ±4.8 | 25.7 ±4.8 | 25.9 ±4.4 | 26.0 ±6.5 | 26.1 ±6.5 | 26.2 ±5.9 |
| | N (Nmiss) | 103 (13) | 100 (12) | 82 (8) | 106 (7) | 104 (7) | 79 (6) |
| Gender, N (%) | Female | 53 (45.7) | 53 (47.3) | 40 (44.4) | 60 (53.1) | 59 (53.2) | 44 (51.8) |
| | Male | 63 (54.3) | 59 (52.7) | 50 (55.6) | 53 (46.9) | 52 (46.8) | 41 (48.2) |
| Race, N (%) | Caucasian/ White | 92 (79.3) | 88 (78.6) | 71 (78.9) | 96 (85) | 94 (84.7) | 73 (85.9) |
| | Black or African American | 5 (4.3) | 5 (4.5) | 4 (4.4) | 5 (4.4) | 5 (4.5) | 4 (4.7) |
| | Asian | 1 (0.9) | 1 (0.9) | 1 (1.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Hispanic | 6 (5.2) | 6 (5.4) | 5 (5.6) | 2 (1.8) | 3 (2.7) | 1 (1.2) |
| | NA | 12 (10.3) | 12 (10.7) | 9 (10.0) | 9 (8.0) | 8 (7.2) | 6 (7.1) |
| | Other | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.9) | 1 (0.9) | 1 (1.2) |
| Country N (%) | Belgium | 4 (100.0) | 4 (100.0) | 4 (100.0) | 2 (100.0) | 2 (100.0) | 1 (50.0) |
| | France | 12 (100.0) | 12 (100.0) | 9 (75.0) | 9 (100.0) | 8 (88.9) | 6 (66.7) |
| | Germany | 10 (100.0) | 9 (90.0) | 8 (80.0) | 7 (100.0) | 7 (100.0) | 4 (57.1) |
| | Italy | 5 (100.0) | 4 (80.0) | 4 (80.0) | 9 (100.0) | 9 (100.0) | 6 (66.7) |
| | Portugal | 1 (100.0) | 1 (100.0) | 1 (100.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Spain | 5 (100.0) | 5 (100.0) | 4 (80.0) | 6 (100.0) | 6 (100.0) | 6 (100.0) |
| | UK | 13 (100.0) | 13 (100.0) | 12 (92.0) | 11 (100.0) | 11 (100.0) | 7 (63.6) |
| | US | 66 (98.5) | 64 (95.5) | 48 (71.6) | 69 (98.6) | 68 (97.1) | 55 (78.6) |

N: number of patients, Nmiss: number of missing values, SD: standard deviation, BMI: Body-Mass-Index; Body height, body weight and BMI were measured at the baseline visit. NA: not applicable, due to respective local requirements or legal restrictions, the ethnic origin of some patients could not be documented. Country (%): Percentages are based on the number of randomized patients within each country

**Table 22: Diagnosis at screening/eligibility visit: Summary statistics for time since diagnosis (FAS, N = 229; PPS, N=175)**

| | | Treatment | | |
|---|---|---|---|---|
| | | Lutathera | Octreotide LAR | p-value* |
| **FAS (N=229)** | | | | |
| Time since first diagnosis of midgut carcinoid tumor [Months] | Median | 45.7 | 57.8 | 0.0869 |
| | n (Nmiss) | 116 (0) | 113 (0) | |
| Time since first progression of disease (PD) after diagnosis [Months] | Median | 20.2 | 23.4 | 0.3808 |
| | N (Nmiss) | 116 (0) | 111 (2) | |
| Time since first diagnosis of metastases [Months] | Median | 42.6 | 38.3 | 0.2984 |
| | n (Nmiss) | 115 (1) | 111 (2) | |
| **PPS (N=175)** | | | | |
| Time since first diagnosis of midgut carcinoid tumor [Months] | Median | 47.0 | 64.0 | 0.0653 |
| | N (Nmiss) | 90 (0) | 85 (0) | |
| Time since first progression of disease (PD) after diagnosis [Months] | Median | 21.9 | 25.2 | 0. 4452 |
| | N (Nmiss) | 90 (0) | 84 (1) | |
| Time since first diagnosis of metastases [Months] | Median | 45.3 | 46.4 | 0.3215 |
| | N (Nmiss) | 89 (1) | 83 (2) | |

N: number of patients, n: number of patients per treatment group, Nmiss: number of missing values, SD: standard deviation. *: two-sided p-value derived from Wilcoxon's Rank Sum Test.
Note: Times since first diagnosis or progression/metastases are calculated in relation to the date of randomization

**Table 23: Diagnosis at screening visit: Primary tumour site, sites of metastases (FAS, N = 229; PPS, N=175)**

| | | | Treatment | |
|---|---|---|---|---|
| | | | Lutathera n (%) | Octreotide LAR n (%) |
| FAS (N=229) | Primary tumor site | Jejunum | 6 (5.2) | 9 (8.0) |
| | | Illeum | 86 (74.1) | 82 (72.6) |
| | | Appendix | 1 (0.9) | 2 (1.8) |
| | | Right colon | 3 (2.6) | 1 (0.9) |
| | | Other | 20 (17.2) | 19 (16.8) |
| | Metastases present? | Yes | 116 (100.0) | 111 (98.2) |
| | | No | 0 (0.0) | 2 (1.8) |
| | Site of metastases (Yes): | | | |
| | | Bone | 12 (10.3) | 12 (10.6) |
| | | Brain | 0 (0.0) | 0 (0.0) |
| | | Liver | 98 (84.5) | 94 (83.2) |
| | | Lungs | 11 (9.5) | 5 (4.4) |
| | | Lymph nodes | 77 (66.4) | 66 (58.4) |
| | | Other | 40 (34.5) | 36 (31.9) |
| PPS (N=175) | Primary tumor site | Jejunum | 5 (5.6) | 7 (8.2) |
| | | Illeum | 63 (70.0) | 61 (71.8) |
| | | Appendix | 1 (1.1) | 2 (2.4) |
| | | Right colon | 3 (3.3) | 1 (1.2) |
| | | Other | 18 (20.0) | 14 (16.5) |
| | Metastases present? | Yes | 90 (100.0) | 83 (97.6) |
| | | No | 0 (0.0) | 2 (2.4) |
| | Site of metastases (Yes): | | | |
| | | Bone | 7 (7.8) | 8 (9.4) |
| | | Brain | 0 (0.0) | 0 (0.0) |
| | | Liver | 74 (82.2) | 68 (80.0) |
| | | Lungs | 10 (11.1) | 5 (5.9) |
| | | Lymph nodes | 60 (66.7) | 49 (57.6) |
| | | Other | 31 (34.4) | 28 (32.9) |

**Table 24: Prior cancer surgery (FAS, N=229; PPS, N=175)**

| | | | Treatment | | |
|---|---|---|---|---|---|
| | | | Lutathera n (%) | Octreotide LAR n (%) | All n (%) |
| FAS (N=229) | Any prior cancer surgery | Yes | 93 (80.2) | 94 (83.2) | 187 (81.7) |
| | | No | 23 (19.8) | 19 (16.8) | 42 (18.3) |
| | Number of patients with: | | | | |
| | Resection | | 90 (77.6) | 94 (83.2) | 184 (80.3) |
| | Ablation | | 6 (5.2) | 11 (9.7) | 17 (7.4) |
| | Chemo-embolization | | 14 (12.1) | 11 (9.7) | 25 (10.9) |
| | Time since last intervention [years] | Mean (SD) | 3.3 (3.3) | 4.3 (3.5) | 3.8 (3.4) |
| PPS (N=175) | Any prior cancer surgery | Yes | 72 (80.0) | 71 (83.5) | 143 (81.7) |
| | | No | 18 (20.0) | 14 (16.5) | 32 (18.3) |
| | Number of patients with: | | | | |
| | Resection | | 69 (76.7) | 71 (83.5) | 140 (80.0) |
| | Ablation | | 5 (5.6) | 8 (9.4) | 13 (7.4) |
| | Chemo-embolization | | 13 (14.4) | 10 (11.8) | 23 (13.1) |
| | Time since last intervention [years] | Mean (SD) | 3.6 (3.5) | 4.3 (3.5) | 3.9 (3.5) |

The sites 'primary tumour' (72.9%) and 'bowel' (69.0%) were most frequently reported as resection site in patients of the FAS. The treatment groups did not differ with regard to the reported prior cancer surgery.

## Numbers analysed

Evaluation was performed for the FAS (N = 229), the PPS (N = 175) and the SAF (N = 223).

## Outcomes and estimation

Primary efficacy endpoint: PFS

The median PFS was not reached for Lutathera and was 8.5 months for 60 mg Octreotide LAR [95% CI: 5.8-9.1 months]; differences in PFS between treatment groups was statistically significant p<0.0001, with a hazard ratio of 0.18 [95% CI: 0.11-0.29], indicating a significantly lower risk for a PFS event with Lutathera treatment compared to Octreotide LAR.

In the Lutathera arm 82% of the observations were censored (2.6% because of start of new anti-cancer therapy, 2.6% due to death or progression after two or more missed visits, 5.2% because of treatment discontinuations for toxicity or other reason with no additional scans, 7.8% because of no post-baseline tumour assessments and 63.8% due to no documented progression); versus, 38.1% in the Octreotide LAR arm (1.8% due to death or progression after two or more missed visits, 2.7% because of treatment discontinuations for toxicity or other reason with no additional scans, 5.3% because of start of new anti-cancer therapy, 6.2% because of no post-baseline tumour assessments and 22.1% due to no documented progression).

**Table 25: Progression Free Survival (PFS) [months] - Summary of analysis according to Kaplan Meier method (based on CENTRAL tumour assessment) (FAS, N=229; PPS, N=175)**

| | | Treatment | |
|---|---|---|---|
| | | Lutathera | Octreotide LAR |
| FAS (N=229) | Total n | 116 | 113 |
| | Patients with events | 21 (18.1) | 70 (61.9) |
| | Censored patients | 95 (81.9) | 43 (38.1) |
| | Median (95%-CI) | not reached | 8.5 (5.8 ; 9.1) |
| | p-value of Log-rank test | <0.0001 | |
| | Hazard ratio* (95%-CI) | 0.177 (0.108 ; 0.289) | |
| PPS (N=175) | Total n | 90 | 85 |
| | Patients with events | 15 (16.7) | 48 (56.5) |
| | Censored patients | 75 (83.3) | 37 (43.5) |
| | Median (95%-CI) | not reached | 9.0 (6.4; 11.1) |
| | p-value of Log-rank test | <0.0001 | |
| | Hazard ratio* (95%-CI) | 0.167 (0.093 ; 0.301) | |

The Kaplan-Meier graphs for the FAS are presented in the figure below.

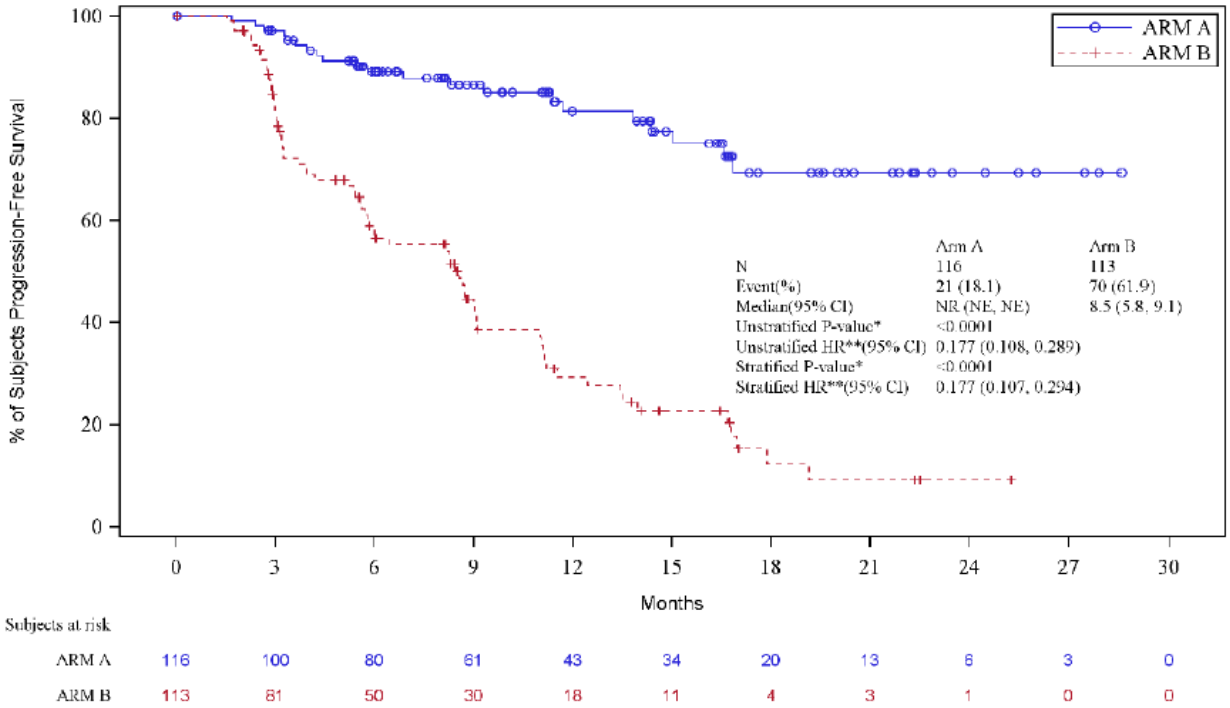



**Figure 18: Progression Free Survival (PFS) - Kaplan-Meier graph (FAS)**

At the cut-off date for post-hoc statistical analysis (30 June 2016), the number of centrally confirmed disease progressions or deaths was 30 events in the Lutathera arm and 78 events in the octreotide LAR arm (Table 26). PFS differed significantly (p<0.0001) between the treatment groups. The median PFS for Lutathera was 28.4 months whereas the one of octreotide LAR was 8.5 months. The hazard ratio for Lutathera was 0.21 (95% CI: 0.14 - 0.33), indicating 79% reduction in the risk for a patient to progress or die under Lutathera compared to octreotide LAR.

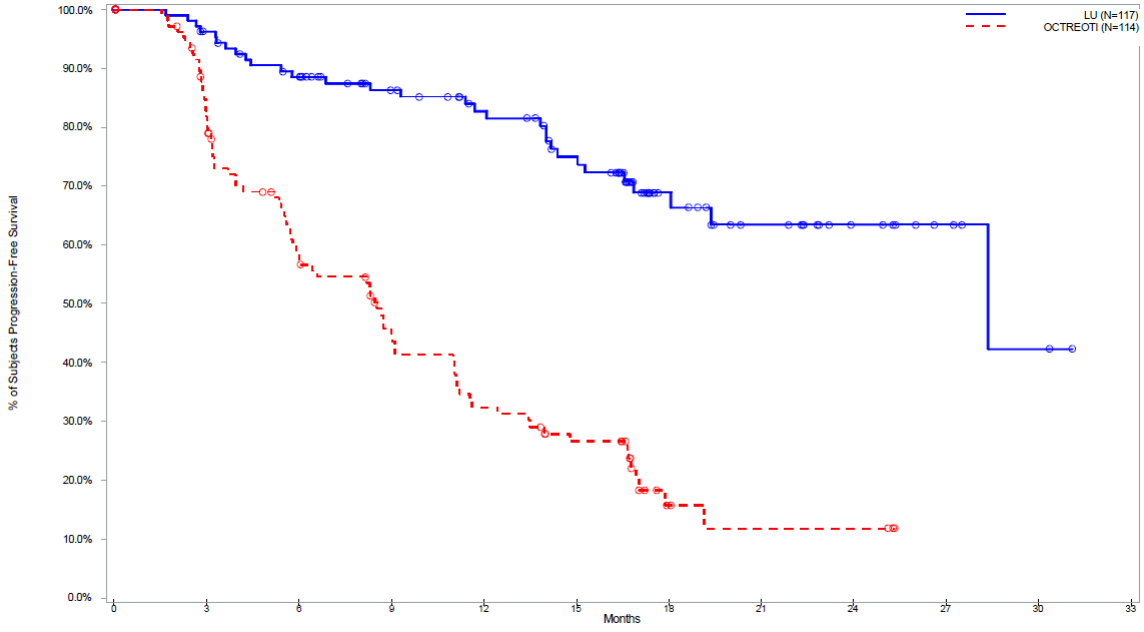
**Table 26: PFS observed in the NETTER-1 phase III study in patients with progressive midgut carcinoid tumour - cut-off date 30 June 2016 (full analyses set (FAS), N=231)**

| | Treatment | |
|---|---|---|
| | **Lutathera** | **Octreotide LAR** |
| N | 117 | 114 |
| Patients with events | 30 | 78 |
| Censored patients | 87 | 36 |
| Median months (95%-CI) | 28.4 (28.4; NE) | 8.5 (5.8; 11.0) |
| p-value of Log-rank test | <0.0001 | |
| Hazard ratio (95%-CI) | 0.214 (0.139 ; 0.331) | |

N: number of patients, CI: confidence interval.

The PFS Kaplan-Meier graph for the full analysis set (FAS) at the cut-off date 30 June 2016 is depicted in Figure 19.

**Figure 19: PFS Kaplan Meier curves of patients with progressive midgut carcinoid tumour - cut-off date 30 June 2016 (NETTER-1 phase III study; FAS, N=231)**




Secondary endpoints: Objective response rate

Best tumour response is shown in Table 27.

**Table 27: Best tumour response (SD, PR, CR) by treatment group; tumour response data as given by the IRC Keosys (FAS, N=229; PPS, N=175)**

| | | Treatment | |
|---|---|---|---|
| | Tumour response | Lutathera n (%) | Octreotide LAR n (%) |
| FAS (N=229) | CR | 1 (0.9) | 0 (0.0) |
| | PR | 14 (12.1) | 4 (3.5) |
| | SD | 80 (69.0) | 71 (62.8) |
| | PD | 7 (6.0) | 25 (22.1) |
| | Not available* | 14 (12.1) | 13 (11.5) |
| PPS (N=175) | CR | 1 (1.1) | 0 (0.0) |
| | PR | 12 (13.3) | 3 (3.5) |
| | SD | 68 (75.6) | 60 (70.6) |
| | PD | 4 (4.4) | 16 (18.8) |
| | Not available* | 5 (5.6) | 6 (7.1) |

**Table 28: Objective Response Rate (ORR; centrally assessed by the IRC Keosys) - Only patients with non-missing central response (FAS, N=229; PPS, N=175)**

| | | Treatment | |
|---|---|---|---|
| | | Lutathera | Octreotide LAR |
| FAS (N=229) | ORR (%) [95%-CI] | 15 (14.7%) [7.8, 21.6] | 4 (4.0%) [0.2, 7.8] |
| | Fisher's exact test, p-value | 0.0141 | |
| PPS (N=175) | ORR (%) [95%-CI] | 13 (15.3%) [7.6, 22.9] | 3 (3.8%) [0.0, 8.0] |
| | Fisher's exact test, p-value | 0.0167 | |

N: number of patients, n: number of patients per treatment group. Patients without post-baseline scans were excluded from the analysis. CI: confidence interval. Source data: Table 14.2.2.1.1, Table 14.2.2.1.2

An additional analysis was provided for ORR based on the results of local tumour responses. As with the PFS results the results with the local assessment were more conservative than the results based on central assessment, but still showing a statistically significant difference favouring the Lutathera arm. Analyses based on local assessment are supportive.

**Table 29: Objective Response Rate (ORR; LOCAL assessment Data source: eCRF) – Only patients with non-missing central response (FAS, N=229)**

| | | Treatment | |
|---|---|---|---|
| | | Lutathera | Octreotide LAR |
| FAS (N=229) | ORR (%) [95%-CI] | 16 (15.2%) | 4 (4.0%) [0.2, 7.8] |
| | Fisher's exact test, p-value | 0.0086 | |

N: number of patients, n: number of patients per treatment group. Patients without post-baseline scans were excluded from the analysis. CI: confidence interval. Source data: Table 14.2.2.1.4

Secondary endpoints: Overall survival (OS)

**Table 30: Overall Survival [number of months] - Summary of analysis according to Kaplan Meier method (FAS, N=229; PPS, N=175) cutoff date 24 July 2015**

| | | Treatment | |
|---|---|---|---|
| | | Lutathera | Octreotide LAR |
| FAS (N=229) | Total n | 116 | 113 |
| | Patients with events | 17 (14.7) | 31 (27.4) |
| | Censored patients | 99 (85.3) | 82 (72.6) |
| | Median (95%-CI) | not reached | 27.4 (20.1, NE) |
| | p-value of Log-rank test* | 0.0083 | |
| | Hazard ratio (95%-CI)* | 0.459 (0.254; 0.830) | |
| PPS (N=175) | Total n | 90 | 85 |
| | Patients with events | 10 (11.1) | 21 (24.7) |
| | Censored patients | 80 (88.9) | 64 (75.3) |
| | Median (95%-CI) | not reached | not reached (20.1, NE) |
| | p-value of Log-rank test* | 0.0106 | |
| | Hazard ratio (95%-CI)* | 0.388 (0.182; 0.824) | |

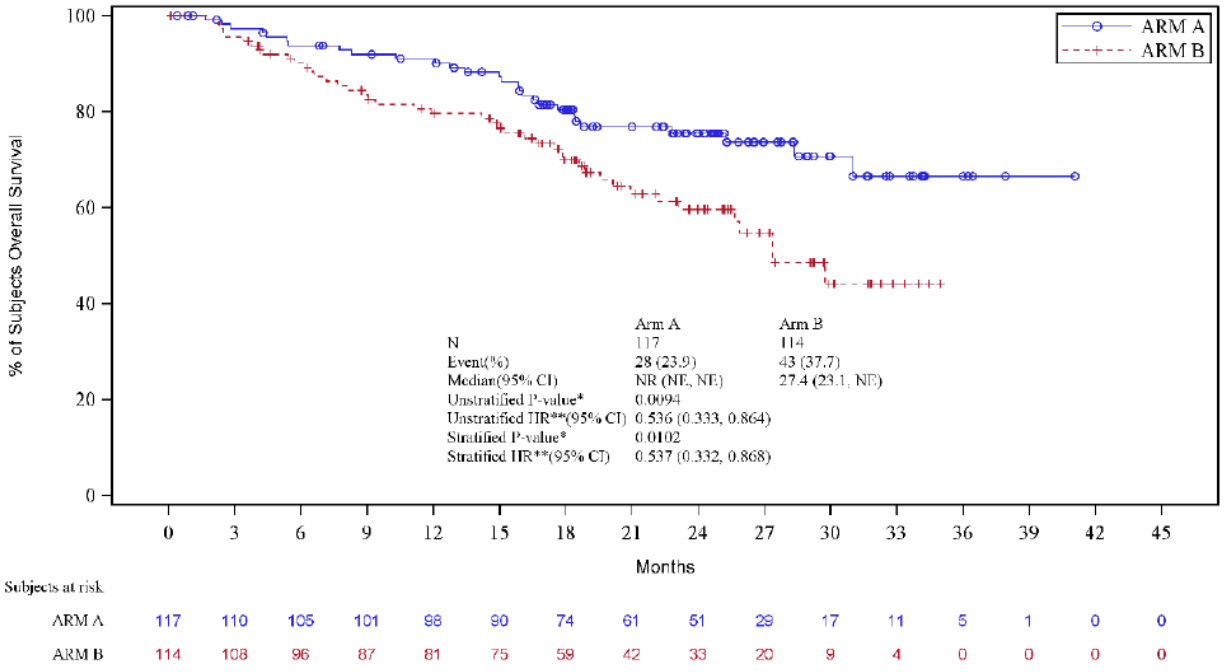


Figure 11-5 Overall Survival (OS) - Kaplan-Meier graph (FAS). Cut-off date 30 June 2016

**Figure 20: Overall Survival (OS) - Kaplan-Meier graph (FAS)**

**Table 31: Overall Survival [number of months] - Summary of analysis according to Kaplan Meier method (All randomized subjects through data cutoff date 30 June 2016, N = 231)**

| | | Treatment | |
|---|---|---|---|
| | | Lutathera | Octreotide LAR |
| All Randomized (N=231) | Total n | 117 | 114 |
| | Patients with events | 28 (23.9) | 43 (37.7) |
| | Censored patients | 89 (76.1) | 71 (62.3) |
| | Median (95%-CI) | not reached | 27.4 (23.1, NE) |
| | p-value of Log-rank test* | 0.0094 | |
| | Hazard ratio (95%-CI)* | 0.536 (0.333; 0.864) | |

For the interim analysis of OS at the cut-off date (24 July 2015), the number of deaths was 17 in the Lutathera arm and 31 in the Octreotide LAR arm and the hazard ratio was 0.459 in favour of Lutathera, but did not reach the level of significance for interim analysis (HR 99.9915% CI: 0.140, 1.506). The median OS for the Lutathera group was not reached at the time of analysis in the FAS population, but was 27.4 months in the Octreotide LAR group.

For the analysis of OS at the cut-off date 30 June 2016, the number of deaths was 28 in the Lutathera arm and 43 in the Octreotide LAR arm with a HR of 0.536, and a median OS of 27.4 months in octreotide LAR arm and still not reached in Lutathera arm. The final OS analysis is foreseen after 158 cumulative deaths.

Secondary endpoints: Time to tumour progression

**Table 32: Time to tumour progression (TTP) [number of months] - Summary of analysis according to Kaplan Meier method (data source: IRC Keosys; FAS, N=229; PPS, N=175)**

| | | Treatment | |
|---|---|---|---|
| | | Lutathera | Octreotide LAR |
| FAS (N=229) | Total n | 116 | 113 |
| | Patients with events | 15 (12.9) | 61 (54.0) |
| | Censored patients | 101 (87.1) | 52 (46.0) |
| | Median (95%-CI) | not reached | 8.7 (6.0; 11.1) |
| | p-value of log-rank test* | < 0.0001 | |
| | Hazard ratio (95%-CI)* | 0.137 (0.077 ; 0.242) | |
| PPS (N=175) | Total n | 90 | 85 |
| | Patients with events | 11 (12.2) | 42 (49.4) |
| | Censored patients | 79 (87.8) | 43 (50.6) |
| | Median (95%-CI) | not reached | 9.1 (8.3 ; 11.5) |
| | p-value of log-rank test* | < 0.0001 | |
| | Hazard ratio (95%-CI)* | 0.134 (0.068 ; 0.262) | |

***Exploratory endpoints***

**Duration of Response (DoR)**

A summary of the analysis for the FAS and PPS is given in the table below.

**Table 33: Duration of Response (DoR) - data source: IRC Keosys (FAS, N=229; PPS, N=175)**

| | | Treatment | |
|---|---|---|---|
| | | Lutathera | Octreotide LAR |
| FAS (N=229) | n (%) | 15 (12.9) | 4 (3.5) |
| | Q1 - Q3 | 5.8, NR | 1.9, NE |
| | Median (95%-CI) | NR (2.8-NE) | 1.9 (1.9-NE) |
| PPS (N=175) | n (%) | 13 (14.4) | 3 (3.5) |
| | Q1 - Q3 | NR, NR | 1.9, NR |
| | Median (95%-CI) | NR (2.8, NE) | NR (1.9, NE) |

## Ancillary analyses

PFS and ORR by local assessment

**Table 34: Progression Free Survival (PFS) [months] - Summary of analysis according to Kaplan Meier method (LOCAL assessment) (FAS, N=229)**

| | | Treatment | |
|---|---|---|---|
| | | Lutathera | Octreotide LAR |
| FAS (N=229) | Total n | 116 | 113 |
| | Patients with events | 31 (26.7) | 62 (54.9) |
| | Censored patients | 85 (73.3) | 51 (45.1) |
| | Median (95%-CI) | 26.0 (18.4; NE) | 8.4 (6.0; 11.01) |
| | p-value of Log-rank test* | <0.0001 | |
| | Hazard ratio (95%-CI)* | 0.260 (0.166; 0.407) | |

*Based on unstratified data; N: number of patients, n: number of patients per treatment group, CI: confidence interval. Source data: Table 14.2.1.7

**Table 35: Objective response rate (ORR; LOCAL assessment data source:eCRF) - Only patients with non-missing central response (FAS, N=229)**

| | | Treatment | |
|---|---|---|---|
| | | Lutathera | Octreotide LAR |
| FAS (N=229) | ORR (%) [95%-CI] | 16 (15.2%) | 4 (4.0%) [0.2, 7.8] |
| | Fisher's exact test, p-value | 0.0086 | |

N: number of patients, n: number of patients per treatment group. Patients without post-baseline scans were excluded from the analysis. CI: confidence interval. Source data: Table 14.2.2.1.4

PFS sensitivity analyses

The results for the sensitivity analysis assigning the event time to the next scheduled imaging time rather than the actual time (to correct for any difference in timing of scans) are presented.

**Table 36: PFS - Sensitivity analysis I - Assigning the event time to the next scheduled imaging time rather than the actual time (FAS, N=229)**

| | | Treatment | |
|---|---|---|---|
| | | Lutathera | Octreotide LAR |
| FAS (N=229) | Total n | 116 | 113 |
| | Patients with events | 21 (18.1) | 70 (61.9) |
| | Censored patients | 95 (81.9) | 43 (38.1) |
| | Median (95%-CI) | Not reached (NE; NE) | 8.4 (8.2-11.0) |
| | p-value of Log-rank test* | <0.0001 | |
| | Hazard ratio (95%-CI)* | 0.179 (0.109; 0.293) | |

A summary of all the sensitivity analyses are presented in the table below.

**Table 37: Progression free survival sensitivity analysis summary (FAS, N=229)**

| | | Lutathera | | | | | | Octreotide LAR | | | | | | Hazard Ratio | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Events | | Time [months] | | | N | Events | | Time [months] | | | | 95%CI | | p-value[a] |
| | | | n | % | Median | 95%CI | | | n | % | Median | 95%CI | | | | | |
| Main | FAS | 116 | 21 | 18.1 | NR | NE | NE | 113 | 70 | 61.9 | 8.5 | 5.8 | 9.1 | 0.177 | 0.108 | 0. 289 | <0.0001 |
| Sens1* | FAS | 116 | 21 | 18.1 | NR | NE | NE | 113 | 70 | 61.9 | 8.4 | 8.2 | 11.0 | 0.179 | 0.109 | 0.293 | <0.0001 |
| Sens2** | FAS | 116 | 21 | 18.1 | NR | NE | NE | 113 | 73 | 64.6 | 8.4 | 5.8 | 9.0 | 0.173 | 0.106 | 0.282 | <0.0001 |
| Sens3*** | FAS | 116 | 24 | 20.7 | NR | 18.7 | NE | 113 | 72 | 63.7 | 8.5 | 5.8 | 11.0 | 0.196 | 0.122 | 0.312 | <0.0001 |
| Sens4[$] | FAS | 116 | 27 | 23.3 | NR | 18.4 | NE | 113 | 78 | 69.0 | 8.5 | 6.0 | 9.1 | 0.207 | 0.133 | 0.322 | <0.0001 |
| Sens5a[&] | FAS | 116 | 21 | 18.1 | NR | NE | NE | 113 | 70 | 61.9 | 9.1 | 6.5 | 11.0 | 0.190 | 0.116 | 0.311 | <0.0001 |
| Sens5b[^] | FAS | 116 | 21 | 18.1 | NR | NE | NE | 113 | 70 | 61.9 | 8.3 | 5.6 | 8.8 | 0.190 | 0.116 | 0.311 | <0.0001 |
| Sens6[#] | FAS | 116 | 31 | 26.7 | 26.0 | 18.4 | NE | 113 | 62 | 54.9 | 8.4 | 6.0 | 11.1 | 0.260 | 0.166 | 0.407 | <0.0001 |

[a]Based on unstratified data
N: Number of patients per group, n: number of events, CI: confidence intervals, PFS: progression free survival, FAS: Full analysis Set; NR: not reached; NE: not evaluable.
*Sens1: PFS sensitivity analysis 1, assigning the event time to the next scheduled imaging time rather than the actual time if between planned visits.
**Sens2: PFS sensitivity analysis 2, ignoring early censoring because of new anti-cancer treatments started before progressive disease or death.
***Sens3: PFS sensitivity analysis 3, ignoring early censoring because of more than 2 missing consecutive visits.
$Sens4: PFS sensitivity analysis 4, ignoring both early censoring because of more than 2 missing consecutive visits and early censoring because of new anti-cancer treatments started before progressive disease or death.
&Sens5a: PFS sensitivity analysis 5a, Calculating PFS times from date of baseline scan (instead of randomization)
^Sens5b: PFS sensitivity analysis 5b, Calculating PFS times from date of first investigational drug administration (instead of randomization)
#Sens6: PFS sensitivity analysis 6, Local assessment

**Correlation Analyses**

For the assessment of the prognostic value, a number of correlation analyses were carried out.

The table below details the correlation of PFS, OS, TTP with the baseline levels of CgA in serum, 5-HIAA, OctreoScan Tumour uptake score and AP.

**Table 38: Correlations of PFS, OS, TTP with the baseline levels of CgA in serum and 5-HIAA in urine (data source: Interlab central lab database for CgA and IRC central lab database for efficacy outcomes, FAS; N=229; PPS, N=182)**

| | Parameter | Lutathera | Octreotide LAR |
|---|---|---|---|
| | | Correlation coefficient (p-value*) | Correlation coefficient (p-value*) |
| **Correlation with baseline serum CgA** | | | |
| **FAS (N=229)** | OS | -0.138 (0.2255) | -0.240 (0.0281) |
| | PFS | -0.119 (0.2959) | -0.223 (0.0419) |
| | TTP | -0.121 (0.2898) | -0.275 (0.0115) |
| **Correlation with baseline urine 5-HIAA** | | | |
| **FAS (N=229)** | OS | -0.083 (0.4631) | -0.052 (0.6439) |
| | PFS | -0.205 (0.0680) | -0.144 (0.1955) |
| | TTP | -0.206 (0.0673) | -0.157 (0.1602) |
| **Correlation with baseline Karnofsky Performance Status** | | | |
| **FAS (N=229)** | OS | 0.069 (0.4661) | 0.311 (0.0009) |
| | PFS | 0.134 (0.1519) | 0.381 (<0.0001) |
| | TTP | 0.140 (0.1370) | 0.412 (<0.0001) |
| **Correlation with baseline OctreoScan® tumour uptake score (data source: IRC central lab database)** | | | |
| **FAS (N=229)** | OS | -0.017 (0.8586) | 0.003 (0.9786) |
| | PFS | 0.078 (0.4023) | 0.078 (0.4104) |
| | TTP | 0.072 (0.4440) | 0.049 (0.6058) |
| **Correlation with baseline serum levels of Alkaline Phosphatase (AP)** | | | |
| **FAS (N=229)** | OS | -0.102 (0.2850) | -0.259 (0.0059) |
| | PFS | -0.172 (0.0696) | -0.253 (0.0071) |
| | TTP | -0.183 (0.0529) | -0.293 (0.0017) |

## Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 39: Summary of efficacy for NETTER-1 trial**

| | | |
|---|---|---|
| **Title:** A multicentre, stratified, open, randomised, comparator-controlled, parallel-group phase III study comparing treatment with 177Lu-Oxodotreotide to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours. | | |
| Study identifier | NETTER-1; EudraCT/IND: AAA-III-01 (2011-005049-11/77219) | |
| Design | A multicentre, stratified, open, randomised, comparator-controlled, parallel-group phase III study. Stratification based on:<br>*1. OctreoScan® tumour uptake score (Grade 2, 3 and 4);*<br>*2. The length of time that patients have been on the most recent constant dose of Octreotide prior to randomisation (≤6 and >6 months).* | |
| | Duration of main phase: | Started with date of first enrolment on 10 Jul 2012<br>Randomisation not complete at time of primary- end-point analysis. |
| Hypothesis | Superiority | |
| Treatments groups | **Test Product** | **177Lu-Oxodotreotide (Lutathera**)<br><br>In total 29.6 GBq (800 mCi) of Lutathera administered in four equally divided doses. Four administrations of 7.4 GBq (200 mCi) of Lutathera, each dose to be infused over 30 minutes<br><br>116 patients randomised |
| | **Reference Therapy/ Comparator** | Octreotide acetate powder for suspension for intramuscular (i.m.) injection.<br><br>60 mg Octreotide acetate (Sandostatin® LAR) treatment every 4 weeks (i.m. injections) ± 3 days until the final overall analysis of PFS, unless the patient progressed or died. After the final PFS analysis, the treatment/assessment period for each patient became fixed and all patients received 60 mg for a maximum of 72 weeks and then proceeded to the long-term follow-up assessment phase for evaluation of survival.<br><br>113 patients randomised |

| | | | |
|---|---|---|---|
| | **Concomitant and Rescue Treatment** | | **In the Lutathera arm only: 30 mg Octreotide LAR treatment for symptoms control** administered until the final overall analysis of, unless the patient progressed or died. After the final PFS analysis, the treatment/assessment period became fixed and all patients received 30 mg for a maximum of 72 weeks and then proceeded to the long-term follow-up assessment phase for evaluation of survival and long term toxicities.<br><br>**In the Lutathera arm only: amino acid infusion (Vamin 18 in Europe and Aminosyn II 10% in USA)** was given concomitantly with each administration of Lutathera for kidney protection.<br><br>**In both arms:** in case patients experienced clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, **Octreotide s.c. rescue injections** were allowed. |
| Endpoints and definitions | Primary endpoint | **Progression free survival (PFS)** | Time from randomisation to documented, centrally assessed disease progression, as evaluated by the Independent Reading Centre (IRC), and death due to any cause. |
| | Secondary endpoint | **Objective Response Rate (ORR)** | Objective Response Rate (ORR) was calculated as the proportion of patients with tumour size reduction (sum of partial responses (PR) and complete responses (CR)). Response duration was calculated from the time of initial response until documented tumour progression. |
| | Secondary endpoint | **Overall Survival (OS)** | Overall Survival (OS) was calculated from the randomisation date until the day of death due to any cause; OS was not censored if a patient received other anti-tumour treatments after study medication. |
| | Secondary endpoint | **Time to Tumour Progression (TTP)** | TTP is defined as the time from randomisation to progression centrally assessed. It includes patients who dropped out due to toxicity, but omits patients who died without measured progression (censored to last follow-up date or death date). |
| | Secondary endpoint | **Duration of Response (DoR)** | The Duration of Response (DoR) is defined as the time from initially meeting the criteria for response (CR or PR) until the time of progression by RECIST. |
| Data Cut-off point | 30th June 2016 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | Full Analysis Set | | |
| Descriptive statistics and estimate variability | **Treatment group** | ***Lutathera*** | ***Octreotide LAR 60 mg*** |
| | **Number of subjects** | 116 | 113 |

| | | | |
|---|---|---|---|
| | **Primary endpoint (Median PFS**-months) | 28.4 | 8.5 |
| | 95% CI | (19.4; NR) | (5.8; 11.0) |
| | **Secondary Endpoint: ORR (%)** | 14.7 | 4.0 |
| | 95% CI | 7.8; 21.6 | 0.2; 7.8 |
| | **Secondary endpoint: median OS** (months) | Not reached | 27.4 |
| | 95% CI | Not reached | 20.1; NE |
| | **Secondary endpoint: TTP** (months) | Not reached | 8.7 |
| | 95% CI | Not reached | 6.0; 11.1 |
| | **Secondary endpoint: DoR** (months) | Not reached | Not reached |
| | <variability statistic> | 2.8; NE | 1.9; NE |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint: **PFS** | Lutathera vs. Octreotide LAR 60 mg | |
| | | Hazard Ratio | 0.230 |
| | | 95% CI | 0.150; 0.361 |
| | | P-value | <0.0001 |
| | Secondary endpoint: **ORR**<br><br>Secondary endpoint: **TTP** | Lutathera vs. Octreotide LAR 60 mg | |
| | | Difference in ORR | 10.7 |
| | | P-value | 0.0141 |
| | | Lutathera vs. Octreotide LAR 60 mg | |
| | Secondary endpoint: **TTP**<br><br>Primary endpoint: **PFS** | Hazard Ratio | 0.137 |
| | | 95% CI | 0.077; 0.242 |
| | | P-value | <0.0001 |
| | | Lutathera vs. Octreotide LAR 60 mg | |
| Notes | | | |

## Analysis performed across trials (pooled analyses and meta-analysis)

The integrated efficacy analysis population was the pooled FAS, which included all patients randomised in the Phase III NETTER-1 study and the subgroup of all Dutch patients with inoperable, progressive, locally advanced or metastatic, somatostatin receptor-positive, midgut carcinoid tumours in the Phase I/II Erasmus MC study. The patients in the Erasmus study included in the pooled FAS were those that

met the main eligibility criteria of the NETTER-1 study. All the ISE efficacy analyses were completed using the pooled FAS.

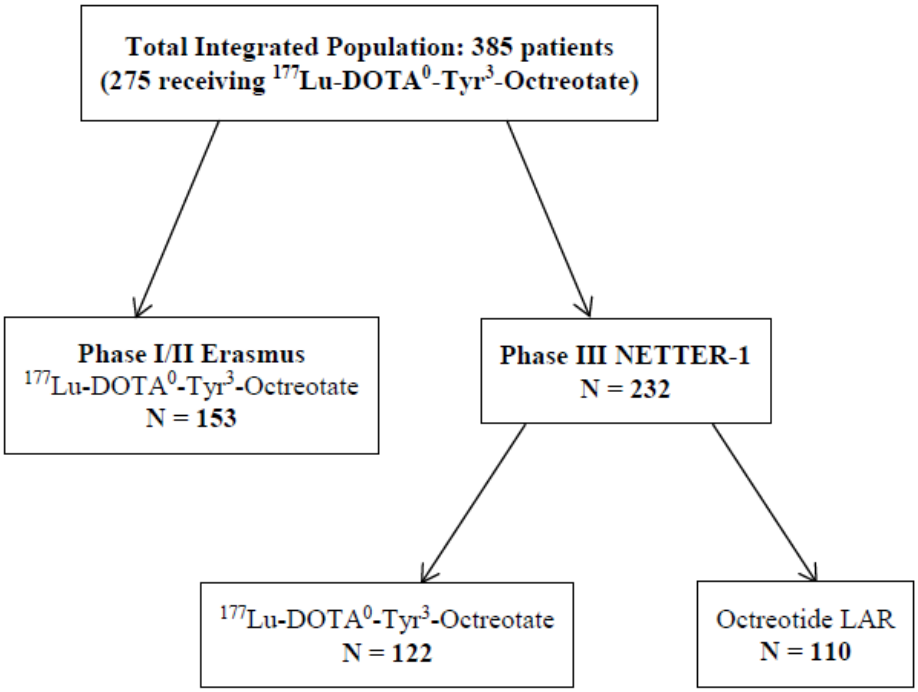



**Figure 21: Patients Disposition in the ISE Population Primary Efficacy Endpoints**

The primary efficacy variables for the integrated analysis were objective response rate/best overall tumour response and duration of response.

*Best Overall Tumour Response/Objective Response Rate*

**Table 40: Best Overall Response Analysis (RECIST) – ISE Population**

| Characteristic | Parameter | $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-octreotate (N: 275)* | Octreotide LAR (N: 110)* |
|---|---|---|---|
| Best Overall Response | PD | 12 (4.4%) | 25 (22.7%) |
| | SD | 146 (53.1%) | 71 (64.5%) |
| | PR | 45 (16.4%) | 4 (3.6%) |
| | CR | 3 (1.1%) | 0 |
| | NE | 58 (21.1%) | 0 |
| | No post-baseline scan | 11 (4.0%) | 10 (9.1%) |
| | p-value | <0.0001 | |
| Best Overall Response | Non Responder | 227 (82.5%) | 106 (96.4%) |
| | CR/PR | 48 (17.5%) | 4 (3.6%) |
| | 95% CI for CR/PR | (13.2, 22.5) | (1.0, 9.0) |
| | p-value | 0.0001 | |

*N=Number of subjects on each treatment in the population.

CR: complete response; NE: non evaluable; PD: progressive disease; PR: partial response; SD: stable disease.

Source: ISS Table 7.1

*Duration of Response*

**Table 41: Duration of Response (RECIST) – ISE Population**

| Characteristic | Parameter | $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-octreotate (N: 275) | Octreotide LAR (N: 110) |
|---|---|---|---|
| Duration of Response (months) | n | 48 | 4 |
| | Mean (sd) | 12 (10.5) | 1.6 (1.2) |
| | Median | 9.4 | 1.9 |
| | (95% CI) | (6.0, 15.9) | (0.03, 2.8) |
| | (Min, Max) | (0.03, 39.6) | (0.03, 2.8) |
| | p-value | 0.0232 | |

**Secondary Efficacy Endpoints**

The secondary efficacy endpoints for the subsequent integrated analysis were overall survival and progression-free survival.

*Overall Survival*

**Table 42: Analysis of Overall Survival – ISE Population**

| Characteristic | Percentile | Parameter | Lutathera (N: 275) | Octreotide LAR (N: 110) |
|---|---|---|---|---|
| Overall Survival (months) | 25th Percentile | Estimate | 21.4 | 15.1 |
| | | (95% CI) | (18.3, 26.9) | (9.00, 20.1) |
| | Median | Estimate | 44.4 | 27.4 |
| | | (95% CI) | (34.4, 54.8) | (20.1, NE) |
| | 75th Percentile | Estimate | 83.2 | NR |
| | | (95% CI) | (61.5, 114.4) | (27.4, NE) |
| | Log-Rank Test | p-value | 0.0049 | |
| | Hazard Ratio | HR (95% CI) | 0.535 (0.344, 0.833) | |

NE: non-estimable; NR: not reported

Data cutoff date for study AAA-III-01: 24Jul2015

Source: ISS Table 9.1

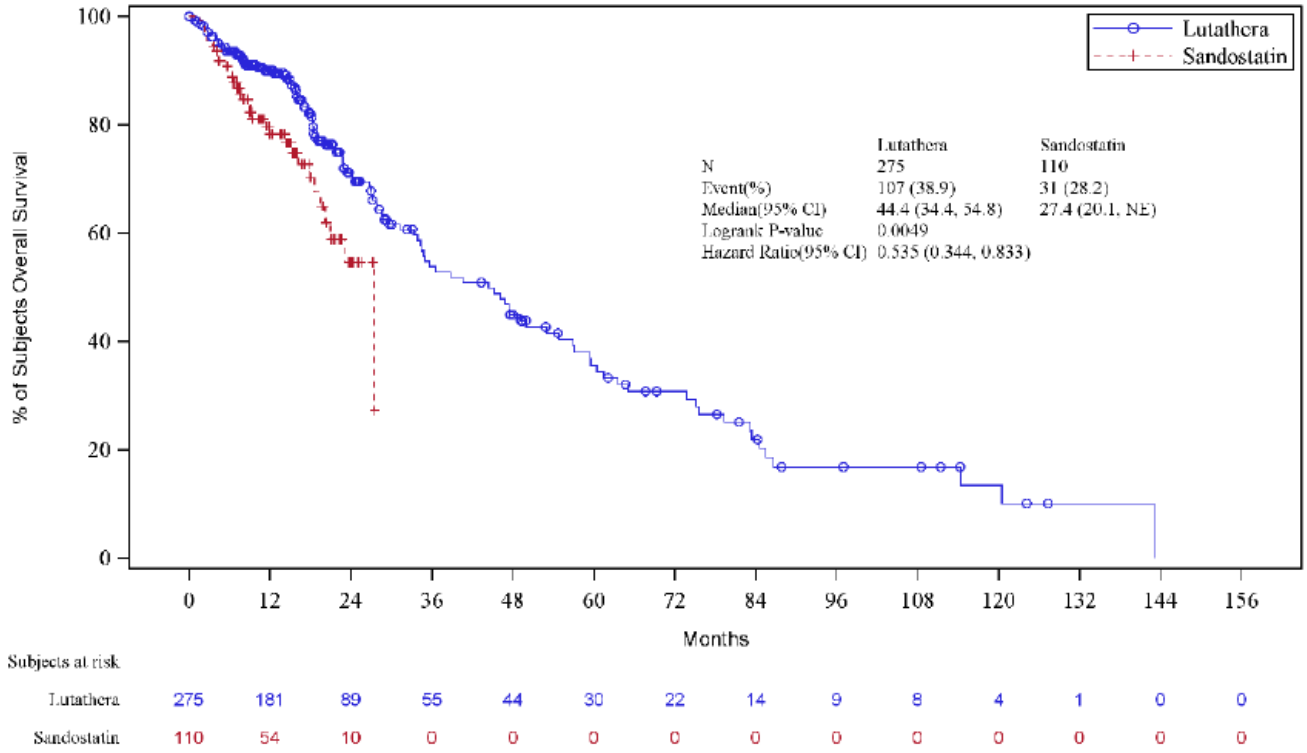



**Figure 22: Overall Survival – Kaplan-Meier Graph – ISE Population**

*Progression Free Survival (PFS)*

**Table 43: Analysis of Progression-free Survival – ISE Population**

| Characteristic | Percentile | Parameter | $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-octreotate (N: 275) | Octreotide LAR (N: 110) |
|---|---|---|---|---|
| Progression Free Survival (months) | 25th Percentile | Estimate | 16.0 | 3.15 |
| | | (95% CI) | (14.4, 18.4) | (3.0, 5.4) |
| | Median | Estimate | 26.9 | 8.5 |
| | | (95% CI) | (22.8, 31.8) | (5.8, 9.1) |
| | 75th Percentile | Estimate | 42.6 | 13.5 |
| | | (95% CI) | (34.0, 53.6) | (11.1, 17.9) |
| | Log-Rank Test | p-value | <0.0001 | |
| | Hazard Ratio | HR (95% CI) | 0.168 (0.117, 0.243) | |

Data cutoff date for study AAA-III-01: 24Jul2015

Source: ISS Table 10.1

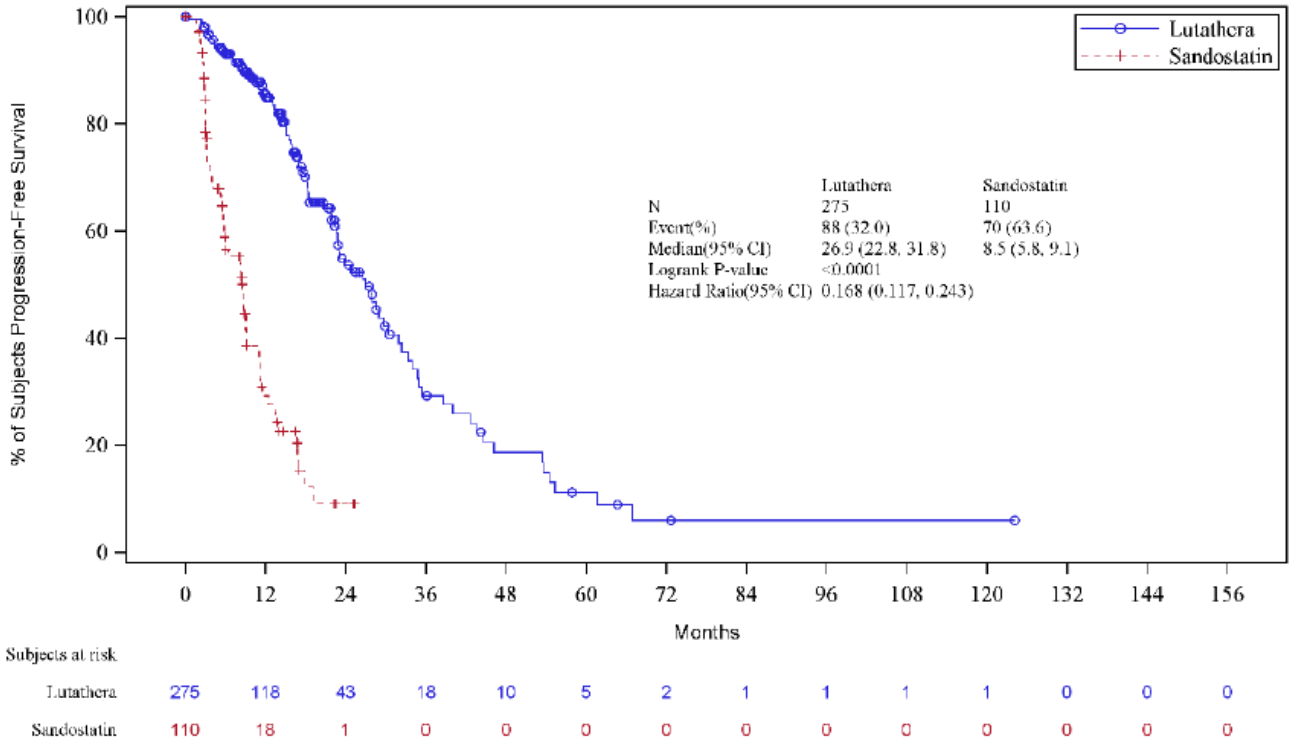



**Figure 23: Progression-free Survival – Kaplan-Meier Graph – ISE Population**

### *Supportive study*

## Phase I/II Study: Erasmus MC Clinical Study

This was an investigator sponsored phase I/II single arm clinical study which was conducted at the Erasmus Medical Center (Erasmus MC), Rotterdam, The Netherlands, to evaluate the efficacy of $^{177}$Lu-Oxodotreotide administered intravenously to patients with somatostatin receptor positive tumours (the majority GEP-NETs) as determined by OctreoScan® scintigraphy. Erasmus phase I/II study was a monocentric single arm open label study to evaluate the efficacy of Lutathera (7,400 MBq administered for 4 times every 8 weeks) co administered with amino acid solution in patients with somatostatin receptor positive tumours. The mean age of patients enrolled in the study was 58.4 years. Most patients were Dutch (811) with the remaining (403) residents of various European and non European countries.

The study was initiated in January 2000 and completed in December 2012.

## Methods

### *Study Participants*

The main inclusion criteria were:

- Presence of histology proven GEP-NET or bronchial carcinoid.

- Presence of somatostatin receptors on the known lesions demonstrated by OctreoScan® within 6 months of the first dose of radiolabelled 177Lu-Oxodotreotide. The uptake on the OctreoScan® should be at least as high as normal liver uptake on planar imaging.
- Life expectancy >12 weeks.
- Serum creatinine <150 µmol/L and a calculated (Cockroft's formula), or preferably a measured creatinine clearance, based on two 24-hour urine collections, of >40 ml/min.
- Hb concentration ≥5.5 mmol/L; WBC ≥2×109/L; platelets ≥75×109/L.
- Total bilirubin ≤3 × Upper Limit of Normal.
- Serum albumin >30 g/L.
- Karnofsky Performance Score ≥50

The main exclusion criteria were:

- Possible surgery with curative intent;
- Surgery, radiotherapy, chemotherapy, or other investigational therapy, within 3 months prior to the start of therapy;
- Patients with known brain metastases, unless these metastases have been treated and stabilized for at least six months prior to study start. Patients with a history of brain metastases must have a head CT scan with contrast to document stable disease prior to study start;
- Uncontrolled congestive heart failure;
- Any patient receiving therapy with short-acting somatostatin analogues in whom these analogues cannot be interrupted for 12 hours before and 12 hours
- after the administration of the radiolabelled somatostatin analogues, or any subject receiving therapy with long-acting somatostatin analogues in whom these analogues cannot be interrupted for at least 6 weeks before the administration of the radiolabelled somatostatin analogues, unless the uptake on the OctreoScan® during continued somatostatin analogue medication is at least as high as normal liver uptake on planar imaging;
- Subjects with another significant medical, psychiatric, or surgical condition, currently uncontrolled by treatment, which may interfere with completion of the study;
- Pregnancy.

**Objectives:**

Primary study objectives were to:

- Determine the efficacy of treatment with $^{177}$Lu-Oxodotreotide in patients with somatostatin receptor positive tumours based on tumour response rate according to the RECIST 1.1 criteria.
- Evaluate the safety of treatment with $^{177}$Lu-Oxodotreotide in patients with somatostatin receptor positive tumours as measured by the rate of serious adverse events and the monitoring of selected laboratory evaluations.

Secondary study objectives were to:

- Evaluate the effect of the treatment with $^{177}$Lu-Oxodotreotide in patients with somatostatin receptor positive tumours on Quality of Life (QoL) as measured by the EORTC QLQC30* questionnaire.
- Evaluate Progression Free Survival, Time To Progression and Overall Survival (PFS, TTP and OS) after treatment with $^{177}$Lu-Oxodotreotide in patients with somatostatin receptor positive tumours.

* In 2012 the EORTC-QLQ-GI.NET21 questionnaire was also added to the QoL evaluation.

## *Outcomes/endpoints*

The ORR (including complete response (CR) and partial response (PR) according to RECIST criteria) and duration of response (DoR) for the FAS Dutch population with gastroenteropancreatic (GEP) and bronchial NETs (360 patients).

The primary variable was tumor response rate (sum of complete response and partial response according to the RECIST 1.1 criteria).

Changes from baseline were assessed 6 weeks and 3-4, 6-8, 9-12, and 12-16 months after the last treatment and every 6 months thereafter or until disease progression occurred.

As part of this analysis duration of response was also assessed. This was defined as the time from initially meeting the criteria for response until the first documented tumor progression (per RECIST 1.1) or until the date of last valid tumor assessment (if no progression observed).

The secondary efficacy parameters of the study included:

- Quality of life
- Progression free survival, time to progression and overall survival
- Examination of subgroups

## *Treatments*

The patients recruited were administered $^{177}$Lu-Oxodotreotide infusion solution. The standard treatment regimen consists of 4 intravenous (i.v.) administrations of 200 mCi (7.4 GBq) at 6-13 week intervals; maximum cumulative administered radioactivity 800 mCi (29.6 GBq).

The regimen was based on estimates for restricting the maximum bone marrow radiation dose to 2 Gy and kidney radiation dose to 23 Gy. Individual kidney doses were calculated based on post-3rd treatment scans. If the kidney dose was predicted to exceed the 23 Gy limit by a subsequent treatment, then the 4th treatment was withheld. If no kidney absorbed dose could be calculated, the administered cumulative dose was 800 mCi.

In the standard treatment regimen, $^{177}$Lu-Oxodotreotide was administered at a rate of 200 mCi per 30 min, with amino acid co-infusion (lysine 2.5%, and arginine 2.5% in 1 L 0.9% NaCl). Amino acids were administered via a separate delivery system over a 4-hour period. Thirty minutes before the administration of $^{177}$Lu-Oxodotreotide, 8 mg Ondansetron® was administered i.v. as a prophylaxis against nausea. The patients were hospitalized for 24 hours during which time adverse events were monitored. Safety monitoring was performed at baseline and 4 weeks after the first treatment and 2 weeks before and 4 weeks after each subsequent treatment. Follow-up occurred at 6 weeks, and 3-4, 6-8, 9-12, and 12-16 months after the last treatment and thereafter every 6 months, up to the moment of tumour progression or death or lost to follow-up.

In total 1,214 patients were enrolled in the study between January 2000 and December 2012. Out of those, 615 patients were enrolled in the time period January 2000 to March 2007 and additional 599 patients were enrolled subsequently between March 2007 and December 2012. The latter cohort included 53 patients that were enrolled in the control arm of the $^{177}$Lu-Oxodotreotide + Xeloda study protocol i.e., received $^{177}$Lu-Oxodotreotide alone.

## Participant flow

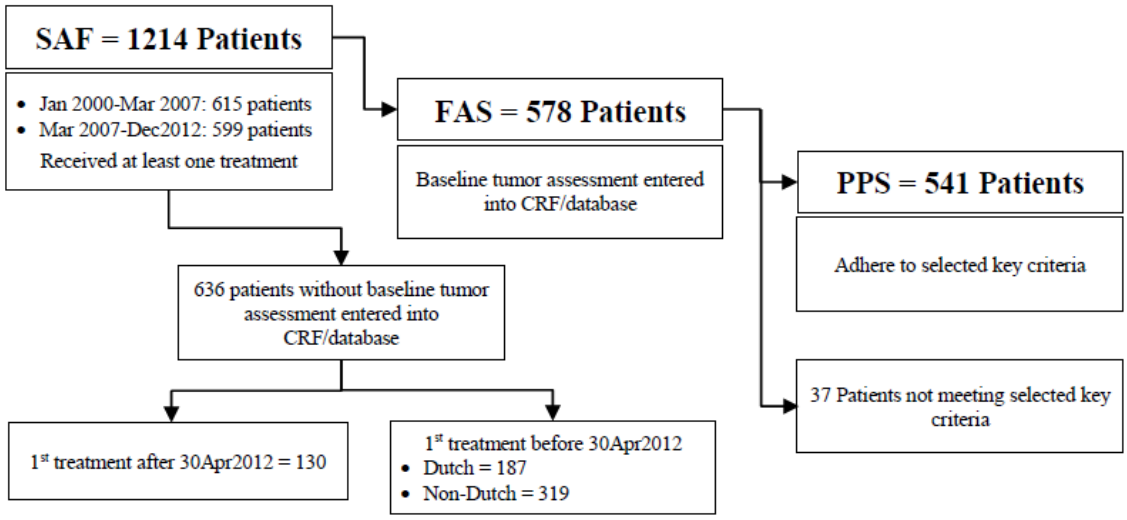



**Figure 24: Disposition of patients for the Erasmus MC study population (N: 1,214)**

Following the discussions with the FDA at the pre-NDA meeting, considering the targeted indication (GEP-NETs), and since data of the national (Dutch) population were the most accurate mainly due to a high rate of lost to follow-up and incomplete data in the non-national (non-Dutch) population [mean follow up of 13.5 months (SD: 19.1) for the non-Dutch population and 41.1 months (SD: 36.9) for the Dutch population], the efficacy analyses focussed on the Dutch GEP-NET population (N: 558) only.

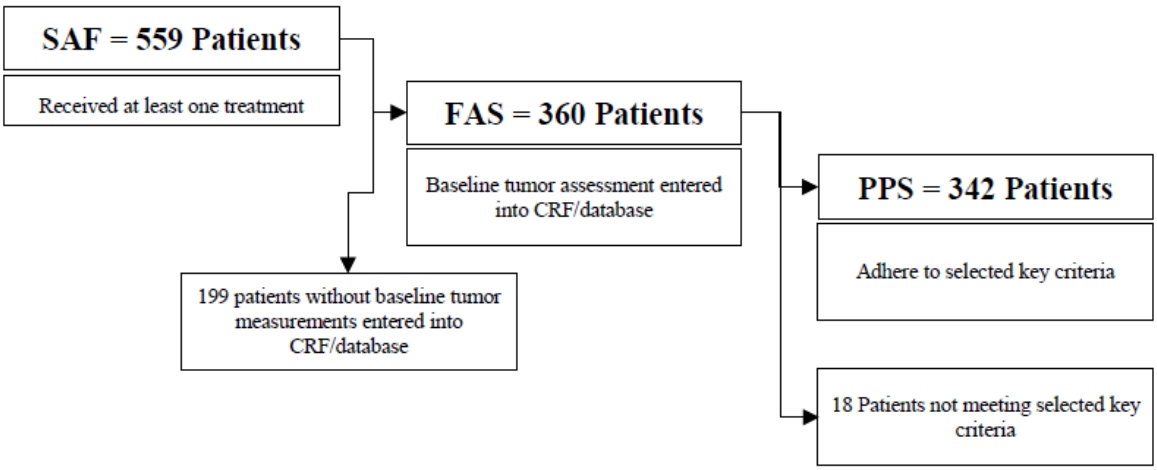



**Figure 25: Disposition of patients for the Erasmus MC study Dutch GEP-NET population (N: 558)**

**Table 44: Overview of datasets analysed**

**Table 11-1. Overview of datasets analysed**

| | Included in Analyses | | Excluded from Analyses | |
|---|---|---|---|---|
| **Study population** | **N** | **(%)** | **N** | **(%)** |
| SAF | 1214 | (100.0) | 0 | (0.0) |
| FAS | 578 | (47.6) | 636 | (52.4) |
| PPS | 541 | (44.6) | 673 | (55.4) |

Source Table 14.1.1.1 (see Appendix 16.2.4.1)

The main analysis has been conducted on 811 Dutch patients with different somatostatin receptor positive tumour types. The following subpopulations were enrolled (SAF population):

- Dutch GEP-NETs: 559 patients
- Dutch Foregut NETs (except bronchial NETs and pancreatic NETs): 18 patients (3.2%)
- Dutch Midgut NETs: 278 patients (49.8%)
- Dutch Hindgut NETs: 26 patients (4.7%)
- Dutch Pancreatic NETs: 197 patients (35.3%)
- Dutch Bronchial NETs (also known as pulmonary NETs): 39 patients (7.0%)

53% of patients in the Dutch population had progressive disease (progression radiologically or clinically detected within 12 months) at baseline.

## Results

## Outcomes and estimation

A summary of the baseline characteristics are presented in the table below.

**Table 45: GEP-NET Dutch patients demographic and baseline characteristics in the Phase I/II Erasmus MC study; SAF (N: 559); FAS (N: 360)**

| Characteristic | Statistic | SAF Dutch GEP-NET | FAS Dutch GEP-NET |
|---|---|---|---|
| **No. of subjects** | N | 559 | 360 |
| Age (Years) | N | 559 | 360 |
| | Mean | 60.0 | 58.9 |
| | SD | 11.0 | 10.8 |
| | Min | 23 | 30 |
| | Median | 60.0 | 60.0 |
| | Max | 88 | 85 |
| Height (cm) | N | 497 | 337 |
| | Mean | 172.5 | 172.8 |
| | SD | 10.0 | 9.7 |
| | Min | 103 | 144 |
| | Median | 172.0 | 172.0 |
| | Max | 203 | 203 |
| Weight (kg) | N | 521 | 346 |
| | Mean | 74.7 | 74.9 |
| | SD | 15.3 | 15.0 |
| | Min | 42 | 46 |
| | Median | 73.0 | 74.0 |
| | Max | 150 | 142 |
| Body Mass Index ($kg/m^2$) | N | 485 | 332 |
| | Mean | 25.0 | 24.9 |
| | SD | 5.4 | 4.1 |
| | Min | 15 | 15 |
| | Median | 24.5 | 24.6 |
| | Max | 97.1 | 45.2 |
| Gender | Male | 289 (51.7%) | 183 (50.8%) |
| | Female | 269 (48.3%) | 177 (49.2%) |
| Octreoscan Uptake Score | 0 | 12 (2.1%) | 0 (0.0%) |
| | 1 | 9 (1.6%) | 2 (0.6%) |
| | 2 | 50 (8.9%) | 20 (5.6%) |
| | 3 | 334 (59.7%) | 226 (62.8%) |
| | 4 | 154 (27.5%) | 112 (31.1%) |
| Karnofsky Performance Score | 40 | 1 (0.2%) | 0 (0.0%) |
| | 50 | 7 (1.3%) | 2 (0.6%) |
| | 60 | 9 (1.6%) | 6 (1.7%) |
| | 70 | 48 (8.6%) | 19 (5.3%) |
| | 80 | 123 (22%) | 75 (20.8%) |
| | 90 | 204 (36.5%) | 137 (38.1%) |
| | 100 | 150 (26.8%) | 120 (33.3%) |
| Tumor Burden | Limited | 93 (16.7%) | 51 (14.2%) |
| | Moderate | 353 (63.3%) | 253 (70.3%) |
| | Extensive | 101 (18.1%) | 56 (15.6%) |
| Progression at baseline (radiologic or clinical) | Non-progressive | 112 (20.1%) | 63 (17.8%) |
| | Progressive | 296 (53.0%) | 184 (51.1%) |
| | Unknown | 149 (26.7%) | 111 (30.8%) |

: Erasmus MC CSR: Table 14.1.2.8 and Table 14.1.2.10

**Outcomes and estimations**

*Objective Response Rate and Duration of Response by tumour type*

The results are summarised in the table below.

**Table 46: Best response, objective response rate and duration of response in the Phase I/II Erasmus MC study by tumour types – FAS GEP-NET Dutch population (N: 360)**

| | N | CR | | PR | | SD | | PD | | ORR* | | | | DoR | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Tumor type** | | n | % | n | % | n | % | n | % | n | % | 95%CI | | Median | 95%CI | |
| **GEP-NET** | 360 | 11 | 3.1% | 151 | 41.9% | 183 | 50.8% | 12 | 3.3% | 162 | 45.0% | 39.8% | 50.3% | 16.3 | 12.22 | 17.84 |
| Bronchial | 19 | 0 | 0.0% | 7 | 36.8% | 11 | 57.9% | 1 | 5.3% | 7 | 36.8% | 16.3% | 61.6% | 23.9 | 1.7 | 30.0 |
| Pancreatic | 133 | 7 | 5.3% | 74 | 55.6% | 47 | 35.3% | 4 | 3.0% | 81 | 60.9% | 52.1% | 69.2% | 16.3 | 12.1 | 21.8 |
| Foregut[$] | 12 | 1 | 8.3% | 6 | 50.0% | 4 | 33.3% | 1 | 8.3% | 7 | 58.3% | 27.7% | 84.8% | 22.3 | 0.0 | 38.0 |
| Midgut | 183 | 3 | 1.6% | 58 | 31.7% | 115 | 62.8% | 5 | 2.7% | 61 | 33.3% | 26.6% | 40.7% | 15.3 | 10.5 | 17.7 |
| Hindgut | 13 | 0 | 0.0% | 6 | 46.2% | 6 | 46.2% | 1 | 7.7% | 6 | 46.2% | 19.2% | 74.9% | 17.8 | 6.2 | 29.9 |

Source: Table 14.2.1.1.4 and Table 14.2.1.1.5 Erasmus MC CSR

A sensitivity analysis was performed on the SAF (N: 559) population, considering all the patients without baseline tumour measurement as non-responders (N: 198). The results are summarised in the table below.

**Table 47: Best response, objective response rate and duration of response in the Phase I/II Erasmus MC study by tumour types – SAF GEP-NET Dutch population (N: 559) – Sensitivity analysis**

| | N | CR | | PR | | SD | | PD | | ORR* | | | | DoR | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Tumor type** | | n | % | n | % | n | % | n | % | n | % | 95%CI | | Median | 95%CI | |
| **GEP-NET** | 559 | 11 | 2.0% | 151 | 27.0% | 183 | 32.7% | 12 | 2.1% | 162 | 29.0% | 25.2% | 32.9% | 16.3 | 12.2 | 17.8 |
| Bronchial | 39 | 0 | 0.0% | 7 | 17.9% | 11 | 28.2% | 1 | 2.6% | 7 | 17.9% | 7.5% | 33.5% | 23.9 | 1.7 | 30.0 |
| Pancreatic | 198 | 7 | 3.5% | 74 | 37.4% | 47 | 23.7% | 4 | 2.0% | 81 | 40.9% | 34.0% | 48.1% | 16.3 | 12.1 | 21.8 |
| Foregut[$] | 18 | 1 | 5.6% | 6 | 33.3% | 4 | 22.2% | 1 | 5.6% | 7 | 38.9% | 17.3% | 64.3% | 22.3 | 0.0 | 38.0 |
| Midgut | 278 | 3 | 1.1% | 58 | 20.9% | 115 | 41.4% | 5 | 1.8% | 61 | 21.9% | 17.2% | 27.3% | 15.3 | 10.5 | 17.7 |
| Hindgut | 26 | 0 | 0.0% | 6 | 23.1% | 6 | 23.1% | 1 | 3.8% | 6 | 23.1% | 9.0% | 43.6% | 17.8 | 6.2 | 29.9 |

*ORR = Objective response rate (CR + PR); All patients with no post baseline tumor assessment are counted as non-responders
[$] Foregut, other than bronchial and pancreatic which are reported as separate categories
CR = Complete Response; PR = Partial Response; SD = Stable Disease; PD = Progression; DoR = Duration of Response

Source: Table 14.2.1.3.4 and Table 14.2.1.3.5 Erasmus MC CSR

*Progression-free Survival by tumour type*

The median PFS as assessed by the Investigator for the GEP-NET Dutch FAS population (N: 360) according to RECIST criteria was 29.8 months with a 95% CI of 25.4-33.0 months. The median PFS for Dutch pancreatic NET was 30.5 months, Dutch hindgut NET 29.3 months, Dutch midgut NET 29.6 months, Dutch bronchial NET 18.3 months, and Dutch foregut NET not reached.

The median PFS in patients progressive at baseline (progression radiologically or clinically assessed within 12 months) was 29.8 months for the FAS Dutch GEP-NET (N: 184), 28.4 months for the Dutch midgut NET (N: 98) and 35.6 months Dutch pancreatic NET (N: 62).

The results are summarised in the Table 48 below.

*Overall Survival by tumour type*

The median OS for the Dutch GEP-NET FAS population (N: 360) was 64.4 months with a 95% CI of 57.0-75.3 months, 70.8 months for Dutch pancreatic NET, 55.4 months for Dutch midgut NET, 50.5 months for Dutch bronchial NET, not reached for Dutch foregut NET and Dutch hindgut NET.

The median OS in patients progressive at baseline (progression radiologically or clinically assessed within 12 months) was 60.2 months for the FAS Dutch GEP-NET (N: 184), 49.0 months for the Dutch midgut NET and 80.7 months Dutch pancreatic NET.

**Table 48: Progression Free Survival and Overall survival in the Phase I/II Erasmus MC study by tumour types – FAS GEP-NET Dutch population (N: 360)**

| | N | PFS events | | PFS | | | OS events | | OS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Tumor type** | | n | % | Median | 95%CI | | n | % | Median | 95%CI | |
| **GEP-NET** | 360 | 235 | 65.3% | 28.5 | 24.8 | 31.4 | 189 | 52.5% | 61.2 | 54.8 | 67.4 |
| Bronchial | 19 | 14 | 73.7% | 18.4 | 10.4 | 25.5 | 12 | 63.2% | 50.6 | 31.3 | 85.4 |
| Pancreatic | 133 | 83 | 62.4% | 30.3 | 24.3 | 36.3 | 57 | 42.9% | 66.4 | 57.2 | 80.9 |
| Foregut[$] | 12 | 5 | 41.7% | 43.9 | 10.9 | | 3 | 25.0% | | 21.3 | |
| Midgut | 183 | 123 | 67.2% | 28.5 | 23.9 | 33.3 | 117 | 63.9% | 54.9 | 47.5 | 63.2 |
| Hindgut | 13 | 10 | 76.9% | 29.4 | 18.9 | 35.0 | 0 | 0.0% | | | |

Considering the number of patients excluded from the FAS, a sensitivity analysis has been conducted on the SAF. The median OS for the Dutch GEP-NET SAF population (N: 558) was 57.0 months with a 95% CI of 52.1-64.9 months.

**Table 49: Overall survival in the Phase I/II Erasmus MC study by tumour types – SAF GEP-NET Dutch population (N: 559) – Sensitivity analysis**

| | N | OS events | | OS | | |
|---|---|---|---|---|---|---|
| **Tumor type** | | n | % | Median | 95%CI | |
| **GEP-NET** | 559 | 266 | 47.6% | 52.6 | 49.3 | 59.9 |
| Bronchial | 39 | 16 | 41.0% | 50.6 | 32.2 | 74.7 |
| Pancreatic | 198 | 86 | 43.4% | 57.9 | 49.4 | 66.4 |
| Foregut[$] | 18 | 3 | 16.7% | | 21.3 | |
| Midgut | 278 | 157 | 56.5% | 49.1 | 38.7 | 54.9 |
| Hindgut | 26 | 4 | 15.4% | | 41.0 | |

In the Erasmus phase I/II study 188 patients (52%) received and 172 (48%) did not receive concomitant octreotide LAR during Lutathera treatment. No statistically significant difference in PFS was observed between the subgroup of patients who did not receive octreotide LAR (25.4 months [95% CI 22.8-30.6]) versus the subgroup who did receive concomitant treatment with octreotide LAR (30.9 months [95% CI 25.6-34.8]) (p= 0.747).

## 2.5.3. Discussion on clinical efficacy

### *Design and conduct of clinical studies*

The efficacy of Lutathera in the proposed indication is based on the results of the single arm ERASMUS study and the open labelled randomised NETTER-1 study. Randomised data from the NETTER-1 study is available only for midgut subset of neuroendocrine tumours. Data for the other subsets of the proposed indication, i.e., foregut and hindgut, as well as the pancreatic sub-group of patients have to derived and interpreted from the results of the single arm ERASMUS study.

The ERASMUS study was a compassionate use programme at the Erasmus Medical Centre that subsequently enrolled 1214 patients. The efficacy data from the ERASMUS study was derived from the sub-group of Dutch patients since they had the most complete and accurate data in comparison to

non-Dutch patients. The patient population which is relevant to the indication included patients with GEP-NETs of foregut, pancreatic and hindgut origin. These patients were included in the ERASMUS study. The pancreatic sub-group of patients constituted the second largest group (n=133) in the Full Analysis set (n=360) of the Dutch GEP-NET patients, after the mid-gut sub-group (n=183). The numbers of other foregut and hindgut GEP-NETs were smaller, 12 and 13, respectively.

In 2011, the applicant conducted a source data verification, including data integrity for efficacy, of the Phase I-II trial at the EMC in a subgroup of patients with midgut carcinoid tumours that were progressive within 12 months of the study entry. The first independent assessment was conducted in 2012, the results from the EMC study led to the development of the Phase III study (NETTER-1).

Enrolment in the Phase III study started in July 2012 for patients with neuroendocrine tumours of mid-gut origin. The first patient was randomised in September 2012. The NETTER-1 study is still ongoing and will be ended as per protocol when 158 deaths will be recorded or when 5 years from the date of randomisation of the last randomised patient have elapsed, whichever occurs first. The enrolment was completed on 14 January 2016. Expected last patient last visit (treatment phase) is Q3 2017. The design of the study is considered appropriate and has been discussed in the CHMP scientific advice. The use of Sandostatin LAR 60 mg in patients as a comparator was agreed. Though not an approved dose for Sandostatin LAR, it was agreed that this was an accepted clinical practice in patients who had progressed on the standard Sandostatin LAR dose of up to 30 mg in GEP-NETs. The endpoints for the study included PFS, OS and ORR which are acceptable endpoints. The CHMP triggered a routine GCP inspection of the 2 study sites. Some critical issues were identified that could have had a potential impact on the data. The applicant performed corrective actions during the procedure and submitted updated endpoint analyses, including all data through the 24 July 2015 clinical cutoff date for final PFS analysis and an interim OS analysis and safety information will be submitted through 30 June 2016. The submission of the updated PFS analyses provided further robustness to the effect on PFS observed in the primary analysis and reassured the CHMP on the validity of the data.

## *Efficacy data and additional analyses*

The NETTER-1 study met its primary efficacy endpoint demonstrating a statistically significant improvement in progression free survival. However, the median PFS has not been reached for the Lutathera arm of the study, with a 53.4% of patients in this arm counted as missing data due to the fact that treatment is ongoing in these patients. The primary efficacy endpoint results, even though immature, favoured the Lutathera arm. The initial PFS analysis, was based on a cut-off date of 24$^{th}$ July 2015, when 94.6% of the intended subjects had completed their Lutathera treatments. The applicant provided updated efficacy analyses for PFS and OS based on data cut-offs of 30 June 2016.

In the updated analysis, the median PFS in the Lutathera arm is 28.4 months (19.4; NE) and 8.5 months (5.8; 11.0) in the Octreotide LAR arm. The updated un-stratified was HR = 0.185, 95%CI 0.113, 0.303, p-value <0.0001 and the stratified was HR = 0.184, 95%CI 0.112, 0.302, p-value <0.0001. An updated PFS and OS analysis from the 30$^{th}$ June 2016 datacut off was submitted and the un-stratified was: HR = 0.177, 95%CI 0.108, 0.289, p-value <0.0001 while the stratified HR = 0.177, 95%CI 0.107, 0.294, p-value <0.0001. The updated data is in line with the original analysis with a clinically and statistically significant benefit favouring Lutathera over Octreotide LAR monotherapy.

In the original analysis, the median OS ranged from 40.5 to 65.8. The highest median OS was in the pancreatic group (70.8 months), followed by the mid-gut group (55.4 months) and the median OS was not reached for the foregut and hindgut groups. Following the cut-off date of the 30th of June 2016, the median overall survival was 27.4 months (23.1, NE) for the control arm; and the median survival was not reached for the Lutathera arm. Only 6 randomised patients (4 randomised to the Lutathera

arm and 2 the comparator arm) finished the study treatment with Octreotide LAR monotherapy and, 30 patients randomised to the control group received Lutathera under different program. The implications of these on the assessment of OS have been acknowledged. After the LPLT visit, patients will continue to be monitored for safety and OS and it is recommended that this follow up data should be provided at the end of the study.

The ORR was also higher in the Lutathera arm compared to the Sandostatin LAR arm (17.8% vs. 3%, respectively). Similar to the PFS results, the median time to tumour progression has not been reached for the Lutathera arm, but shows statistically significant difference to the comparator arm, favouring the Lutathera arm.

ORR, in the FAS Dutch GEP-NET population of the ERASMUS study, ranged from 33.3% to 60.9% with pancreatic and foregut endocrine tumours showing the largest effects (60.9% and 58.3% respectively). Sensitivity analyses including patients without baseline tumour assessment as non-responders showed that the estimated ORR were lower (range: 21.9% to 40.9% for GEP-NETs) but still showing a larger effect in patients with pancreatic and foregut tumours. The lowest ORR is seen in the mid-gut NET sub-group, but this is also considered clinically significant at 33.3% in the FAS results. DoR ranged from 15.3 to 22.3 months for GEP-NETs.

The median PFS ranged from 28.5 to 43.9 months. The highest median PFS was in the foregut group (43.9 months), followed by the pancreatic group (30.3 months) and hindgut group (29.4 months).

For the sensitivity analysis, the applicant discusses that the average possible overestimation of OS and PFS in the Dutch population was 18% for PFS and 15% for OS. However, the benefits observed in the worst case scenario are still highly clinically relevant compared to the benefit described in the same pathology for other drugs (e.g. sunitinib median PFS in progressive pNETs 10.2 months [95% CI: 7.4 - 16.9], PIL 5/2011, OS median not reported; everolimus median PFS in progressive pNETs 13.7 months [95% CI: 11.2 – 18.8], PIL 07/2012, OS not reported; lanreotide in non-functioning GEP-NETs median PFS not reached, PIL 12/2014). This discussion of comparative efficacy is considered relevant and highlights a possible durable response and survival with Lutathera.

There is no relevant use of Lutathera in the paediatric population in the indication of treatment of GEP-NETs (excluding neuroblastoma, neuroganglioblastoma, phaeochromocytoma). The European Medicines Agency has waived the obligation to submit the results of studies with Lutathera in all subsets of the paediatric population in the treatment of GEP-NETs (excluding neuroblastoma, neuroganglioblastoma, phaeochromocytoma). See section 4.2.

## 2.5.4. Conclusions on the clinical efficacy

On the basis of the results of the NETTER-1 study along with the results seen for the mid-gut subgroup of patients in the ERASMUS study there is evidence of efficacy for Lutathera in this sub-group of patients with mid-gut GEP-NETs.

The results seen for the pancreatic GEP-NET in the FAS Dutch GEP-NET population of the ERASMUS study shows evidence of efficacy for Lutathera in this sub-group, possibly even greater than the efficacy seen in the mid-gut GEP-NETs.

The numbers of patients with foregut and hindgut GEP-NETs studied were small. However, the efficacy endpoints' results appear to be in line with that seen for the more common pancreatic and hindgut GEP-NETs. Given the rare nature of GEP-NETS, the limited evidence is considered supportive of the efficacy in these sub-populations as well.

The CHMP recommends the following measures necessary to address issues related to efficacy:

- Submission of the final study report and final analysis of PFS and OS of the NETTER-1 study

## *2.6. Clinical safety*

An integrated safety database was constructed from the individual study databases for the pooled safety analysis. All safety analyses were completed using the pooled safety analysis set (SAF). The pooled safety analysis set consisted of all the Dutch patients (all tumour types) in the Erasmus MC study who received at least 1 dose of 177Lu-DOTA0-Try3-Octreotate at the dose and schedule employed in the NETTER-1 study and all patients randomized in the NETTER-1 study who received at least 1 dose of study drug. All the safety analyses have been conducted using the more recent 30 June 2016 cut-off date.

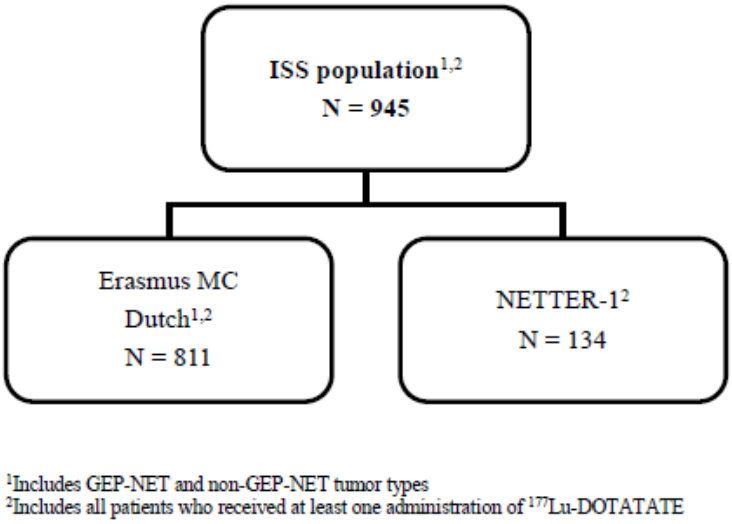



**Figure 26: ISS population diagram**

The 111 patients from NETTER-1 control arm were also included in the integrated summary of safety (ISS) database; their results are also displayed in parallel of the ISS Lutathera group for helping in the interpretation of the pooled results (Figure 2).

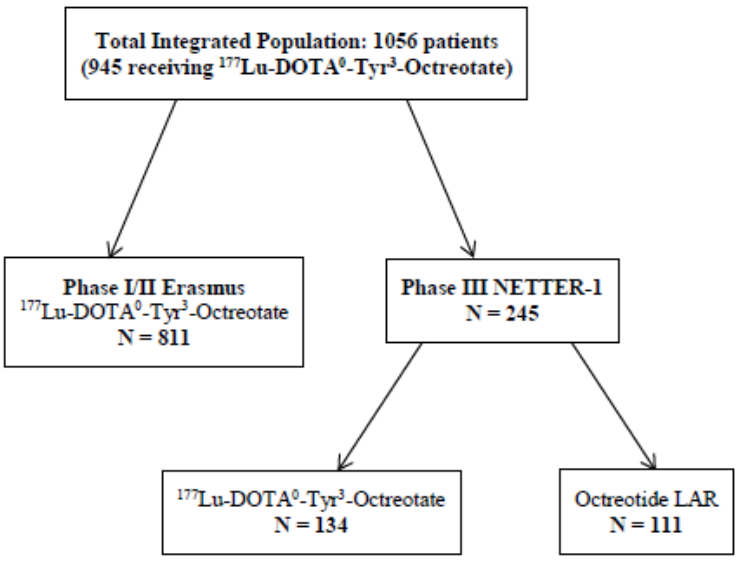



**Figure 27:Diagram of Pooled Safety Analysis Population**

## *Patient exposure*

***NETTER-1 study***

In the NETTER-1 study 26.1% of the SAF population received a total cumulative dose of 177Lu-Oxodotreotide of ≥ 800mCi and 79.3% received over 600 mCi (see table 1). In the control arm (Octreotide LAR 60mg) patients received a weekly mean dose of 14.8 mg and a median of 8 administrations.

**Table 50: Cumulative dose in NETTER-1 study - SAF Lutathera arm (N: 111)**

| Dose range (mCi) | N | % |
|---|---|---|
| | 111 | 100 |
| ≥ 800 | 29 | 26.1 |
| ≥ 600 - < 800 | 59 | 53.2 |
| ≥ 400 - < 600 | 9 | 8.1 |
| < 400 | 14 | 12.6 |

**Table 51: Cumulative dose in NETTER-1 study - SAF Octreotide 60mg arm (N: 111)**

| Average weekly dose of Octreotide LAR (mg) | |
|---|---|
| Mean (SD) | 14.79 (0.468) |
| Q1, Q3 | 14.63 – 15.00 |
| Median | 14.97 |
| (Min, Max) | (12.5, 16.4) |
| **Administrations of treatment** | |
| Mean (SD) | 9.51 (6.64) |
| Q1, Q3 | 4.00 – 15.00 |
| Median | 8.00 |
| (Min, Max) | (1.0, 27.0) |

***Erasmus MC study***

In the Erasmus MC study 65.1% of the SAF Dutch population received a total cumulative dose of 177Lu-Oxodotreotide of ≥ 800mCi and 81.4% received over 600 mCi.

**Table 52: Cumulative dose in the Erasmus MC – SAF Dutch (N: 811)**

| Dose range (mCi) | N | % |
|---|---|---|
| | 811 | 100 |
| ≥ 800 | 528 | 65.1 |
| ≥ 600 - < 800 | 132 | 16.3 |
| ≥ 400 - < 600 | 77 | 9.5 |
| < 400 | 74 | 9.1 |

***ISS Population***

In the pooled ISS population (NETTER-1 + Erasmus MC studies, N: 945), most of the patients received a cumulative dose of ≥ 800 mCi of the drug (59.5% of patients), and 80.7% received over 600 mCi (see Table 4). Less than 10% of patients received a cumulative dose between 400 and 600 mCi or <400 mCi. Overall, the mean cumulative dose was 754.1 ± 283.06 mCi and the median cumulative dose was 800 mCi.

**Table 53: Cumulative dose in the pooled ISS population – Lutathera treatment (N: 945)**

| Dose range (mCi) | N | % |
|---|---|---|
| | 945 | |
| 800 | 562 | 59.5 |
| ≥ 600 - < 800 | 200 | 21.2 |
| ≥ 400 - < 600 | 90 | 9.5 |
| < 400 | 92 | 9.7 |

For NETTER-1, the safety population comprised of patients with mid-gut GEP-NETs who had received at least one dose of Lutathera. For the Erasmus MC study, the safety analysis was not limited to GEP-NETs and includes all tumour types enrolled in the Erasmus MC study. The disposition of the entire study population is presented in the figure below.

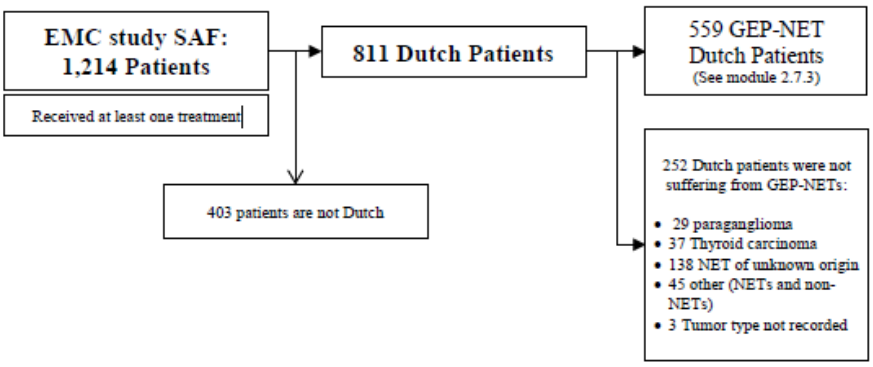



**Figure 28: Disposition of patients for the Erasmus MC study safety set population (N: 1,214)**

## *Adverse events*

Adverse events were not collected in the case report form (CRF) of the Erasmus MC study, with the exception of the pre-coded symptoms "nausea", "vomiting", "pain" and "hair loss". After July 2010, this list also included "diarrhoea", "flushes", "stomatitis", "hand and foot syndrome" and "malaise". These symptoms were only scored as yes/no. These data were not MedDRA coded and are listed in the Erasmus MC clinical study report (CSR). Since in the Erasmus MC study, only SAE summary data are available, only treatment-emergent serious adverse event (TESAE) information are summarized and presented for patients in the pooled safety analysis set.

*Common Adverse Events in the NETTER-1 study*

In the pivotal NETTER-1 study all adverse events (AEs), whether or not spontaneously reported by the patient, were recorded starting from the signing of the ICF until the last study-related visit.

AEs were coded by primary system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA v18).

A complete summary of all adverse events as reported from the SAF is displayed by category in the table below.

**Table 54: Summary of adverse events in NETTER-1 study – SAF (N: 223)**

| | Lutathera (N = 112) | Octreotide LAR (N = 111) | All (N = 223) |
|---|---|---|---|
| **Number and percent of patients with:** | **N (%)** | **N (%)** | **N (%)** |
| At least one adverse event (AE) | 111 (99.1) | 105 (94.6) | 216 (96.9) |
| At least one non-treatment emergent AE | 50 (44.6) | 38 (34.2) | 88 (39.5) |
| At least one treatment emergent AE (TEAE)[1] | 110 (98.2) | 103 (92.8) | 213 (95.5) |
| At least one TEAE related to study medication (ADR)[2] | 102 (91.1) | 45 (40.5) | 147 (65.9) |
| At least one TEAE leading to premature study discontinuation | 14 (12.5) | 12 (10.8) | 26 (11.7) |
| At least one TEAE related to study medication leading to premature study discontinuation | 8 (7.1) | 1 (0.9) | 9 (4.0) |

[1] Treatment emergent adverse events are defined as AEs that started or worsened on or after the date of the first dose of study medication.
[2] TEAEs classified as 'possibly related' or 'related' to study medication.

99% of the patients in the Lutathera arm and 95% in the Octreotide LAR arm experienced at least one AE during the study. 98% of the patients in the Lutathera arm and 93% in the Octreotide LAR arm experienced at least one treatment emergent AE (TEAE).

TEAEs leading to premature withdrawal occurred in 14 patients (12.5%) in the Lutathera arm and in 12 patients (10.8%) in the Octreotide LAR arm; the difference observed in the two arms was not statistically significant. Eight patients (7.1%) in the Lutathera arm and one patient (0.9%) in the Octreotide LAR arm reported TEAEs leading to premature withdrawal which were considered by the investigator to be related to study treatment.

In the Lutathera arm, the most frequent possible cause of treatment emergent adverse events based on the number of episodes was study treatment for 701 (38.3%) AEs, followed by pre-existing/ underlying disease for 425 (23.2%) AEs, unknown for 271 (14.8%) AEs, other causes for 144 (7.9%) AEs, other treatment for 44 (2.4%) AEs and protocol related procedure for 23 (1.3%) AEs.

In the Octreotide LAR arm, the most frequent possible cause of treatment emergent adverse event based on the number of episodes was pre-existing / underlying disease for 332 (35.5%) AEs, followed by unknown for 231 (24.7%) AEs, other causes for 134 (14.36%) AEs, study treatment for 97 (10.7%) AEs, other treatment for 12 (1.3%) AEs and protocol related procedure for 5 (0.5%) AEs.

**Table 55: Treatment emergent adverse events in NETTER-1 study – SAF (N: 223)**

| | Lutathera (N = 112) | Octreotide LAR (N = 111) | All (N = 223) |
|---|---|---|---|
| **Treatment emergent adverse event** | **n (%)** | **n (%)** | **n (%)** |
| General information | | | |
| Number of patients with at least one TEAE | 110 (98.2) | 103 (92.8) | 213 (95.5) |
| Number of events | 1608 | 811 | 2419 |
| Maximal severity (based on number of patients)[1] | | | |
| Grade 1 (Mild) | 11 (9.8) | 28 (25.2) | 39 (17.5) |
| Grade 2 (Moderate) | 35 (31.3) | 34 (30.6) | 69 (30.9) |
| Grade 3 (Severe) | 51 (45.5) | 28 (25.2) | 79 (35.4) |
| Grade 4 (Threatening/ disabling) | 6 (5.4) | 4 (3.6) | 10 (4.5) |
| Grade 5 (Death) | 7 (6.3) | 9 (8.1) | 16 (7.2) |
| Possible cause of TEAEs (based on number of episodes) | | | |
| Pre-existing / underlying disease | 425 (23.2) | 332 (35.5) | 757 (27.4) |
| Study treatment | 701 (38.3) | 97 (10.4) | 798 (28.9) |
| Other treatment | 44 (2.4) | 12 (1.3) | 56 (2.0) |
| Protocol-related procedure | 23 (1.3) | 5 (0.5) | 28 (1.0) |
| Unknown | 271 (14.8) | 231 (24.7) | 502 (18.1) |
| Other | 144 (7.9) | 134 (14.3) | 278 (10.1) |

[1] Patients are counted only once at the maximum severity.
TEAEs were defined as AEs that started or worsened on or after the date of the first dose of study medication.
N: number of patients in treatment group; n: number of patients; SAF: Safety set; TEAE: treatment emergent adverse event; %: percentage based on N.

The table below provides an overview on the number of patients with at least one TEAE by SOC and preferred term (PT) for the SAF (for AEs reported in at least 10% of the patients who received Lutathera).

**Table 56: Treatment-emergent adverse events reported in at least 10% of the patients who received Lutathera in NETTER-1 study by SOC and PT – SAF (N: 223)**

| | | Lutathera (N = 112) | | | | Octreotide LAR (N = 111) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | All grades | | Grade 3 to 5 | | All grades | | Grade 3 to 5 | |
| SOC | PT | $n_{pat}$ | % | $n_{pat}$ | % | $n_{pat}$ | % | $n_{pat}$ | % |
| All SOCs | All PTs | 102 | 91.1 | 34 | 30.4 | 45 | 40.5 | 5 | 4.5 |
| Gastrointestinal disorders | Nausea | 66 | 58.9 | 4 | 3.6 | 4 | 3.6 | 0 | 0.0 |
| | Vomiting | 51 | 45.5 | 4 | 3.6 | 0 | 0.0 | 0 | 0.0 |
| General disorders and administration site conditions | Fatigue | 27 | 24.1 | 0 | 0 | 5 | 4.5 | 0 | 0.0 |
| Blood and lymphatic system disorders | Thrombocytopenia | 15 | 13.4 | 3 | 2.7 | 0 | 0.0 | 0 | 0.0 |
| | Lymphopenia | 15 | 13.4 | 9 | 8.0 | 0 | 0.0 | 0 | 0.0 |
| | Anaemia | 14 | 12.5 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Metabolism and nutrition disorders | Decreased appetite | 15 | 13.4 | 0 | 0.0 | 2 | 1.8 | 0 | 0.0 |

N: number of patients in treatment group; $n_{pat}$: number of patients, PT: preferred term, SAF: Safety set, SOC: system organ class; TEAE: treatment emergent adverse event.

The numbers of patients experiencing any TEAEs (all grades) from PTs 'nausea', vomiting', 'diarrhoea', 'abdominal distension', 'fatigue', 'thrombocytopenia', 'lymphopenia', 'anaemia', 'platelet count decreased', 'lymphocyte count decreased', 'white blood cell count decreased', 'neutropenia', 'decreased appetite', 'alopecia', 'dizziness', and 'dysgeusia' was higher under Lutathera treatment compared to Octreotide LAR. The incidences of Grade 3 to 5 AEs of these PTs were also higher in Lutathera treatment compared to Octreotide LAR. In the Lutathera arm, the majority (about 81.3%) of the "nausea" and "vomiting" episodes were considered related to the amino acid co-infusion by the investigators. Also, about 13% of the 'diarrhoea' events, 20% of the 'decreased appetite' events, and 8% of the 'fatigue' events that occurred in the Lutathera arm were attributable to the commercial amino acid co-infusion according to the investigators. Fatigue could also be related to anaemia, nausea, vomiting and the related decreased appetite, all known transient secondary effects of PRRT[14, 18].

**Adverse drug reactions**

There were 701 ADR episodes for patients in the Lutathera arm and 97 for patients in the Octreotide LAR arm. The most frequent ADRsin the Lutathera arm were "nausea" and "vomiting" (136 "nausea" events in the Lutathera arm vs 5 in the Octreotide LAR arm and 110 "vomiting" episodes in the Lutathera arm vs 0 in the Octreotide LAR arm).

Among the TEAE, 91.1% of patients in the Lutathera arm and 40.5% in the Octreotide LAR arm experienced TEAEs related to study medication (ADRs).

The severity of TEAEs related to treatment based on the number of patients was mild (grade 1) for 24 (21.4%) patients, moderate (grade 2) for 44 (39.3%) patients, severe (grade 3) for 30 (26.8%) patients, threatening/disabling (grade 4) for 4 (3.6%) AEs. The incidences of Grade 2 to Grade 4 ADRs in Lutathera arm were higher compared to that in Octreotide LAR arm.

[18] Kam BL, Teunissen JJM, Krenning EP, de Herder WW, Khan S, van Vliet EI, Kwekkeboom DJ (2012). Lutetium-labelled peptides for therapy of neuroendocrine tumours. Eur J Nucl Med Mol Imaging 39 Suppl 1:S103--S112

**Table 57: Treatment emergent adverse events related to study medication in NETTER-1 study (ADR) –SAF (N: 223)**

| | Lutathera (N = 112) | Octreotide LAR (N = 111) | All (N = 223) |
|---|---|---|---|
| **TEAE related to study medication (ADR)** | **n (%)** | **n (%)** | **n (%)** |
| General information | | | |
| Number of patients with at least one TEAE related to study medication[1] | 102 (91.1) | 45 (40.5) | 147 (65.9) |
| Number of events | 701 | 97 | 798 |
| Number of patients with at least one TEAE related to study medication by maximum severity[2] | | | |
| Grade 1 (Mild) | 24 (21.4) | 25 (22.5) | 49 (22.0) |
| Grade 2 (Moderate) | 44 (39.3) | 15 (13.5) | 59 (26.5) |
| Grade 3 (Severe) | 30 (26.8) | 5 (4.5) | 35 (15.7) |
| Grade 4 (Threatening/ disabling) | 4 (3.6) | 0 (0.0) | 4 (1.8) |
| Grade 5 (Death) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

N: number of patients in treatment group; n: number of patients/events; %: percentage based on N.

[1] TEAEs classified as 'possibly related' or 'related' to study medication.

[2]At each level of summarization, a patient is counted only once, according to the maximum severity.

The table below provides an overview on the number of patients with at least one ADR by SOC and PT for the SAF (for ADRs reported in at least 5% of the patients who received Lutathera).

Tabulated list of adverse reactions

The adverse reactions are listed in Table 58 according to the frequency and the MedDRA System Organ Class (SOC). The frequencies are categorized as follows: 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) and not known (cannot be estimated from the available data).

**Table 58: Frequency of adverse reactions reported from clinical trials and from post-marketing surveillance**

| MedDRA System Organ Class (SOC) | Very common | Common | Uncommon |
|---|---|---|---|
| **Infections and infestations** | | | Conjunctivitis (0.9%)<br>Respiratory tract infection (0.9%)<br>Cystitis (0.2%)<br>Pneumonia (0.2%)<br>Herpes zoster (0.1%)<br>Ophthalmic herpes zoster (0.1%)<br>Influenza (0.1%)<br>Staphylococcal infections (0.1%)<br>Streptococcal bacteraemia (0.1%) |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | | Refractory cytopenia with multilineage dysplasia (Myelodysplastic syndrome) (1.6%) | Acute myeloid leukaemia (0.3%)<br>Acute leukaemia (0.1%)<br>Chronic myelomonocytic leukaemia (0.1%) |
| **Blood and lymphatic system disorders** | Thrombocytopenia[2] (25%)<br>Lymphopenia[3] (22.3%)<br>Anaemia[4] (13.4%)<br>Pancytopenia (10.2%) | Leukopenia[5] (9.9%)<br>Neutropenia[6] (7.2%) | Refractory cytopenia with unilineage dysplasia (0.9%)<br>Nephrogenic anaemia (0.1%)<br>Bone marrow failure (0.3%)<br>Thrombocytopenic purpura (0.1%) |
| **Immune system disorders** | | | Hypersensitivity (0.9%) |

| MedDRA System Organ Class (SOC) | Very common | Common | Uncommon |
|---|---|---|---|
| **Endocrine disorders** | | Secondary hypothyroidism (1.8%) | Hypothyroidism (0.9%)<br>Diabetes mellitus (0.9%)<br>Carcinoid crisis (0.2%)<br>Hyperparathyroidism (0.1%) |
| **Metabolism and nutrition disorders** | Decreased appetite (13.4%) | Hyperglycaemia (2.7%)<br>Dehydration (1.8%)<br>Hypomagnesaemia (1.8%)<br>Hyponatremia (1.8%) | Hypoglycaemia (0.9%)<br>Hypernatremia (0.9%)<br>Hypophosphatemia (0.9%)<br>Tumor lysis syndrome (0.4%)<br>Hypercalcaemia (0.2%)<br>Hypocalcaemia (0.1%)<br>Hypoalbuminaemia (0.1%)<br>Metabolic acidosis (0.1%) |
| **Psychiatric disorders** | | Sleep disorders (1.8%) | Anxiety (0.9%)<br>Hallucination (0.9%)<br>Disorientation (0.1%) |
| **Nervous system disorders** | | Dizziness (6.3%)<br>Dysgeusia (5.4%)<br>Headache[10] (4.5%)<br>Lethargy (2.7%)<br>Syncope (1.8%) | Formication (0.9%)<br>Hepatic encephalopathy (0.9%)<br>Paraesthesia (0.9%)<br>Parosmia (0.9%)<br>Somnolence (0.2%)<br>Spinal cord compression (0.1%) |
| **Eye disorders** | | | Eye disorders (0.9%) |
| **Ear and labyrinth disorders** | | | Vertigo (0.9%) |
| **Cardiac disorders** | | Electrocardiogram QT prolonged (1.8%) | Atrial fibrillation (0.9%)<br>Palpitations (0.9%)<br>Myocardial infarction (0.2%)<br>Angina pectoris (0.1%)<br>Cardiogenic shock (0.1%) |
| **Vascular disorders** | | Hypertension[7] (4.5)<br>Flushing (3.6%)<br>Hot flush (1.8%)<br>Hypotension (1.8%) | Vasodilatation (0.9%)<br>Peripheral coldness (0.2%)<br>Pallor (0.2%)<br>Orthostatic hypotension (0.1%)<br>Phlebitis (0.1%) |
| **Respiratory, thoracic and mediastinal disorders** | | Dyspnoea (1.8%) | Oropharyngeal pain (0.91%)<br>Pleural effusion (0.9%)<br>Sputum increased (0.9%)<br>Chocking sensation (0.1%) |
| **Gastrointestinal disorders** | Nausea (58,9%)<br>Vomiting (45.5%) | Abdominal distension (8.9%)<br>Diarrhoea (7.1%)<br>Abdominal pain (3.6%)<br>Constipation, (3.6%)<br>Abdominal pain upper (1.8%)<br>Dyspepsia (1.8%)<br>Gastritis (1.8%) | Dry mouth (0.9%)<br>Flatulence (0.9%)<br>Ascities (0.9%)<br>Gastrointestinal pain (0.9%)<br>Stomatitis (0.9%)<br>Haematochezia (0.2%)<br>Abdominal discomfort (0.9%)<br>Intestinal obstruction (0.9%)<br>Colitis (0.2%)<br>Pancreatitis acute (0.2%)<br>Rectal haemorrhage (0.2%)<br>Melaena (0.1%)<br>Abdominal pain lower (0.1%)<br>Haematemesis (0.1%)<br>Haemorrhagic ascites (0.1%)<br>Ileus (0.1%) |
| **Hepatobiliary disorders** | | Hyperbilirubinaemia[9] (1.8%) | Pancreatic enzymes decreased (0.9%)<br>Hepatocellular injury (0.2%)<br>Cholestasis (0.1%)<br>Hepatic congestion (0.1%)<br>Hepatic failure (0.1%) |
| **Skin and subcutaneous** | | Alopecia (8.9%) | Rash (0.9%) |

| MedDRA System Organ Class (SOC) | Very common | Common | Uncommon |
|---|---|---|---|
| **tissue disorders** | | | Dry skin (0.9%)<br>Swelling face (0.2%)<br>Hyperhidrosis (0.2%)<br>Pruritus generalized (0.2%) |
| **Musculoskeletal and connective tissue disorders** | | Musculoskeletal pain[8] (9%)<br>Muscle spasms (2.7%) | |
| **Renal and urinary disorders** | | Acute kidney injury (2.7%)<br>Haematuria (1.8%)<br>Renal failure (1.8%)<br>Proteinuria (1.8%) | Leukocyturia (0.9%)<br>Urinary incontinence (0.9%)<br>Glomerular filtration rate decreased (0.9%)<br>Renal disorder (0.9%)<br>Acute prerenal failure (0.2%)<br>Renal impairment (0.1%) |
| **General disorders and administration site conditions** | Fatigue[1] (27.7%) | Injection site reaction[11] (5.4%)<br>Oedema peripheral (4.5%)<br>Administration site pain (4.5%)<br>Chills (1.8%)<br>Influenza like illness (1.8%) | Injection site mass (0.9%)<br>Chest discomfort (0.9%)<br>Chest pain (0.9%)<br>Pyrexia (0.9%)<br>Malaise (0.4%)<br>**Pain** (0.3%)<br>Deaths (0.2%)<br>Feeling abnormal (0.1%) |
| **Investigations** | | Blood creatinine increased (3.6%)<br>GGT* increased (3.6%)<br>ALAT** increased (1.8%)<br>ASAT*** increased (1.8%)<br>Blood ALP**** increased (1.8%) | Blood potassium decreased (0.9%)<br>Blood urea increased (0.9%)<br>Glycosylated haemoglobin increased (0.9%)<br>Haematocrit decreased (0.9%)<br>Protein urine (0.9%te)<br>Weight decreased (0.3%)<br>Blood creatine phosphokinase increased (0.2%)<br>Blood lactate dehydrogenase increased (0.2%)<br>Blood catecholamines (0.1%)<br>c-reactive protein increased (0.1%) |
| **Injury, poisoning and procedural complications** | | | Clavicle fracture (0.1%) |
| **Surgical and medical procedures** | | Transfusion (1.6%) | Abdominal cavity drainage (0.1%)<br>Dialysis (0.1%)<br>Gastrointestinal tube insertion (0.1%)<br>Stent placement (0.1%)<br>Abscess drainage (0.1%)<br>Bone marrow harvest (0.1%)<br>Polypectomy (0.1%) |
| **Social circumstances** | | | Physical disability (0.1%) |

[1] Includes Asthenia and Fatigue
[2] Includes Thrombocytopenia and Platelet count decreased
[3] Includes Lymphopenia and Lymphocyte count decreased
[4] Includes Anaemia and Haemoglobin decreased
[5] Includes Leukopenia and White blood cell count decreased
[6] Includes Neutropenia and Neutrophil count decreased
[7] Includes Hypertension and Hypertensive crisis
[8] Includes Arthralgia, Pain in extremity, Back pain, Bone pain, Flank pain, Musculoskeletal chest pain and Neck pain
[9] Includes Blood bilirubin increased and Hyperbilirubinaemia
[10] Includes Headache and migraine
[11] Includes injection site reaction, injection site hypersensibility, injection site induration, injection site swelling
* Gamma-glutamyltransferase increased
**Alanine amino transferase
*** Aspartate amino transferase
**** Alkaline phosphatase

**Table 59: Adverse drug reactions reported in at least 5% of patients who received Lutathera in NETTER-1 study by SOC and PT – SAF (N: 223)**

| | | Lutathera (n = 112) | | | | Octreotide LAR (n = 111) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | All grades | | Grade 3 to 5 | | All grades | | Grade 3 to 5 | |
| SOC | PT | npat | % | npat | % | npat | % | npat | % |
| All SOCs | All PTs | 102 | 91.1 | 34 | 30.4 | 45 | 40.5 | 5 | 4.5 |
| Gastrointestinal disorders | Nausea | 66 | 58.9 | 4 | 3.6 | 4 | 3.6 | 0 | 0.0 |
| | Vomiting | 51 | 45.6 | 4 | 3.6 | 0 | 0.0 | 0 | 0.0 |
| | Diarrhoea | 8 | 7.2 | 1 | 0.9 | 4 | 3.6 | 0 | 0.0 |
| | Abdominal distension | 10 | 8.9 | 0 | 0.0 | 5 | 4.5 | 0 | 0.0 |
| General disorders and administration site conditions | Fatigue | 27 | 24.1 | 0 | 0.0 | 5 | 4.5 | 0 | 0.0 |
| Blood and lymphatic system disorders | Thrombocytopenia | 15 | 13.5 | 3 | 2.7 | 0 | 0.0 | 0 | 0.0 |
| | Lymphopenia | 15 | 13.4 | 9 | 8.0 | 0 | 0.0 | 0 | 0.0 |
| | Anaemia | 14 | 12.5 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| | Platelet count decreased | 13 | 11.6 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| | Lymphocyte count decreased | 10 | 8.9 | 4 | 3.6 | 0 | 0.0 | 0 | 0.0 |
| | White blood cell count decreased | 7 | 6.3 | 0 | 0.0 | 1 | 0.9 | 0 | 0.0 |
| | Neutropenia | 6 | 5.4 | 1 | 0.9 | 1 | 0.9 | 0 | 0.0 |
| Metabolism and nutrition disorders | Decreased appetite | 15 | 13.4 | 0 | 0.0 | 2 | 1.8 | 0 | 0.0 |
| Skin and subcutaneous tissue disorders | Alopecia | 10 | 8.9 | 0 | 0.0 | 1 | 0.9 | 0 | 0.0 |
| Nervous system disorders | Dizziness | 7 | 6.3 | 0 | 0.0 | 1 | 0.9 | 0 | 0.0 |
| | Dysgeusia | 6 | 5.4 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

## *Serious adverse event/deaths/other significant events*

### ***SAEs and TESAEs in the NETTER-1 Study***

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).

**Table 60: Any treatment emergent serious adverse event reported in NETTER-1 study – SAF (N: 223)**

| | Lutathera (N = 112) | Octreotide LAR (N = 111) | All (N = 223) |
|---|---|---|---|
| **Treatment emergent serious adverse event** | **n (%)** | **n (%)** | **n (%)** |
| General information | | | |
| Number of patients with SAE | 37 (33.0) | 30 (27.0) | 67 (30.0) |
| Number of episodes | 85 | 52 | 137 |
| Maximal severity (based on number of patients) | | | |
| Grade 1 (Mild) | 1 (0.9) | 0 (0.0) | 1 (0.4) |
| Grade 2 (Moderate) | 3 (2.7) | 1 (0.9) | 4 (1.8) |
| Grade 3 (Severe) | 20 (17.9) | 16 (14.4) | 36 (16.1) |
| Grade 4 (Threatening/ disabling) | 5 (4.5) | 4 (3.6) | 9 (4.0) |
| Grade 5 (Death) | 8 (7.1) | 9 (8.1) | 17 (7.6) |
| Missing | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Possible cause of event (based on number of episodes) | | | |
| Pre-existing / underlying disease | 50 (58.8) | 39 (75.0) | 89 (65.0) |
| Study treatment | 16 (18.8) | 3 (5.8) | 19 (13.9) |
| Other treatment | 2 (2.4) | 0 (0.0) | 2 (1.5) |
| Protocol-related procedure | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Unknown | 4 (4.7) | 2 (3.9) | 6 (4.4) |
| Other | 13 (15.3) | 8 (15.4) | 21 (15.3) |
| Missing | 0 (0.0) | 0 (0.0) | 0 (0.0) |

**Table 61: Treatment emergent serious adverse events reported more commonly in patients who received Lutathera than in patients given Octreotide LAR in NETTER-1 study – SAF (N: 223)**

| | | Lutathera (N = 112) | | Octreotide LAR (N = 111) | |
|---|---|---|---|---|---|
| SOC | PT | $n_{pat}$ | % | $n_{pat}$ | % |
| All SOCs | All PTs | 35 | 31.3 | 27 | 24.3 |
| Blood and lymphatic system disorders | Lymphopenia | 2 | 1.8 | 0 | 0.0 |
| | Neutropenia | 1 | 0.9 | 0 | 0.0 |
| | Refractory cytopenia with multilineage dysplasia | 1 | 0.9 | 0 | 0.0 |
| Injury, poisoning and procedural complications | Femur fracture | 2 | 1.8 | 0 | 0.0 |
| | Limb traumatic amputation | 1 | 0.9 | 0 | 0.0 |
| | Procedural complication | 1 | 0.9 | 0 | 0.0 |
| Cardiac disorders | Acute myocardial infarction | 1 | 0.9 | 0 | 0.0 |
| | Angina pectoris | 1 | 0.9 | 0 | 0.0 |
| | Atrioventricular block second degree | 1 | 0.9 | 0 | 0.0 |
| | Cardiac arrest | 1 | 0.9 | 0 | 0.0 |
| | Silent myocardial infarction | 1 | 0.9 | 0 | 0.0 |
| Gastrointestinal disorders | Abdominal pain | 3 | 2.7 | 1 | 0.9 |
| | Vomiting | 2 | 1.8 | 2 | 1.8 |
| | Ascites | 1 | 0.9 | 1 | 0.9 |
| | Small intestinal obstruction | 1 | 0.9 | 2 | 1.8 |
| | Gastritis | 1 | 0.9 | 0 | 0.0 |
| | Haematochezia | 1 | 0.9 | 0 | 0.0 |
| | Intestinal obstruction | 1 | 0.9 | 0 | 0.0 |
| General disorders and administration site conditions | Complication of device insertion | 1 | 0.9 | 0 | 0.0 |
| | Device occlusion | 1 | 0.9 | 0 | 0.0 |
| | Injection site hypersensitivity | 1 | 0.9 | 0 | 0.0 |
| | Pyrexia | 1 | 0.9 | 0 | 0.0 |
| | General physical health deterioration | 2 | 1.8 | 1 | 0.9 |
| | Pyrexia | 1 | 0.9 | 0 | 0.0 |
| Hepatobiliary disorders | Cholecystitis | 1 | 0.9 | 0 | 0.0 |
| | Cholestasis | 1 | 0.9 | 0 | 0.0 |
| | Hepatocellular injury | 1 | 0.9 | 0 | 0.0 |
| | Hepatic encephalopathy | 1 | 0.9 | 0 | 0.0 |
| Infections and infestations | Clostridium difficile infection | 1 | 0.9 | 0 | 0.0 |
| | Device related infection | 1 | 0.9 | 0 | 0.0 |
| | Diverticulitis | 1 | 0.9 | 0 | 0.0 |
| | Pneumocystis jirovecii pneumonia | 1 | 0.9 | 0 | 0.0 |
| | Respiratory tract infection | 1 | 0.9 | 0 | 0.0 |
| | Sepsis | 1 | 0.9 | 0 | 0.0 |
| Metabolism and nutrition disorders | Fluid retention | 1 | 0.9 | 0 | 0.0 |
| | Hypokalaemia | 1 | 0.9 | 0 | 0.0 |

| | | | | | |
|---|---|---|---|---|---|
| | Dehydration | 1 | 0.9 | 1 | 0.9 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | Malignant neoplasm progression | 2 | 1.8 | 5 | 4.5 |
| | Diffuse large B-cell lymphoma | 1 | 0.9 | 0 | 0.0 |
| | Oesophageal adenocarcinoma | 1 | 0.9 | 0 | 0.0 |
| | Tumour invasion | 1 | 0.9 | 0 | 0.0 |
| | Refractory cytopenia with multilineage dysplasia | 1 | 0.9 | 0 | 0 |
| Psychiatric disorders | Anxiety | 1 | 0.9 | 0 | 0.0 |
| | Delirium | 1 | 0.9 | 0 | 0.0 |
| Renal and urinary disorders | Acute kidney injury | 4 | 3.6 | 1 | 0.9 |
| | Acute prerenal failure | 1 | 0.9 | 0 | 0.0 |
| Respiratory, thoracic and mediastinal disorders | Acute respiratory failure | 1 | 0.9 | 0 | 0.0 |
| | Cough | 1 | 0.9 | 0 | 0.0 |
| Surgical and medical procedures | Coronary artery bypass | 1 | 0.9 | 0 | 0.0 |
| Vascular disorders | Inferior vena cava syndrome | 1 | 0.9 | 0 | 0.0 |
| | Pulmonary embolism | 1 | 0.9 | 0 | 0.0 |
| | Shock | 1 | 0.9 | 0 | 0.0 |
| | Syncope | 1 | 0.9 | 0 | 0.0 |

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.

**Table 62: Treatment emergent serious adverse events related to study medication in NETTER-1 study – SAF (N: 223)**

| | Lutathera (N = 112) | Octreotide LAR (N = 111) | All (N = 223) |
|---|---|---|---|
| **Treatment emergent serious adverse event related to study medication** | **n (%)** | **n (%)** | **n (%)** |
| General information | | | |
| Number of patients with at least one TESAE related to study medication | 13 (11.6) | 3 (2.7) | 16 (7.2) |
| Number of events | 16 | 3 | 19 |
| Number of patients with at least one TESAE related to study medication by maximum severity | | | |
| Grade 1 (Mild) | 1 (0.9) | 0 (0.0) | 1 (0.4) |
| Grade 2 (Moderate) | 2 (1.8) | 0 (0.0) | 2 (0.9) |
| Grade 3 (Severe) | 8 (7.1) | 3 (2.7) | 11 (4.9) |
| Grade 4 (Threatening/disabling) | 2 (1.8) | 0 (0.0) | 2 (0.9) |
| Grade 5 (Death) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

During the long-term follow-up, the investigator had to report only SAEs related to Lutathera.

N: number of patients per treatment group; n: number of patients/events; TESAE: treatment emergent serious adverse event.

At each level of summarization, a patient is counted only once.

The treatment emergent SAEs considered by the investigator to be related to Lutathera were lymphopenia Grade 3, neutropenia Grade 4, refractory cytopenia with multilineage dysplasia Grade 4, ascites Grade 3, intestinal obstruction Grade 3, vomiting Grade 1, injection site hypersensitivity Grade 2, hepatic encephalopathy Grade 3, respiratory tract infection Grade 3, dehydration Grade 3, acute kidney injury Grade 1, Grade 2 and Grade 3, refractory cytopenia with multilineage dysplasia Grade 3, syncope Grade 3.

The treatment emergent SAEs in the Lutathera group related to amino acid treatment were hepatic encephalopathy, vomiting, dehydration (2 episodes), syncope.

The treatment emergent SAE related to Octreotide LAR was injection site hypersensitivity Grade 2.

From non-randomized patients enrolled in the Dosimetry/PK/ECG sub-study (N=31), TESAEs were reported in 14 patients (i.e. 45% patients in the sub study experienced at least one TESAE). Among those patients, the reported outcome was fatal in 3 patients and the possible cause was pre-existing/underlying disease.

***SAEs and TESAEs in the Erasmus MC Study***

Severe adverse events were not typically reported in the CRF of the Erasmus MC study (with the exception of a few pre-coded symptoms). A post-hoc review of the patient's medical charts was conducted to retrospectively collect all SAEs data. Except for laboratory toxicities, SAEs were not graded for their severity. The principal investigator scored the causality of all these retrospectively collected SAEs.

Among all enrolled Dutch patients included in the SAF analysis (N=811), 508 (62.8%) experienced a serious adverse event. Regarding specific SAEs, those with the highest frequencies were pancytopenia (10.5%), abdominal pain (5.8%), diarrhoea (6.4%); anaemia (5.3%), death (5.1%), pyrexia (4.3%), vomiting (4.1%), nausea (3.6%) and thrombocytopenia (3.3%).

In the retrospective SAEs data collection, an event was classified as pancytopenia when there was a simultaneous reduction in the number of red and white blood cells, as well as platelets, according to the laboratory reports. At least for one out of the three parameters (haemoglobin level, WBC and platelet counts) the CTC grade was 3-4, while for the other two parameters the CTC grade was ≥1.

In terms of relationship to study medication, out of the 508 Dutch patients in the SAF population who experienced an SAE, in 163 (20.1%) patients the SAE was related to the study medication.

There were 14 cases (1.7%) of MDS diagnosed 2-4 years after the first treatment with 177Lu-Oxodotreotide and considered possibly or probably related to the treatment in the Dutch population. In two of these cases, the patients received two extra treatments (exceeding 29.7 GBq) and in both cases the MDS was considered related to the additional treatments.

In the Dutch population the incidence of serious renal disorders related to 177Lu-Oxodotreotide was 0.4% (3 cases)

***SAEs in the ISS population***

Since in the Erasmus MC study, only SAE summary data are available, only serious adverse event (SAE) information was summarized and presented for patients in the pooled safety analysis set.

Gastrointestinal disorders were the most frequently reported SAEs for both the Pooled 177Lu-DOTA0-Try3-Octreotate group (21.0% of subjects) and the Octreotide LAR group (13.5% of subjects). SOC designations with the next most frequently reported SAEs in the Pooled 177Lu-DOTA0-Try3-Octreotate group were surgical and medical procedures (19.0% of subjects), blood and lymphatic system disorders (16.5% of subjects), and general disorders and administration site conditions (15.3% of subjects). Besides Gastrointestinal disorders and neoplasms, no SOC had more than 5 subjects (4.5% of subjects) reporting a particular SAE in the Octreotide LAR group. The most common preferred terms for SAEs in the Lutathera group were pancytopenia (9.0%), followed by diarrhoea (5.7%), abdominal pain (5.4%), and anaemia (4.8%). The most common preferred terms for SAEs in the Octreotide LAR group were malignant neoplasm progression (4.5%), followed by diarrhoea, abdominal pain, vomiting, and small intestinal obstruction (1.8% each).

***Deaths***

- **Deaths in the NETTER-1 Study**

**Table 63: Fatal TEAEs reported in NETTER-1 study – SAF (N: 223)**

| | Lutathera (N = 112) | Octreotide LAR (N = 111) | All (N = 223) |
|---|---|---|---|
| **Any fatal adverse event** | **N %** | **N %** | **N %** |
| General information | | | |
| Number of patients with AE | 7 (6.3) | 9 (8.1) | 16 (7.2) |
| Number of events | 11 | 11 | 22 |
| | | | |
| TEAEs leading to death, by system organ class and preferred term | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 3 (2.7) | 6 (5.4) | 9 (4.0) |
| General disorders and administration site conditions | 3 (2.7) | 2 (1.8) | 5 (2.2) |
| Renal and urinary disorders | 1 (0.9) | 1 (0.9) | 2 (0.9) |
| Cardiac disorders | 1 (0.9) | 0 (0.0) | 1 (0.4) |
| Gastrointestinal disorders | 0 (0.0) | 1 (0.9) | 1 (0.4) |
| Infections and infestations | 1 (0.9) | 0 (0.0) | 1 (0.4) |
| Respiratory, thoracic and mediastinal disorders | 1 (0.9) | 0 (0.0) | 1 (0.4) |
| Vascular disorders | 1 (0.9) | 0 (0.0) | 1 (0.4) |

N: number of patients; %: percentage based on N; TEAE: treatment emergent adverse event; at each level of summarization, a subject is counted only once.

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.

- **Deaths in the Erasmus MC Study**

In the Dutch patient population (811 patients) there were 397 deaths (49.0 %) in the 12 years follow-up period. The highest death rate was among patients with other tumour types and thyroid carcinomas; 75.6% and 64.9% of patients, respectively.

In the 30-day period after the last study medication was administered there were 17 deaths recorded in the Dutch population, all of which were judged by the PI as unrelated to study treatment.

**Table 64: Deaths reported in the Erasmus MC study (Dutch population) by tumor type – SAF (N=811)**

| | N | Total number of recorded deaths n (%) |
|---|---|---|
| All tumor types | 811 | 397(48.95) |
| GEP-NETs | 559 | 266 (47.58) |
| Bronchial NET | 39 | 16 (41.03) |
| Pancreatic NET | 198 | 86 (43.43) |
| Foregut NET* | 18 | 3 (16.67) |
| Midgut NET | 278 | 157 (56.47) |
| Hindgut NET | 26 | 4 (15.38) |
| NETs of unknown origin | 138 | 67 (48.55) |
| Other NETs and Non-NETs | 45 | 34 (75.56) |
| Paraganglioma | 29 | 6 (20.69) |
| Thyroid carcinoma | 37 | 24 (64.86) |
| Tumor type not recorded | 3 | 0 (0.0) |

Foregut NET = Foregut except pancreatic and bronchial NETs
Other = Includes other NETs and non-NETs

**Table 65: Relationship of deaths to study drug - SAF Dutch population (N= 811)**

| | Unrelated N (%) | Unlikely related N (%) | Possibly related N (%) | Probably related N (%) | Not assessable N (%) | Total N (%) |
|---|---|---|---|---|---|---|
| **Any dose (N=811)** | 349 (43.0) | 2 (0.2) | 6 (0.7) | 13 (1.6) | 29 (3.6) | 399 (49.2) |
| **Dose <29.6 GBq (N=325)** | 151 (46.5) | 1 (0.3) | 5 (1.5) | 4 (1.2) | 18 (5.5) | 179 (55.1) |
| **Dose ≥29.6 GBq (N=486)** | 198 (40.7%) | 1 (0.2%) | 1 (0.2%) | 9 (1.9%) | 11 (2.3%) | 220 (45.3%) |

***Other significant events***

- **AESI in the NETTER-1 study**

AEs, SAEs and laboratory data were analysed post-hoc to account for the toxicity categories hematotoxicity, secondary haematological malignancies, nephrotoxicity and cardiovascular events.

**Table 66: Adverse events reported in NETTER-1 study selected post-hoc as of special interest**

| Preferred Term/*Lab abnormality | Lutathera N=112 n (%) | Octreotide LAR N=111 n (%) |
|---|---|---|
| **Hematotoxicity** | **56 (50.0%)** | **7 (6.3%)** |
| *Leukopaenia | 50 (44.6%) | 4 (3.6%) |
| *Thrombocytopenia | 10 (8.9%) | 2 (1.8%) |
| Haematotoxicity multilineage | 4 (3.6%) | 0 (0.0%) |
| *Anaemia | 0 (0.0%) | 1 (0.9%) |
| **Secondary haematological malignancies** | **3 (2.7%)** | **3 (2.7%)** |
| Leukocytosis | 0 (0.0%) | 3 (2.7%) |
| Diffuse large B-cell lymphoma | 1 (0.9%) | 0 (0.0%) |
| Refractory cytopenia with multilineage dysplasia | 1 (0.9%) | 0 (0.0%) |
| Refractory cytopenia with unilineage dysplasia | 1 (0.9%) | 0 (0.0%) |
| White blood cell count increased | 0 (0.0%) | 1 (0.9%) |
| **Nephrotoxicity** | **51 (45.5%)** | **31 (27.9%)** |
| Radiation-induced nephropathy | 38 (33.9%) | 21 (18.9%) |
| Renal disorder | 20 (17.9%) | 9 (8.1%) |
| Acute radiation toxicity | 12 (10.7%) | 4 (3.6%) |
| **Cardiovascular events** | 37 (33.0%) | 29 (26.1%) |
| Hypertension | 14 (12.5%) | 14 (12.6%) |
| Arrhythmia | 13 (11.6%) | 9 (8.1%) |
| Hypotension | 6 (5.4%) | 2 (1.8%) |
| Coronary artery disease and atherosclerosis | 5 (4.5%) | 2 (1.8%) |
| Heart valve disease | 2 (1.8%) | 2 (1.8%) |
| Cardiac conduction disturbances | 1 (0.9%) | 1 (0.9%) |
| Changes on electrocardiogram or echocardiography | 0 (0.0%) | 2 (1.8%) |
| Congestive heart failure | 1 (0.9%) | 1 (0.9%) |
| Cardiomyopathy | 1 (0.9%) | 0 (0.0%) |
| Other | 1 (0.9%) | 0 (0.0%) |

AESI: adverse events of special interest; N: number of patients in treatment group; n: number of patients; SAF: safety set.

The most frequent haematological toxicities based on laboratory CTCAE grading were Grade 2 or higher leukopaenia 50 patients (44.6%),thrombocytopenia 10 patients (8.9%), hematotoxicity multilineage 4 patients (3.6%). None of the patients experienced anaemia Grade 3-4.

For secondary haematological malignancies, the PTs in the Lutathera arm were "diffuse large B-cell lymphoma", "refractory cytopenia with multilineage dysplasia", and "refractory cytopenia with unilineage dysplasia" with each PT accounting for 1 patient (0.9%).

For nephrotoxicity, the most frequent AESIs in the Lutathera arm were "radiation-induced nephropathy" (38 patients [33.9%]), "renal disorder" (20 patients [17.9%]), and "acute radiation

toxicity" (12 patients [10.7%]). There were three renal failure/impairment cases recognized by PTs/SOC, however all 3 renal failure cases were mild to moderate.

The most frequent cardiovascular events were "hypertension" (14 patients [12.5%]), "arrhythmias" (13 patients [11.6%]), "hypotension" (6 patients [5.4%]), and "coronary artery disease and atherosclerosis" (5 patients [4.5%]).

At the cut-off date for the primary end-point analysis, 2 MDS occurred in the Lutathera arm. An additional MDS case was notified after the cut-off date for the safety analyses.

- **AESI in the Erasmus MC study**

The identified treatment emergent AESIs in the Dutch population were: thrombocytopenia (129 cases, 15.9%), leukopenia (40 cases, 4.9%), anaemia (33 cases, 4.1%), cardiac disorders (62 cases, 7.6%), renal and urinary disorders (49 cases, 6.0%), secondary haematological malignancies (20, 2.5%).

All AESI belonging to the neoplasms SOC were of haematological origin. More specifically, there were 16 Dutch patients (2.0%) who developed myelodysplastic syndrome (MDS). The other AESI with a frequency greater/equal to 1% were hypotension (10 patients, 1.2%), cardiac failure (12 patients, 1.5%), myocardial infarction (9 patients 1.1%), renal failure (8 patients, 1.0%), and renal impairment (10 patients, 1.2%). The incidence of other blood neoplasms was, 0.1% for acute leukaemia and 0.4% for acute myeloid leukaemia, 0.1% for chronic myeloid leukaemia and 0.1% for chronic myelomonocytic leukaemia.

## *Laboratory findings*

Periodic laboratory assessments were performed locally in the Erasmus MC and NETTER-1 studies.

***Clinical laboratory evaluations in the NETTER-1 study***

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 randomization. In each of the following categories, between 4 and 7 patients (3.6% to 6.3%) showed post randomization 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.

***Clinical laboratory evaluations in the ERASMUS MC study***

The results of the association between the worst post baseline CTCAE grade 3-4 laboratory toxicities and administered dose (<29.6 GBq and ≥29.6 GBq) are presented below for the SAF Dutch population (N= 811).

**Table 67: Worst post-baseline CTCAE grade laboratory toxicities according to administered dose (<29.6 GBq and ≥29.6 GBq) - SAF Dutch population (N=811)**

| Haemoglobin | N | G1 N (%) | G2 N (%) | G3 N (%) | G4 N (%) | p |
|---|---|---|---|---|---|---|
| <29.6 GBq | 272 | 147 (54.0) | 54 (19.9) | 18 (6.6) | - | 0.0003 |
| ≥29.6 GBq | 486 | 321 (66.1) | 69 (14.2) | 9 (1.9) | - | |
| | | | | | | |
| **Platelets** | | | | | | |
| <29.6 GBq | 272 | 77 (28.3) | 36 (13.2) | 19 (7.0) | 13 (4.8) | <0.0001 |
| ≥29.6 GBq | 486 | 212 (43.6) | 44 (9.1) | 15 (3.1) | 2 (0.4) | |
| | | | | | | |
| **WBC** | | | | | | |
| <29.6 GBq | 272 | 41 (15.1) | 50 (18.4) | 19 (7.0) | 1 (0.4) | 0.0718 |
| ≥29.6 GBq | 486 | 103 (21.2) | 103 (21.2) | 19 (3.9) | 1 (0.2) | |
| | | | | | | |
| **Neutrophils** | | | | | | |
| <29.6 GBq | 269 | 41 (15.2) | 30 (11.2) | 11 (4.1) | - | 0.5026 |
| ≥29.6 GBq | 486 | 95 (19.6) | 52 (10.7) | 14 (2.9) | 1 (0.2) | |
| | | | | | | |
| **Lymphocytes** | | | | | | |
| <29.6 GBq | 269 | 29 (10.8) | 94 (34.9) | 112 (41.6) | 15 (5.6) | 0.3540 |
| ≥29.6 GBq | 486 | 52 (10.7) | 168 (34.6) | 225 (46.3) | 15 (3.1) | |
| | | | | | | |
| **Creatinine** | | | | | | |
| <29.6 GBq | 270 | 40 (14.8) | 9 (3.3) | - | - | 0.0538 |
| ≥29.6 GBq | 486 | 57 (11.7) | 4 (0.8) | 1 (0.2) | 1 (0.2) | |
| | | | | | | |
| **Alkaline Phoshatase** | | | | | | |
| <29.6 GBq | 269 | 93 (34.6) | 37 (13.8) | 21 (7.8) | 2 (0.7) | 0.0309 |
| ≥29.6 GBq | 486 | 169 (34.8) | 38 (7.8) | 29 (6.0) | 1 (0.2) | |
| | | | | | | |
| **Albumin** | **N** | **G1** | **G2** | **G3** | **G4** | |
| <29.6 GBq | 269 | 36 (13.4) | 16 (6.0) | 1 (0.4) | - | <0.0001 |
| ≥29.6 GBq | 486 | 32 (6.6) | 7 (1.4) | 1 (0.2) | - | |
| | | | | | | |
| **Bilirubin** | | | | | | |
| <29.6 GBq | 269 | 32 (11.9) | 20 (7.4) | 2 (0.7) | 1 (0.4) | 0.5459 |
| ≥29.6 GBq | 486 | 49 (10.1) | 28 (5.8) | 9 (1.9) | 1 (0.2) | |
| | | | | | | |
| **AST (SGOT)** | | | | | | |
| <29.6 GBq | 269 | 115 (42.8) | 12 (4.5) | 16 (6.0) | - | 0.0093 |
| ≥29.6 GBq | 486 | 246 (50.6) | 18 (3.7) | 9 (1.9) | 3 (0.6) | |
| | | | | | | |
| **ALT (SGPT)** | | | | | | |
| <29.6 GBq | 269 | 93 (34.6) | 14 (5.2) | 11 (4.1) | 1 (0.4) | 0.0888 |
| ≥29.6 GBq | 486 | 215 (44.2) | 19 (3.9) | 11 (2.3) | 2 (0.4) | |
| | | | | | | |
| **GGT** | | | | | | |
| <29.6 GBq | 269 | 61 (22.7) | 45 (16.7) | 70 (26.0) | 18 (6.7) | 0.2519 |
| ≥29.6 GBq | 486 | 133 (27.4) | 99 (20.4) | 114 (23.5) | 23 (4.7) | |

Post-baseline, results where the frequency of CTC Grade 3 and 4 was above 1% were for platelets (1.7%), leukopenia (2.4%), neutrophils (1.1%), anemia (1.1%) and lymphopenia (29.6%). At the last 30-month follow-up, it was only lymphopenia where CTC Grade 3 and 4 haematology test results had a frequency above 1% (4.8% Grade 3).

The haematology test results for the duration of treatment with study medication showed a trend towards lower values for haemoglobin, platelets, neutrophils, lymphocytes and white blood cell counts following each treatment.

For serum chemistry, in general, the changes observed did not show a clear trend towards worsening of the laboratory parameters during the study. In the Dutch population the worst post-baseline serum chemistry CTCAE grade 3 and 4 with a frequency above 1% at any point during the study was observed for GGT (18.9%), ALAT (2.8%), and alkaline phosphatase (1.9%).

## *Safety in special populations*

**Age**

Within the ISS population, similar fractions of patients across all age groups reported TESAEs (between 53.7% and 62% of patients per age group).

Among patients in the ≤ 50 year age group, TESAEs were most frequently reported in the following SOCs: surgical and medical procedures (23.5%), blood and lymphatic system disorders (21.2%), gastrointestinal disorders (18.4%), general disorders and administration site conditions (18.4%), and neoplasms benign, malignant and unspecified (10.1%). Within the surgical and medical procedures SOC, the AE preferred terms were each reported by between 0.6% and 2.8% of patients. Within the blood and lymphatic system disorders SOC, the most frequently reported AE preferred terms were pancytopenia (12.3%), anaemia (6.7%) and thrombocytopenia (2.8%).

In the 50 to ≤ 60 year age group, TESAEs were most frequently reported in the following SOCs: gastrointestinal disorders (20.1%), surgical and medical procedures (19%), blood and lymphatic system disorders (12.6%), general disorders and administration site conditions (12.6%), and infections and infestations (11.5%). The most frequently reported preferred terms within the gastrointestinal disorders SOC were diarrhoea (5.6%) and abdominal pain (4.1%). Within the surgical and medical procedures SOC, the AE preferred terms were each reported by between 0.4% and 2.2% of patients. Within the blood and lymphatic system disorders SOC, the most frequently reported AE preferred terms were pancytopenia (6.7%), anaemia (4.1%) and thrombocytopenia (2.6%)

In the 60 to ≤ 70 year age group, TESAEs were most frequently reported in the following SOCs: gastrointestinal disorders (20.6%), surgical and medical procedures (15%), blood and lymphatic system disorders (12.5%), general disorders and administration site conditions (12.9%), and metabolism and nutrition disorders (10.8%). The most frequently reported preferred terms within the gastrointestinal disorders SOC were diarrhoea (6.6%) and abdominal pain (5.6%). Within the surgical and medical procedures SOC, the AE preferred terms were each reported by between 0.3% and 3.1% of patients. Within the blood and lymphatic system disorders SOC, the most frequently reported AE preferred terms were pancytopenia (7.0%), anaemia (3.5%) and thrombocytopenia (3.1%)

In the > 70 year age group, TESAEs were most frequently reported in the following SOCs: blood and lymphatic system disorders (19.9%), gastrointestinal disorders (18.8%), surgical and medical procedures (16.7%), and general disorders and administration site conditions (13.4%). The most frequently reported preferred terms within the gastrointestinal disorders SOC were diarrhoea (6.6%) and abdominal pain (5.6%). The most frequently reported preferred term within the blood and lymphatic system disorders SOC were pancytopenia (11.3%), anaemia (4.8%) and thrombocytopenia (4.3%); and within the Gastrointestinal disorders SOC the most commonly reported preferred terms were abdominal pain (7%) and diarrhoea (5.4%).

**Table 68: treatment emergent adverse events by age group for Lutathera treated patients (Safety analysis set)**

| MedDRA Terms | Age < 65 (N=58) | Age 65-74 (N=40) | Age 75 - 84 (N=12) | Age 85+ (N=0) |
|---|---|---|---|---|
| Total AEs | 58 (100.0) | 40 (100.0) | 12 (100.0) | 0 |
| Serious AEs - Total | 17 (29.3) | 15 (37.5) | 3 (25.0) | 0 |
| - Fatal | 2 (3.4) | 4 (10.0) | 1 (8.3) | 0 |
| - Hospitalization/ prolong existing hospitalization | 14 (24.1) | 11 (27.5) | 2 (16.7) | 0 |
| - Life-threatening | 0 | 1 (2.5) | 0 | 0 |
| - Disability/ incapacity | 0 | 0 | 0 | 0 |
| - Other (medically significant) | 5 (8.6) | 6 (15.0) | 2 (16.7) | 0 |
| AE leading to drop-out | 6 (10.3) | 7 (17.5) | 1 (8.3) | 0 |
| Psychiatric disorders | 18 (31.0) | 6 (15.0) | 4 (33.3) | 0 |
| Nervous system disorders | 26 (44.8) | 15 (37.5) | 5 (41.7) | 0 |
| Injury, poisoning and procedural complications | 13 (22.4) | 1 (2.5) | 3 (25.0) | 0 |
| Cardiac disorders | 12 (20.7) | 3 (7.5) | 1 (8.3) | 0 |
| Vascular disorders | 23 (39.7) | 13 (32.5) | 3 (25.0) | 0 |
| Cerebrovascular disorder | 0 | 0 | 0 | 0 |
| Infections and infestations | 22 (37.9) | 9 (22.5) | 3 (25.0) | 0 |
| Anticholinergic syndrome | 0 | 0 | 0 | 0 |
| Quality of life decreased | 0 | 0 | 0 | 0 |
| Anaemia | 6 (10.3) | 8 (20.0) | 4 (33.3) | 0 |

| MedDRA Terms | Age < 65 (N=58) | Age 65-74 (N=40) | Age 75 - 84 (N=12) | Age 85+ (N=0) |
|---|---|---|---|---|
| Arthralgia | 4 (6.9) | 7 (17.5) | 1 (8.3) | 0 |
| Asthenia | 6 (10.3) | 2 (5.0) | 0 | 0 |
| Back pain | 9 (15.5) | 4 (10.0) | 1 (8.3) | 0 |
| Constipation | 3 (5.2) | 5 (12.5) | 3 (25.0) | 0 |
| Cough | 10 (17.2) | 2 (5.0) | 0 | 0 |
| Decreased appetite | 11 (19.0) | 7 (17.5) | 5 (41.7) | 0 |
| Delirium | 0 | 0 | 2 (16.7) | 0 |
| Diarrhoea | 16 (27.6) | 8 (20.0) | 5 (41.7) | 0 |
| Dizziness | 9 (15.5) | 6 (15.0) | 4 (33.3) | 0 |
| Fatigue | 21 (36.2) | 14 (35.0) | 7 (58.3) | 0 |
| Flatulence | 4 (6.9) | 0 | 2 (16.7) | 0 |
| Haematuria | 3 (5.2) | 1 (2.5) | 3 (25.0) | 0 |
| Hyponatraemia | 4 (6.9) | 1 (2.5) | 2 (16.7) | 0 |
| Injection site reaction | 1 (1.7) | 0 | 2 (16.7) | 0 |
| Leukopenia | 3 (5.2) | 0 | 2 (16.7) | 0 |
| Muscle spasms | 4 (6.9) | 1 (2.5) | 2 (16.7) | 0 |
| Nausea | 39 (67.2) | 23 (57.5) | 10 (83.3) | 0 |
| Platelet count decreased | 3 (5.2) | 6 (15.0) | 4 (33.3) | 0 |
| Thrombocytopenia | 8 (13.8) | 5 (12.5) | 3 (25.0) | 0 |

| MedDRA Terms | Age < 65 (N=58) | Age 65-74 (N=40) | Age 75 - 84 (N=12) | Age 85+ (N=0) |
|---|---|---|---|---|
| Vomiting | 30 (51.7) | 21 (52.5) | 8 (66.7) | 0 |
| Sum of Orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, ataxia, fracture | 15 (25.9) | 9 (22.5) | 4 (33.3) | 0 |

| MedDRA Terms | Age < 65 (N=50) | Age 65-74 (N=38) | Age 75 - 84 (N=14) | Age 85+ (N=1) |
|---|---|---|---|---|
| Total AEs | 50 (100.0) | 38 (100.0) | 14 (100.0) | 1 (100.0) |
| Serious AEs - Total | 13 (26.0) | 10 (26.3) | 4 (28.6) | 0 |
| - Fatal | 5 (10.0) | 2 (5.3) | 2 (14.3) | 0 |
| - Hospitalization/ prolong existing hospitalization | 11 (22.0) | 8 (21.1) | 4 (28.6) | 0 |
| - Life-threatening | 1 (2.0) | 0 | 0 | 0 |
| - Disability/ incapacity | 1 (2.0) | 0 | 1 (7.1) | 0 |
| - Other (medically significant) | 2 (4.0) | 1 (2.6) | 0 | 0 |
| AE leading to drop-out | 7 (14.0) | 2 (5.3) | 3 (21.4) | 0 |
| Psychiatric disorders | 7 (14.0) | 5 (13.2) | 1 (7.1) | 0 |
| Nervous system disorders | 10 (20.0) | 8 (21.1) | 7 (50.0) | 0 |
| Injury, poisoning and procedural complications | 5 (10.0) | 5 (13.2) | 0 | 0 |
| Cardiac disorders | 4 (8.0) | 5 (13.2) | 2 (14.3) | 0 |
| Vascular disorders | 10 (20.0) | 10 (26.3) | 4 (28.6) | 0 |
| Cerebrovascular disorder | 0 | 0 | 0 | 0 |
| Infections and infestations | 15 (30.0) | 15 (39.5) | 4 (28.6) | 0 |
| Anticholinergic syndrome | 0 | 0 | 0 | 0 |
| Quality of life decreased | 0 | 0 | 0 | 0 |
| Anaemia | 6 (12.0) | 1 (2.6) | 2 (14.3) | 0 |

| MedDRA Terms | Age < 65 (N=50) | Age 65-74 (N=38) | Age 75 - 84 (N=14) | Age 85+ (N=1) |
|---|---|---|---|---|
| Arthralgia | 5 (10.0) | 2 (5.3) | 4 (28.6) | 0 |
| Asthenia | 1 (2.0) | 3 (7.9) | 3 (21.4) | 1 (100.0) |
| Back pain | 3 (6.0) | 5 (13.2) | 3 (21.4) | 0 |
| Constipation | 2 (4.0) | 2 (5.3) | 2 (14.3) | 0 |
| Cough | 3 (6.0) | 1 (2.6) | 3 (21.4) | 0 |
| Decreased appetite | 5 (10.0) | 4 (10.5) | 2 (14.3) | 1 (100.0) |
| Delirium | 0 | 0 | 0 | 0 |
| Diarrhoea | 6 (12.0) | 9 (23.7) | 4 (28.6) | 1 (100.0) |
| Dizziness | 3 (6.0) | 3 (7.9) | 3 (21.4) | 0 |
| Fatigue | 17 (34.0) | 9 (23.7) | 3 (21.4) | 0 |
| Flatulence | 2 (4.0) | 3 (7.9) | 1 (7.1) | 0 |
| Haematuria | 2 (4.0) | 0 | 0 | 0 |
| Hyponatraemia | 2 (4.0) | 0 | 2 (14.3) | 0 |
| Injection site reaction | 1 (2.0) | 2 (5.3) | 0 | 0 |
| Leukopenia | 0 | 0 | 0 | 0 |
| Muscle spasms | 1 (2.0) | 0 | 1 (7.1) | 0 |
| Nausea | 8 (16.0) | 4 (10.5) | 1 (7.1) | 0 |
| Platelet count decreased | 1 (2.0) | 0 | 1 (7.1) | 0 |
| Thrombocytopenia | 0 | 0 | 0 | 0 |

| MedDRA Terms | Age < 65 (N=50) | Age 65-74 (N=38) | Age 75 - 84 (N=14) | Age 85+ (N=1) |
|---|---|---|---|---|
| Vomiting | 7 (14.0) | 2 (5.3) | 2 (14.3) | 0 |
| Sum of Orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, ataxia, fracture | 5 (10.0) | 3 (7.9) | 4 (28.6) | 0 |

**Gender**

The frequencies of TESAEs in male (n=490) and female (n=455) patients were similar in the individual SOCs and AE preferred terms with the highest percentages of reported events, except for SOC Blood and lymphatic system disorders, with a frequency slightly higher in females compared to males (13.3% vs 20.0%). Within both male and female patients, TESAEs were most frequently reported in the

following SOCs: gastrointestinal disorders (21.6% male, 20.2% female), surgical and medical procedures (20.8% male, 17.1% female), , general disorders and administration site conditions (12.9% male, 18.0% female).

The most frequently reported AE preferred terms in the gastrointestinal disorders SOC were abdominal pain (5.9% male, 4.8% female) and diarrhea (5.3% male, 6.2% female). The most frequently reported AE preferred terms in the blood and lymphatic system disorders SOC were pancytopenia (6.7% male, 11.4% female), anemia (3.9% male, 5.7% female) and thrombocytopenia (2.7% male and 3.3% in female). AE preferred terms in the surgical and medical procedures and general disorders and administration site conditions SOCs were reported to occur in 0.2% to 2.0% of male patients and 0.2% to 2.2% of female patients.

**Use in Pregnancy and Lactation**

No adequate and well-controlled studies have been performed in pregnant or lactating women.

### *Drug Interactions*

In the NETTER-1 study, concomitant medications were recorded in 223 patients (100%) of the FAS. The most frequent concomitant medications by ATC for patients in the FAS were "antiemetics and antinauseants", followed by "analgesics". Ondansetron was the most frequently documented concomitant medications substance for Lutathera group with 97 (86.6%) patients (ondansetron was used by 18 [16.2%] patients in Octreotide LAR group). "Paracetamol" was the most frequently documented concomitant medications substance for Octreotide LAR group (Octreotide LAR group: 44 [39.6%] patients [32.8%]; Lutathera group: 46 [41.1%] patients).

No concomitant medications were recorded in the Erasmus MC study.

### *Discontinuation due to adverse events*

The commonest TEAE related to Lutathera leading to study drug withdrawal was related to haematological toxicity, followed by renal toxicity and to a lesser extent GI toxicity possibly as a result of the amino acids infused with Lutathera. ERASMUS study shows haematological toxicity, mainly thrombocytopenia; and renal toxicity to be the commonest adverse events leading to study drug discontinuation and this correlates with the data from the NETTER-1 study.

## 2.6.1. Discussion on clinical safety

The safety analysis consisted of all patients (all tumour types) in the Erasmus MC study who received at least one dose of 177Lu-DOTA0-Try3-Octreotate at the dose and schedule employed in the NETTER-1 study and all patients randomised in the NETTER-1 study who receive d at least 1 does of study drug. The cut-off date for the analyses was 30 June 2016.

Though a large number of patients were recruited in the ERASMUS study, safety information was not routinely recorded. Safety analyses presented form this study were produced by re-evaluation of the patient data. The safety information from this study is therefore limited and correlation of adverse events including SAEs, and deaths is limited and difficult to interpret.

More comprehensive safety information was collected in the randomised, comparative NETTER-1 study. Comparative safety data is available from the 2 arms of the study. Data also was collected through compassionate use programs.

The most common adverse reactions in patients receiving Lutathera treatment were nausea and vomiting which occurred at the beginning of the infusion in 58.9% and 45.5% of patients, respectively. The causality of nausea / vomiting is confounded by the emetic effect of the concomitant amino acids infusion administered for renal protection. Due to the bone marrow toxicity of Lutathera, the most expected adverse reactions were related to haematological toxicity: thrombocytopenia (25%), lymphopenia (22.3%), anaemia (13.4%), pancytopenia (10.2%). Other very common adverse reactions reported include fatigue (27.7%) and decreased appetite (13.4%). SAEs were reported in almost equal proportions in both arms of the study. A higher proportion of patients in the Sandostatin LAR arm had SAE's attributed to underlying disease, compared to the Lutathera arm. A higher proportion of patients in the Lutathera arm had SAE's considered related to the study treatment compared to the Sandostatin LAR arm. The incidence of non-serious adverse events has not been presented for the ERASMUS study. The common adverse events nausea and vomiting noted in the NETTER-1 studies have been attributed to the amino acid infusion. Patients presenting with certain clinical conditions are more prone to develop adverse reactions, a list of risk factors is included in the SmPC section 4.4. Therefore, it is recommended to monitor those patients more frequently during the treatment. In some circumstances, it might be necessary to temporarily discontinue treatment with Lutathera, adapt the dose after the first administration or even discontinue the treatment (see SmPC Table 3 - Table 5 and Figure 1).

To avoid treatment-related nausea and vomiting, an intravenous bolus of an antiemetic medicinal product should be injected 30 minutes before the start of amino acid solution infusion (see section 4.2).

Adverse events of special interest included hematotoxicity, secondary haematological malignancies, nephrotoxicity and cardiovascular events.

Bone marrow toxicity (myelo /hematotoxicity) manifested with reversible / transient reductions in blood counts affecting all lineages (cytopenias in all combinations, i.e., pancytopenia, bicytopenias, isolated monocytopenias – anaemia, neutropenia, lymphocytopenia, and thrombocytopenia). In spite of an observed significant selective B cell depletion, no increase in the rate of infectious complications occured after PRRT. Myelosuppression/cytopenias (immediate hematoxcicity) have been included in the RMP as important identified risks. Because of the potential for undesirable effects, blood counts must be monitored at baseline and during treatment, and until resolution of any eventual toxicity (see section 4.2).

Cases of irreversible haematological pathologies, i.e., premalignant and malignant blood neoplasms (i.e., myelodysplastic syndrome and acute myeloid leukaemia, respectively) have been reported following lutetium (177Lu) PRRT. Late-onset myelodisplastic syndrome (MDS) and acute leukaemia (AL) have been observed after treatment with Lutathera (see section 4.8), occurring approximately 28 months (9 – 41) for MDS and 55 months (32 - 125) for AL after the end of treatment. (SmPC section 4.4 and SmPC 4.8). The median latency from exposure was 4.4 years. For comparison, 15-year cumulative risk of AML after chemotherapy is reported in literature as high as 10 percent, specifically e.g. in Hodgkin lymphoma patients treated with MOPP (mechlorethamine, vincristine, procarbazine and prednisone). Moreover, data in the target population suggest that the development of bone marrow neoplasms is most likely a consequence of previous treatments, such as chemotherapy. From the data available from the clinical trials and literature it is agreed that patients who have had prior treatment with alkylating chemotherapeutics should have a thorough risk/benefit assessment before receiving PRRT. Myelodysplastic syndrome (MDS) / acute leukemia (AL) (late hematotoxicity) has been included in the RMP as an important identified risk. Therefore, the CHMP has imposed a PASS study to investigate the risk of secondary malignancies.

Lutetium ($^{177}$Lu) oxodotreotide is excreted by the kidney, mostly during the initial phase of the blood decay as demonstrated by the urinary recovery of about 60% of the administered dose within the first 16/23 hours, and renal excretion within 24/48 hours of dosing accounts for about 70% of systemic clearance. Adequate renal function is considered essential for patients to be eligible for treatment with the proposed dosing regimen of Lutathera (4 treatments of 7.4 GBq each), in order to maximize elimination and prevent unnecessary radiation exposure to the whole body. Kidney function, as measured by creatinine clearance (serum creatinine must be <150 µmol/L or 1.7 mg/dL, or a measured creatinine clearance must be ≥50 mL/min), was one of the criteria applied in the NETTER Phase III study for patient recruitment and the same restriction for 177Lu-Oxodotreotide use is recommended in the proposed product information. The minimum threshold of measured creatinine clearance ≥50 mL/min was defined according to Erasmus MC Phase I/II study clinical experience and the ENETS guidelines for PRRT (Kwekkeboom 2009). Somatostatin analogue peptides used in PRRT are known to be partially retained in the kidney and the kidney is a "critical organ" for radiotoxicity. The studies with Lutathera used amino acid solution co-infusion during 177Lu-Oxodotreotide treatment to significantly reduce (by about half) the radiation absorbed dose to the kidneys, limiting possible kidney toxicities. Without adequate renal function the co-infusion of amino acid solution during 177Lu-Oxodotreotide administration could not be effective, therefore adequate renal function is considered essential for a patient to be treated with the proposed dosing regimen of 177Lu-Oxodotreotide (4 treatments of 7.4 GBq each). The long-term trend of progressive glomerular filtration function deterioration demonstrated in the clinical studies confirms that Lutathera-related nephropathy is a chronic kidney disease that develops progressively over months or years after exposure. Renal impairment has been included in the RMP as missing information. An individual benefit-risk assessment is recommended prior to treatment with Lutathera in patients with mild and moderate renal impairment, for additional details see SmPC section 4.2 and section 4.4 for measures to be taken for renal protection. The use of Lutathera is contraindicated in patients with severe kidney failure (see SmPC section 4.3).

For patients with urinary incontinence, during the first 2 days following administration of this medicinal product, special precautions should be taken with patients with urinary incontinence to avoid spread of radioactive contamination. This includes the handling of any materials possibly contaminated with urine.

The applicant did not submit studies on hepatic impaired patients (SmPC section 4.2). Therefore exposure in patients with severe hepatic impairment has been included in the RMP as missing information and as a warning for the need for liver monitoring in the SmPC section 4.4.

In the NETTER-1 study, 22 patients in the Lutathera arm (19.7%) had an increased GGT (Grade 3 or 4) diagnosed post randomization. In each of the following categories, between 4 and 7 patients (3.6% to 6.3%) showed post randomization Grade 3 or 4 hyperglycemia, hyperuricemia, hypokalemia, alkaline phosphatase increased, ASAT increased and ALAT increased. There is high uptake of lutathera in the liver (see SmPC section 11) and therefore, there is a risk for liver toxicity. Dose modification for liver toxicity has been included in section 4.2 of the SmPC and hepatotoxicity has been included as an important potential risk in the RMP.

Subtype 2 somatostatin receptors (sst2) are expressed not only in malignant cells but also in various non-neoplastic human tissues such as vessels, nerve plexus, pancreatic islets, prostatic stroma, adrenal medulla, spleen and germinal centres of the lymphoid tissues (Reubi 2001: Eur J Nucl Med, 28:836–846). As demonstrated by the observed adverse events/adverse reactions regarding bone marrow depression, radiation-induced destruction of surrounding and/or distant receptor-positive normal tissues could occur following administration of Lutathera.

Ionizing radiations of lutetium ($^{177}$Lu) oxodotreotide may potentially have temporary toxic effects on female and male gonads and hypogonadism, sexual dysfunction is therefore listed as an important identified risk in the RMP. The SmPC includes a recommendation for genetic consultation if the patient wishes to have children after treatment and that cryopreservation of sperm or eggs can be discussed as an option to patients before the treatment. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect. Radiotoxicity, including occupational exposure and inadvertent exposure, has been included in the RMP as important potential risks.

In the NETTER-1 study, concomitant medications were recorded in 223 patients (100%) of the FAS. The most frequent concomitant medications by ATC for patients in the FAS were "antiemetics and antinauseants", followed by "analgesics". No concomitant medications were recorded in the Erasmus MC study.

The absence of inhibition or significant induction of the human CYP450 enzymes and the absence of specific interaction with P-glycoprotein (efflux transporter) in preclinical studies suggest that 177Lu-Oxodotreotide has a low probability of causing other significant drug-drug interactions. Moreover, from the very low mass dose (200 µg) of Lutathera resultant plasma concentrations are expected not to have any pharmacological effect.

Somatostatin and its analogs competitively bind to somatostatin receptors. Therefore, this justifies stopping treatment with long-acting analogs of somatostatin, as far as possible, at least 4 weeks prior to 177Lu-Oxodotreotide administration. If necessary, patients may be treated with short-acting analogs of somatostatin during the 4 weeks preceding 177Lu-Oxodotreotideadministration, and until 24 hours before the administration of 177Lu-Oxodotreotide, as done in the clinical studies. Drug interaction with somatostatin/ Somatostatin analogues has been included in the RMP as an important identified risk.
The absence of drug interactions with respect to pharmacokinetics is acknowledged and thus, in general concomitant medication seemed not to be crucial, this is true particularly with antiemetics in order to reduce gastrointestinal adverse events like nausea and others. Furthermore, this issue is also adequately reflected in the product information.

There is evidence from in vitro and in vivo studies that concomitant use of glucocorticosteroids could induce SSTR2 down-regulation and there was a trend towards more PFS events in patients concomitantly treated with glucocorticosteroids. Therefore, as a matter of cautiousness, in line with the study protocol for the NETTER-1 study, glucocorticosteroids should be avoided as preventive anti-emetic treatment because of potential receptor down-regulation (SmPC section 4.5).

No adequate and well-controlled studies have been performed in pregnant or lactating women. Radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. The use of 177Lu-Oxodotreotide is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded, due to the risk associated with the ionizing radiation. It is unknown whether lutetium ($^{177}$Lu) oxodotreotide is excreted in breast milk. A risk to the suckling child associated with ionising radiation cannot be excluded. Breast-feeding should be avoided during treatment with this medicinal product. If treatment with Lutathera during breast-feeding is necessary, the child must be weaned. Radiation exposure during breastfeeding has been included as missing information in the RMP. During treatment with Lutathera and for a minimum of the following 6 months after the end of the treatment, appropriate measures must be taken to avoid pregnancy; this applies to patients of both genders.

It is unknown whether 177Lu-Oxodotreotide is excreted in breast milk. A risk to the suckling child associated with ionising radiation cannot be excluded. The medicinal product is contraindicated during

breast-feeding. If treatment with this medicinal product during breast-feeding is necessary, the child must be weaned (SmPC section 4.6).

Neither overdose nor drug abuse are expected to be a concern with 177Lu-Oxodotreotide, because it is administered by a trained clinician with appropriate prior training and provided as a single-dose, ready-to-use product containing a predefined amount of radioactivity. The product information nevertheless provides recommendations to the healthcare professional, in case of administration of a radiation overdose (SmPC section 4.9), to reduce the absorbed dose where possible by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding during the first 48 hours after infusion. Furthermore, hematologic and blood chemistry monitoring are recommended to be carried out the following 10 weeks. Lutathera belongs to a pharmacologic class of drugs for which withdrawal is not expected to be a concern (see radioprotection rules SmPC section 4.4). In addition, further precaution must be taken in case of extravasation of Lutathera to the surrounding tissues ( SmPC section 4.4). For each patient, the radiation exposure must be justifiable by the likely benefit.

Lutathera is contraindicated  if patients have hypersensitivity to the active substance, to any of the excipients listed in section 6.1 of the SmPC.

Clinical experience has not identified differences in responses between the elderly and younger patients. However, since increased risk of presenting haematotoxicity has been described in elderly patients (≥ 70 years old), a close follow up allowing for prompt dose adaptation (DMT) in this population is advisable.

Hormonal crises related to bioactive substances release (probably due to lysis of the neuroendocrine tumour cells) have rarely been observed and resolved after appropriate medical treatment. Hormonal crises due to excessive release of hormones or bioactive substances may occur following treatment with lutetium (177Lu) oxodotreotide, therefore 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, recommended treatments are: intravenous high dose somatostatin analogues, intravenous fluids, corticosteroids, and correction of electrolyte disturbances in patients with diarrhoea and/or vomiting. Tumour cell lysis-related hormone release-induced crises (HRIC) has been included in the RMP as an identified potential risk.

Although Lutathera is not expected to have an influence on the ability to drive and use machines, the general condition of the patient and the possible adverse reactions to treatment must be taken into account before driving or using machines. This is appropriately reflected in the SmPC section 4.7.

This medicinal product contains up to 3.5 mmol (81.1 mg) sodium per dose. This should be taken into consideration in patient on controlled sodium diet.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

# Conclusions on the clinical safety

Overall, the safety data provided is limited owing to the lack of routine safety recording in the ERASMUS study and the limited long term follow-up data from the NETTER-1 study. Therefore continued monitoring and collection of safety data is considered important to address the missing safety concern secondary malignancy and to further characterise the important identified and potential risks associated with the use of 177Lu-Oxodotreotide. To this purpose, a post-authorisation safety

study is required to assess the long-term safety of Lutathera in routine clinical practice settings, as reflected in the RMP.

The CHMP considers the following measures necessary to address issues related to safety:

- An international post-authorization safety registry to assess the long-term safety of Lutathera for unresectable or metastatic, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs).

## *2.7. Risk Management Plan*

### *Safety concerns*

**Table 69: Summary of the Safety Concerns**

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | Renal dysfunction<br>Myelosuppression / cytopenias (immediate hematotoxicity)<br>Myelodysplastic syndrome (MDS) / acute leukemia (AL) (late hematotoxicity)<br>Hypogonadism, sexual dysfunction<br>Drug interaction with somatostatin/ Somatostatin analogues |
| Important potential risks | Tumor cell lysis-related hormone release-induced crises<br>Hepatotoxicity<br>Radiotoxicity, including occupational exposure and inadvertent exposure |
| Missing information | Radiation exposure during breast feeding<br>Exposure in patients with renal impairment<br>Exposure in patients with severe hepatic impairment<br>Secondary malignancies (solid tumors)<br>Long term safety data |

### *Pharmacovigilance plan*

**Table 70: Pharmacovigilance plan**

| Study/activity Type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| An international post-authorization safety registry to assess the long-term safety of Lutathera for | To evaluate and quantify the incidence of secondary malignancies (solid tumours and haematological | Secondary malignancies (solid tumours)<br>Long term safety | Planned | Protocol 30/03/2018<br>Final report |

| Study/activity Type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| unresectable or metastatic, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs).<br><br>Category 3 | malignancies) over a long-term follow-up in patients with unresectable or metastatic, well-differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) treated with Lutathera.<br><br>To quantify the incidence of other important identified and potential risks specified in the Lutathera Risk Management Plan (RMP)<br><br>To detect new potential risks, including in those patients under-represented in the clinical trial | | | 31/12/2025 |
| Netter-1 study:<br><br>According to the NETTER-1 Protocol, follow-up data are collected up to 5 years from the date of randomization of the last patient.<br><br>End-of-Study (EOS) is defined as a timepoint when 158 death events are recorded or within 5 years from the date of last randomization, whichever occurs first. | To evaluate the safety of Lutathera: collection of the toxicities suspected in relation with the study drug (including haematology, biochemistry, urine analyses), anti-tumour treatment administered after progression /discontinuation, disease status based on local CT/MRI assessment, and OS data; monitoring of the long-term toxicity to critical organs suspected to be related to Lutathera. | Secondary malignancies (solid tumours)<br><br>Long term safety | Started | 31/12/2021 |

| Study/activity Type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| Category 3 | | | | |

## *Risk minimisation measures*

**Table 71: Risk minimisation measures**

| **Safety concern** | **Routine risk minimisation measures** | **Additional risk minimisation measures** |
|---|---|---|
| Renal dysfunction | **SmPC wording in sections 4.2, 4.4 and 4.8** | none |
| Myelosuppression / cytopenias (immediate hematotoxicity) Myelodysplastic syndrome (MDS) / acute leukemia (AL) (late hematotoxicity) | **SmPC wording in sections 4.2, 4.4 and 4.8** | none |
| Hypogonadism, sexual dysfunction | **SmPC wording in section 4.6** | none |
| Drug interaction with somatostatin/somatostatin/analogs | **SmPC wording in sections 4.4 and 4.5** | none |
| Tumor cell lysis-related hormone release-induced crises | **SmPC wording in section 4.4 and 4.8** | none |
| Hepatotoxicity | **SmPC wording in sections 4.2 and 4.4** | none |
| Radiotoxicity, including occupational exposure and inadvertent exposure | **SmPC wording in sections 6.6 and 12** | Patient guide |
| Radiation exposure during breastfeeding | **SmPC wording in section 4.6** | none |
| Exposure in patients with renal impairment | **SmPC wording in sections 4.2 and 4.4** | none |
| Patients exposure with severe hepatic impairment | **SmPC wording in section 4.2 and 4.4** | none |

## 2.8. Pharmacovigilance

### 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.

### Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The new EURD list entry will use the EBD to determine the forthcoming Data Lock Points.

## 2.9. New Active Substance

The applicant declared that the radiopharmaceutical substance 'lutetium ($^{177}$Lu) oxodotreotide' has not been previously authorised in a medicinal product in the European Union and the coupling mechanism to link the ligand (Oxodotreotide) and the radionuclide ($^{177}$Lu) has not been authorised previously in the European Union.

The CHMP, based on the available data, considers that this radiopharmaceutical substance, which is complex resulting from the sequestration of radioisotope lutetium-177 ($^{177}$Lu) with Oxodotreotide, is a new active substance as it is a not constituent of a medicinal product previously authorised within the European Union.

## 2.10. Product information

### 2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

### 2.10.2. Labelling exemptions

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

The applicant requested the omission of the manufacturer's details from the Package Leaflet due to the complexity of handling the numerous manufacturing sites. The manufacturer's details will, however, be included in the lead container.

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.

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

An English only vial label with minimum particulars, i.e. name of the medicinal product, method of administration, batch number, expiry date, and contents is acceptable because 1) Lutathera is delivered only to healthcare professionals and not directly to the patient, 2) the minimum info on the immediate packaging label is considered understandable in English language and reported in national language on the outer packaging and 3) The 30 mL vial is enclosed in a lead shielded container that will constitute the outer packaging (labelled with full particulars) and will be used during transport and storage and the opening of the shielding to access the immediate packaging is not recommended due to the radioactive properties of the medicinal product.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

### 2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, LUTATHERA (lutetium ($^{177}$Lu) oxodotreotide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Lutathera is proposed to be used for the unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults.

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) constitute a heterogeneous group of neoplasms arising from the diffuse neuroendocrine system. Well-differentiated carcinoid tumours over-express somatostatin subtype 2 receptors (sstr2) which is a common feature of all GEP-NETs.

### 3.1.2. Available therapies and unmet medical need

Typically, the clinical management involves a multi-modal approach including surgery and other means of cytoreductive treatment and medical treatment with chemotherapy, interferons and somatostatin analogues.

Only a minority of the patients with GEP-NETs can be cured by surgery[19, 20]. At the time of GEP-NET diagnoses, the majority of patients have hepatic metastases[21]. The clinical symptoms associated with

[19] Öberg K (2004a). Management of neuroendocrine tumours. Ann Oncol 15 Suppl 4:iv293--iv298
[20] Modlin IM, Moss SF, Oberg K, Padbury R, Hicks RJ, Gustafsson BI, Wright NA, Kidd M (2010). Gastrointestinal neuroendocrine (carcinoid) tumours: current diagnosis and management. Med J Aust 193(1):46-52

metastases may differ, as these are often related to the extent of metastatic tumour-mass. NE tumour hepatic metastases may lead to rapid liver dysfunction but are more often associated with a long, but deteriorating disease course, in many cases with debilitating clinical symptoms, either due to hormonal overproduction or to local compression of abdominal organs.

Without treatment, as many as 80% of patients with metastatic disease die within 5 years of diagnosis[22]. Even with currently available treatments, patients with multiple risk factors (age, number of liver metastases, tumour progression, or primary not removed), have extremely poor prognoses. For example, a patient with metastatic disease with 3 of the noted risk factors has a median life expectancy of approximately 2 years, versus 8 years for patients with only 1 risk factor. Another study which examined additional risk factors, including the primary tumour site location, found that only 35% of patients with advanced NETs survive longer than five years[23], which is only slighter better than the SEER statistic for stage IV prostate cancer (28%).

The clinical management of unresectable GEP-NETs involves a multi-modal approach including surgery and other means of cytoreductive treatment, embolization, chemo-embolization, radiotherapy and medical treatment with chemotherapy, interferons or somatostatin analogues[24] .

The therapeutic effects in metastatic disease may be limited because metastases are usually multiple, unresectable, and relatively unresponsive to radiotherapy and chemotherapy. Therefore therapeutic options predominantly aim at palliative care to improve the patient's quality of life, rather than attempting cure[25, 26].

### 3.1.3. Main clinical studies

The efficacy of Lutathera in the proposed indication is based on the results of the single arm ERASMUS study and the open labelled randomised phase III NETTER-1 study. Randomised data from the NETTER-1 study is available only for midgut subset of neuroendocrine tumours. Data for the other subsets of the proposed indication, i.e., foregut and hindgut, as well as the pancreatic sub-group of patients have to derived and interpreted from the results of the single arm ERASMUS study.

The ERASMUS study started enrolment as a compassionate use study at the Erasmus Medical Centre but subsequently enrolled 1214 patients. Enrolment in the Phase III study started in July 2012 and the first patient was randomised in September 2012. The NETTER-1 study is still ongoing and will be ended as per protocol when 158 deaths will be recorded or when 5 years from the date of randomisation of the last randomised patient have elapsed, whichever occurs first. The expected last patient last visit (treatment phase) is Q3 2017.

## *3.2. Favourable effects*

The pivotal NETTER-1 study met its primary efficacy endpoint demonstrating a statistically significant improvement in progression free survival in patients with midgut GEP-NETs. At the date of the updated

[21] Chamberlain RS, Canes D, Brown KT, Saltz L, Jarnagin W, Fong Y, Blumgart LH (2000). Hepatic neuroendocrine metastases: does intervention alter outcomes? J Am Coll Surg 190(4):432-445
[22] Taal BG, Visser O (2004). Epidemiology of neuroendocrine tumours. Neuroendocrinology 80 Suppl 1:3-7
[23] Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB (2008). One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 26(18):3063-3072
[24] Öberg K, Knigge U, Kwekkeboom D, Perren A, Group ESMOGW (2012). Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 23 Suppl 7:vii124--vii130
[25] Que FG, Nagorney DM, Batts KP, Linz LJ, Kvols LK (1995). Hepatic resection for metastatic neuroendocrine carcinomas. Am J Surg 169(1):36--42; discussion 42-3
[26] Ahlman H, Westberg G, W, Nilsson O, Tyl, Scherst, Tisell LE (1996). Treatment of liver metastases of carcinoid tumors. World J Surg 20(2):196-202

PFS and OS analyses, the median PFS for the control arm was 8.5 months while the median PFS for the Lutathera arm was 28.4 months. The improvement in median PFS in the Lutathera arm was statistically significant ($p<0.0001$) with a hazard ratio of 0.23 (95% Confidence Interval (CI): 0.15-0.361).

The PFS data is supported by an increased ORR seen in the Lutathera arm compared to the Sandostatin LAR arm (14.7% vs. 4%, respectively). The median overall survival was not reached in the Lutathera arm, compared to a median overall survival of 27.4 month in the Octreotide LAR arm.

ORR, in the FAS Dutch GEP-NET population of the ERASMUS study, ranged from 33.3% to 60.9% with pancreatic and foregut endocrine tumours showing the largest effects (60.9% and 58.3% respectively). DoR ranged from 15.3 to 22.3 months for GEP-NETs.

The median PFS ranged from 28.5 to 43.9 months. The highest median PFS was in the foregut group (43.9 months), followed by the pancreatic group (30.3 months) and hindgut group (29.4 months).

The median OS ranged from 54.9 to 66.4 months. The highest median OS was in the pancreatic group (66.4 months), followed by the mid-gut group (54.9 months) and the median OS was not reached for the foregut and hindgut groups.

## *3.3. Uncertainties and limitations about favourable effects*

The median overall survival has not been reached for the Lutathera arm in the NETTER-1 study, but remains favourable in comparison to a median OS of 27.4 months in the Octreotide LAR arm. No detrimental effect on OS has been observed in the Lutathera arm compared to Octreotide LAR arm. There is no efficacy data in patients with known brain metastases therefore individual benefit-risk must be assessed in these patients (SmPC section 4.4). This will be monitored through routine pharmacovigilance.

## *3.4. Unfavourable effects*

The overall safety profile of lutetium ($^{177}$Lu) oxodotreotide is based on pooled data from patients from clinical trials (NETTER-1 phase III and Erasmus phase I/II Dutch patients) and from post-marketing surveillance (compassionate use programs).

Several gastrointestinal disorders have been attributable in many cases to the underlying metastatic neuroendocrine tumour (NET).

The commonest adverse events, noted in the NETTER-1 study, were nausea and vomiting.

Lutathera is extensively eliminated by the kidney, mostly during the initial phase of the blood decay as demonstrated by the urinary recovery of about 60% of the administered dose within the first 16/23 hours, and renal excretion within 24/48 hours of dosing accounts for about 70% of systemic clearance. Adequate renal function is considered essential for patients to be eligible for treatment with the proposed dosing regimen of Lutathera. Somatostatin analogue peptides used in PRRT are known to be partially retained in the kidney and the kidney is a "critical organ" for radiotoxicity. The studies with Lutathera used amino acid solution co-infusion during 177Lu-Oxodotreotide treatment to significantly reduce (by about half) the radiation absorbed dose to the kidneys, limiting possible kidney toxicities (SmPC section 4.2). Without adequate renal function the co-infusion of amino acid solution during 177Lu-Oxodotreotide administration could not be effective, therefore adequate renal function is considered essential for a patient to be treated with the proposed dosing regimen of 177Lu-Oxodotreotide (4 treatments of 7.4 GBq each). Therefore, Lutathera is contraindicated in patients with

kidney failure with creatinine clearance < 30 mL/min. The common adverse events of nausea and vomiting noted in the NETTER-1 studies have been attributed to the amino acid infusion.

In addition 14 cases of myelodysplastic syndrome have been identified in the Dutch patient population of ERASMUS study, and in 2 Lutathera treated patients in the NETTER-1 study after the data cut-off point. This is of concern of the risk of developing myelodysplastic syndrome and acute leukemia, given the limitation of the safety analyses data provided (SmPC section 4.4). Therefore, a PASS study has been requested to collect post-authorisation safety data to investigate secondary malignancies.

Due to the bone marrow toxicity of lutetium ($^{177}$Lu) oxodotreotide, the most expected adverse reactions were related to haematological toxicity: thrombocytopenia (25%), lymphopenia (22.3%), anaemia (13.4%), pancytopenia (10.2%).

Other very common adverse reactions reported include fatigue (27.7%) and decreased appetite (13.4%).
Lutathera is radiolabelled with lutetium 177, a radiopharmaceutical with a short half-life of 6.647 days which decays by β emission and also emits low energy γ radiation. For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect. Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases it is necessary to ensure that the risks of the radiation exposure are less than from the disease itself.

Therefore, as with any radiopharmaceutical, there is risk for radiotoxicity, including occupational exposure and inadvertent exposure to patients which has been included in the RMP as an important potential risk and recommendations are given in the SmPC on radioprotection (SmPC section 4.4). An educational material for patients to address the risk(s) of radiotoxicity, including occupational exposure and inadvertent exposure has also been included as an additional risk minimisation measure in the RMP and in the Annex II.

## *3.5. Uncertainties and limitations about unfavourable effects*

The incidence of non-serious adverse events has not been presented for the ERASMUS study. The method of collection of safety data in the ERASMUS study limits the full assessment of safety from that study. The data provided from the results of the NETTER-1 study provides comparative safety data with octreotide LAR treatment. All patients in the Lutathera arm received all the intended doses of Lutathera, with only a few patients in both arms remaining to complete treatment with octreotide. Therefore, long term safety data of Lutathera is missing (RMP) and will be collected by routine monitoring of the safety through the pharmacovigilance plan with the follow-up data from the NETTER-1 study where data will be collected up to 5 years from the date of randomization of the last patient. Long term safety will be evaluated by the collection of the toxicities suspected in relation with the study drug (including haematology, biochemistry, urine analyses) and monitoring of the long-term toxicity to critical organs suspected to be related to Lutathera (RMP).

## *3.6. Effects Table*

**Table 72: Effects Table for Lutathera in GEP-NETs (data cut-off: 30/06/2016)**

| Effect | Short Description | Unit | Treatment | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|

| Effect | Short Description | Unit | Treatment | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| Improved Progression Free Survival | 28.4 vs 8.5 (Hazard Ratio: 0.230 95% CI: 0.15; 0.361<br><br>P-value: <0.0001) | months | Lutathera | Sandostatin LAR 60 mg | | |
| Improved ORR | 14.7 vs 4.0<br><br>(p-value= 0.0141) | | | | | |
| | | | | | | |
| **Unfavourable Effects** | | | | | | |
| Haematological toxicity | thrombocytopenia, lymphopenia and anaemia | | | | | |
| Nausea and Vomiting | | | | | Attributed to amino acid infusion given concomitantly | |
| Longer term haematological toxicity | Myelodysplastic syndrome and leukaemia | | | | Large proportions of patients on NETTER-1 study still receiving treatment. | |

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

There is a large amount of clinical experience with the use of peptide receptor radionuclide therapy. The pivotal phase II study NETTER-1 has shown a statistically significant and clinically relevant benefit with improved response rates and improvements in progression free survival. The most common adverse reactions in patients receiving lutetium ($^{177}$Lu) oxodotreotide were nausea and vomiting which occurred at the beginning of the infusion in 58.9% and 45.5% of patients, respectively. The causality of nausea / vomiting is confounded by the emetic effect of the concomitant amino acids infusion administered for renal protection. There are concerns regarding long term haematological effects including myelodysplastic syndrome and leukaemia, however, these risks will be addressed by a post-authorisation safety study.

### 3.7.2. Balance of benefits and risks

The clinical benefits demonstrated in terms of PFS and ORR are considered clinically relevant and outweigh the safety risks that appear manageable with the recommendations in the SmPC and the additional risk minimisation measures proposed.

### 3.7.3. Additional considerations on the benefit-risk balance

The efficacy of Lutathera has been demonstrated in the NETTER-1 study, which recruited patients with inoperable, progressive, OctreoScan positive (confirmed presence of somatostatin receptors on all target lesions (RECIST Criteria, Version 1.1) documented by CT/MRI scans), well-differentiated neuroendocrine tumours of the small bowel (midgut carcinoid tumours). Therefore, the inclusion criteria for the study included only tumours that were considered to have a histological classification of G1 or G2. According to the WHO classification, G1 and G2 histological subtypes of GEP-NETs are classified as well-differentiated and moderately-differentiated tumours, respectively. These tumours are known to express high levels of SSRs whereas G3 subtypes have lower expression of SSRs. In addition, literature references indicate that G3 tumours appear not to respond to peptide receptor radionuclide therapy (PRRT) although they may show receptor-mediated tracer uptake and the ESMO GEP-NET guideline algorithm states the use of PRRT in G1 and G2 tumours only. Therefore, as G3 tumours are expected to respond poorly to somatostatin analogues, the CHMP was of the opinion that it was not considered appropriate to extend the indication to this patient subpopulation as the extrapolation would not be feasible based on the differential biological expression of somatostatin receptors (SSRs) as well as the poorer prognosis in patients with G3 tumours which are poorly differentiated tumours. However, based on the mechanism of action, the CHMP considered that there was no need to restrict the indication to midgut tumours as Lutathera would be expected to have efficacy in GEP-NET tumours irrespective of their location as long as the tumours expressed SSRs. Therefore, the CHMP restricted the indication to patients with well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP NETs).

## *3.8. Conclusions*

The overall the benefit risk balance of Lutathera is positive.

# 4. Recommendations

## *Outcome*

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

Lutathera is indicated for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP NETs) in adults.
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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

**Risk Management Plan (RMP)**

The 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.

**Additional risk minimisation measures**

Prior to launch of Lutathera in each Member State the marketing authorisation holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing patients' awareness on the risk of radiotoxicity by occupational exposure and inadvertent exposure to peptide receptor radionuclide therapy, and at providing information concerning the necessary precautions to take to limit unnecessary exposure to themselves and the people around them.

The MAH shall ensure that in each Member State where Lutathera is marketed, all patients/carers who are expected to be administered Lutathera have access to/are provided with a patient educational material containing:

- The package leaflet

- Patient guide

**The patient guide** shall contain the following key elements:

  - Brief introduction to the treatment and the administration procedure
  - Information on the precautions the patient should take before, during and after the administration procedure, at the hospital and at home, to limit unnecessary exposure to radiations of themselves and their entourage.
  - Information that PPRT can cause serious side effects during or after treatment and that any side effect should be reported to the physician.

## *New Active Substance Status*

Based on the CHMP review of the available data, the CHMP considers that 'lutetium ($^{177}$Lu) oxodotreotide' is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.