LUTATHERA for the Treatment of Somatostatin Receptor-Positive GEP-NETs

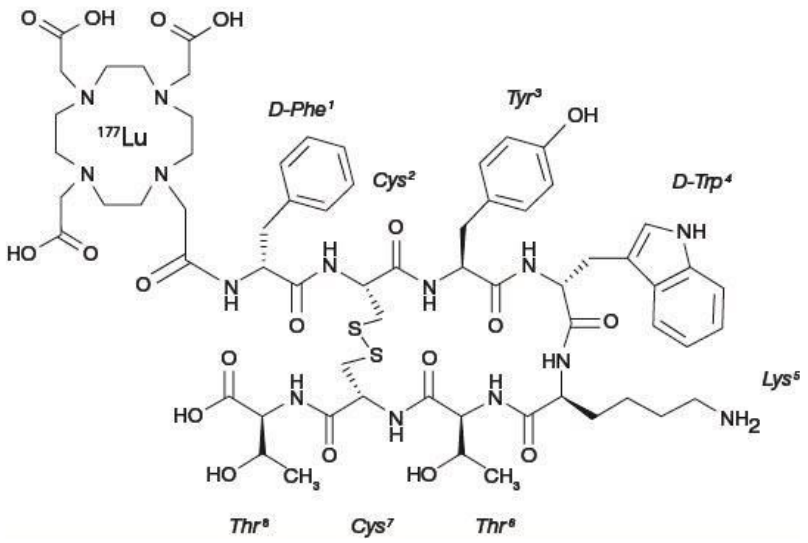
1. INDICATIONS AND USAGE

LUTATHERA is a therapeutic radiopharmaceutical indicated for the treatment of somatostatin receptor-positive **gastroenteropancreatic neuroendocrine tumors** (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

2. DRUG DESCRIPTION

LUTATHERA (lutetium Lu-177 dotatate) is a radiolabeled somatostatin analog. The drug substance lutetium Lu-177 dotatate is a cyclic peptide linked with the covalently bound chelator 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid to a radionuclide.

Lutetium Lu-177 dotatate has a molecular weight of 1609.6 Daltons and the structural formula is as follows:



LUTATHERA (lutetium Lu-177 dotatate) 370 MBq/mL (10 mCi/mL) is a sterile, clear, colorless to slightly yellow solution for intravenous use. Each single-dose vial contains acetic acid (0.48 mg/mL), sodium acetate (0.66 mg/mL), gentisic acid (0.63 mg/mL), sodium hydroxide (0.65 mg/mL), ascorbic acid (2.8 mg/mL), diethylenetriaminepentaacetic acid (0.05 mg/mL), sodium chloride (6.85 mg/mL), and Water for Injection (ad 1 mL). The pH range of the solution is 4.5-6.0.

Physical Characteristics

Lutetium (Lu-177) decays to stable hafnium (Hf-177) with a half-life of 6.647 days, by emitting beta radiation with a maximum energy of 0.498 MeV and photonic radiation (γ) of 0.208 MeV (11%) and 0.113 MeV (6.4%). The main radiations and physical decay chart are detailed in Table below.

Lu 177 Main Radiations

Radiation	Energy (keV)	Iβ%	Iγ%
β^-	176.5	12.2	
β^-	248.1	0.05	
β^-	384.9	9.1	
β^-	497.8	78.6	
γ	71.6		0.15
γ	112.9		6.40
γ	136.7		0.05
γ	208.4		11.0
γ	249.7		0.21
γ	321.3		0.22

Physical Decay Chart: Lutetium Lu 177 Half-life = 6.647 days

Hours	Fraction Remaining	Hours	Fraction Remaining
0	1.000	48 (2 days)	0.812
1	0.996	72 (3 days)	0.731
2	0.991	168 (7 days)	0.482
5	0.979	336 (14 days)	0.232
10	0.958	720 (30 days)	0.044
24 (1 day)	0.901	1080 (45 days)	0.009

3. Dose Administration

LUTATHERA should be administered intravenously. One must use waterproof gloves and effective radiation shielding when handling LUTATHERA. In addition, one MUST verify pregnancy status of females of reproductive potential prior to initiating LUTATHERA due to significant risk to the fetus.

3. Recommended Dosage

The recommended LUTATHERA dose is 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses.

4. Premedication and Concomitant Medications

a. **Before initiating LUTATHERA**: Discontinue long-acting somatostatin analogs (e.g., long-acting octreotide) for at least 4 weeks prior to initiating LUTATHERA. Administer short-acting octreotide as needed; discontinue at least 24 hours prior to initiating LUTATHERA

b. **During LUTATHERA treatment**: Administer long-acting octreotide 30 mg intramuscularly between 4 to 24 hours after each LUTATHERA dose. Do not administer long-acting octreotide within 4 weeks of each subsequent LUTATHERA dose. Short-acting octreotide may be given for symptomatic management during LUTATHERA treatment, but must be withheld for at least 24 hours before each LUTATHERA dose.

c. Following LUTATHERA treatment: Continue long-acting octreotide 30 mg intramuscularly every 4 weeks after completing LUTATHERA until disease progression or for up to 18 months following treatment initiation.

d. Administer anti-emetics 30 minutes before the recommended amino acid solution.

5. Amino Acid Solution

Initiate an intravenous amino acid solution containing L-lysine and L-arginine (Table below) 30 minutes before administering LUTATHERA. Use a three-way valve to administer amino acids using the same venous access as LUTATHERA or administer amino acids through a separate venous access in the patient's other arm. Continue the infusion during, and for at least 3 hours after LUTATHERA infusion.

Do not decrease the dose of the amino acid solution if the dose of LUTATHERA is reduced.

Amino Acid Solution

Item	Specification
Lysine HCl content	Between 18 g and 24 g
Arginine HCl content	Between 18 g and 24 g
Volume	1.5 L to 2.2 L
Osmolarity	< 1050 mOsmol

6. Dose Modifications for Adverse Reactions **(This section is for reference only and no test questions come from it)**

Most common adverse reactions are listed in chart below.

- Thrombocytopenia
- Recurrent Grade 2, 3 or 4 Anemia and Neutropenia
- Recurrent Grade 3 or 4 Renal Toxicity
- Recurrent hepatotoxicity
- Other Non-Hematologic Toxicity

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7. Preparation and Administration

1. Use aseptic technique and radiation shielding when administering the LUTATHERA solution. Use tongs when handling vial to minimize radiation exposure.
2. Do not inject LUTATHERA directly into any other intravenous solution.
3. Confirm amount of radioactivity of LUTATHERA in the radiopharmaceutical vial with an appropriate dose calibrator prior to and after LUTATHERA administration.
4. Inspect the product visually for particulate matter and discoloration prior to administration under a shielded screen. Discard vial if particulates or discoloration are present.

Administration Instructions

1. Insert a 2.5 cm, 20 gauge needle (short needle) into the LUTATHERA vial and connect via a catheter to 500 mL 0.9% sterile sodium chloride solution (used to transport LUTATHERA during the infusion). Ensure that the short needle does not touch the LUTATHERA solution in the vial and do not connect this short needle directly to the patient. Do not allow sodium chloride solution to flow into the LUTATHERA vial prior to the initiation of the LUTATHERA infusion and do not inject LUTATHERA directly into the sodium chloride solution.

2. Insert a second needle that is 9 cm, 18 gauge (long needle) into the LUTATHERA vial ensuring that this long needle touches and is secured to the bottom of the LUTATHERA vial during the entire infusion. Connect the long needle to the patient by an intravenous catheter that is prefilled with 0.9% sterile sodium chloride and that is used exclusively for the LUTATHERA infusion into the patient.

3. Use a clamp or pump to regulate the flow of the sodium chloride solution via the short needle into the LUTATHERA vial at a rate of 50 mL/hour to 100 mL/hour for 5 to 10 minutes and then 200 mL/hour to 300 mL/hour for an additional 25 to 30 minutes (the sodium chloride solution entering the vial through the short needle will carry the LUTATHERA from the vial to the patient via the catheter connected to the long needle over a total duration of 30 to 40 minutes).

4. Do not administer LUTATHERA as an intravenous bolus.

5. During the infusion, ensure that the level of solution in the LUTATHERA vial remains constant

6. Disconnect the vial from the long needle line and clamp the saline line once the level of radioactivity is stable for at least five minutes.

7. Follow the infusion with an intravenous flush of 25 mL of 0.9% sterile sodium chloride.

8. Dispose of any unused medicinal product or waste material in accordance with local and federal laws.

8. Radiation Dosimetry

The mean and standard deviation (SD) of the estimated radiation absorbed doses for adults receiving LUTATHERA are shown in Table below. The maximum penetration in tissue is 2.2 mm and the mean penetration is 0.67 mm.

Critical organs are spleen, kidneys, and bladder wall.

Estimated Radiation Absorbed Dose for LUTATHERA in NETTER-1

	Absorbed dose per unit activity (Gy/GBq) (N=20)		Calculated absorbed dose for 4 x 7.4 GBq (29.6 GBq cumulative activity) (Gy)	
Organ	**Mean**	**SD**	**Mean**	**SD**
Adrenals	0.037	0.016	1.1	0.5
Brain	0.027	0.016	0.8	0.5
Breasts	0.027	0.015	0.8	0.4
Gallbladder Wall	0.042	0.019	1.2	0.6
Heart Wall	0.032	0.015	0.9	0.4
Kidneys	0.654	0.295	19.4	8.7
Liver*	0.299	0.226	8.9	6.7
Lower Large Intestine Wall	0.029	0.016	0.9	0.5
Lungs	0.031	0.015	0.9	0.4
Muscle	0.029	0.015	0.8	0.4
Osteogenic Cells	0.151	0.268	4.5	7.9
Ovaries**	0.031	0.013	0.9	0.4
Pancreas	0.038	0.016	1.1	0.5
Red Marrow	0.035	0.029	1.0	0.8
Skin	0.027	0.015	0.8	0.4
Small Intestine	0.031	0.015	0.9	0.5
Spleen	0.846	0.804	25.1	23.8
Stomach Wall	0.032	0.015	0.9	0.5
Testes***	0.026	0.018	0.8	0.5
Thymus	0.028	0.015	0.8	0.5
Thyroid	0.027	0.016	0.8	0.5
Total Body	0.052	0.027	1.6	0.8
Upper Large Intestine Wall	0.032	0.015	0.9	0.4
Urinary Bladder Wall	0.437	0.176	12.8	5.3
Uterus	0.032	0.013	1.0	0.4

*N=18 (two patients excluded because the liver absorbed dose was biased by the uptake of the liver metastases)
**N=9 (female patients only)
***N=11 (male patients only)

9. DOSAGE FORMS AND STRENGTHS

Injection: 370 MBq/mL (10 mCi/mL) of lutetium Lu-177 dotatate as a clear and colorless to slightly yellow solution in a single-dose vial.

10. CONTRAINDICATIONS

None.

11 WARNINGS AND PRECAUTIONS

a. Risk from Radiation Exposure

- LUTATHERA contributes to a patient's overall long-term radiation exposure.
- Long-term cumulative radiation exposure is associated with an increased risk for cancer.
- Radiation is detectable in the urine for up to 30 days following LUTATHERA administration.
- Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with LUTATHERA consistent with institutional good radiation safety practices and patient management procedures

b. Myelosuppression

In the clinical trial referred to as NETTER-1, myelosuppression occurred more frequently in patients receiving LUTATHERA with long-acting octreotide compared to patients receiving high-dose long-acting octreotide (all grades/grade 3 or 4): anemia (81%/0) versus (54%/1%); thrombocytopenia (53%/1%) versus (17%/0); and neutropenia (26%/3%) versus (11%/0).

c. Secondary Myelodysplastic Syndrome and Leukemia

- In NETTER-1, with a median follow-up time of 24 months, myelodysplastic syndrome (MDS) was reported in 2.7% of patients receiving LUTATHERA with long-acting octreotide compared to no patients receiving high-dose long-acting octreotide.
- In ERASMUS, 15 patients (1.8%) developed MDS and 4 (0.5%) developed acute leukemia. The median time to the development of MDS was 28 months (9 to 41 months) for MDS and 55 months (32 to 155 months) for acute leukemia.

d. Renal Toxicity

In ERASMUS, 8 patients (<1%) developed renal failure 3 to 36 months following LUTATHERA. Two of these patients had underlying renal impairment or risk factors for renal failure (e.g., diabetes or hypertension) and required dialysis.

Patients with baseline renal impairment may be at greater risk of toxicity; perform more frequent assessments of renal function in patients with mild or moderate impairment. LUTATHERA has not been studied in patients with severe renal impairment (creatinine clearance < 30 mL/min).

e. Hepatotoxicity

In ERASMUS, 2 patients (<1%) were reported to have hepatic tumor hemorrhage, edema, or necrosis, with one patient experiencing intrahepatic congestion and cholestasis. Patients with hepatic metastasis may be at increased risk of hepatotoxicity due to radiation exposure.

f. Neuroendocrine Hormonal Crisis

Neuroendocrine hormonal crises, manifesting with flushing, diarrhea, bronchospasm and hypotension, occurred in 1% of patients in ERASMUS and typically occurred during or within 24 hours following the initial LUTATHERA dose. Two (<1%) patients were reported to have hypercalcemia.

g. Embryo-Fetal Toxicity

Based on its mechanism of action, LUTATHERA can cause fetal harm. There are no available data on the use of LUTATHERA in pregnant women. No animal studies using lutetium Lu-177 dotatate have been conducted to evaluate its effect on female reproduction and embryo-fetal development.

h. Risk of Infertility

LUTATHERA may cause infertility in males and females. The recommended cumulative dose of 29.6 GBq of LUTATHERA results in a radiation absorbed dose to the testis and ovaries within the range where temporary or permanent infertility can be expected following external beam radiotherapy.

i. Adverse Reactions

1. Myelosuppression
2. Secondary Myelodysplastic Syndrome and Leukemia
3. Renal Toxicity
4. Hepatotoxicity
5. Neuroendocrine Hormonal Crisis

12. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data reflect exposure to LUTATHERA in 111 patients with advanced, progressive midgut neuroendocrine tumors (NETTER-1). Safety data in Warnings and Precautions were also obtained in an additional 22 patients in a non-randomized pharmacokinetic substudy of NETTER-1 and in a subset of patients (811 of 1214) with advanced somatostatin receptor-positive tumors enrolled in ERASMUS.

Tables below summarize the incidence of adverse reactions and laboratory abnormalities, respectively. The most common Grade 3-4 adverse reactions occurring with a greater frequency among patients receiving LUTATHERA with octreotide compared to patients receiving high-dose octreotide include: lymphopenia (44%), increased GGT (20%), vomiting (7%), nausea and elevated AST (5% each), and increased ALT, hyperglycemia and hypokalemia (4% each).

Laboratory Abnormalities Occurring in ≥ 5% (All Grades) of Patients Receiving LUTATHERA with Octreotide in NETTER-1[*,1]

Laboratory Abnormality[1]	LUTATHERA and Long-Acting Octreotide (30 mg) (N = 111)		Long-Acting Octreotide (60 mg) (N = 112)	
	All grades %	Grade 3-4 %	All grades %	Grade 3-4 %
Hematology				
Lymphopenia	90	44	39	4
Anemia	81	0	54	1
Leukopenia	55	2	20	0
Thrombocytopenia	53	1	17	0
Neutropenia	26	3	11	0
Renal/Metabolic				
Creatinine increased	85	1	73	0
Hyperglycemia	82	4	67	2
Hyperuricemia	34	6	29	6
Hypocalcemia	32	0	14	0
Hypokalemia	26	4	21	2
Hyperkalemia	19	0	11	0
Hypernatremia	17	0	7	0
Hypoglycemia	15	0	8	0
Hepatic				
GGT increased	66	20	67	16
Alkaline phosphatase increased	65	5	54	9
AST increased	50	5	35	0
ALT increased	43	4	34	0
Blood bilirubin increased	30	2	28	0

*Values are worst grade observed after randomization

[1]National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Only displays laboratory abnormalities occurring at a higher incidence in LUTATHERA-treated patients [between arm difference of ≥5% (all grades) or ≥2%(grades 3-4)]

Adverse Reactions Occurring in ≥ 5% (All Grades) of Patients Receiving LUTATHERA with Octreotide in NETTER-1[1]

Adverse Reaction[1]	LUTATHERA and Long-Acting Octreotide (30 mg) (N = 111)		Long-Acting Octreotide (60 mg) (N = 112)	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Cardiac disorders				
Atrial fibrillation	5	1	0	0
Gastrointestinal disorders				
Nausea	65	5	12	2
Vomiting	53	7	9	0
Abdominal pain	26	3	19	3
Diarrhea	26	3	18	1
Constipation	10	0	5	0
General disorders				
Fatigue	38	1	26	2
Peripheral edema	16	0	9	1
Pyrexia	8	0	3	0
Metabolism and nutrition disorders				
Decreased appetite	21	0	11	3
Musculoskeletal and connective tissue disorders				
Back pain	13	2	10	0
Pain in extremity	11	0	5	0
Myalgia	5	0	0	0
Neck Pain	5	0	0	0
Nervous system disorders				
Headache	17	0	5	0
Dizziness	17	0	8	0
Dysgeusia	8	0	2	0
Psychiatric disorders				
Anxiety	12	1	5	0
Renal and urinary disorders				
Renal failure*	12	3	3	1
Radiation-related urinary tract toxicity**	8	0	3	0
Respiratory, thoracic and mediastinal disorders				
Cough	11	1	6	0
Skin and subcutaneous tissue disorders				
Alopecia	12	0	2	0
Vascular disorders				
Flushing	14	1	9	0
Hypertension	12	2	7	2

[1]National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Only displays adverse reactions occurring at a higher incidence in LUTATHERA-treated patients [between arm difference of ≥5% (all grades) or ≥2% (grades 3-4)]

*Includes the terms: Glomerular filtration rate decreased, acute kidney injury, acute prerenal failure, azotemia, renal disorder, renal failure, renal impairment

**Includes the terms: Dysuria, micturition urgency, nocturia, pollakiuria, renal colic, renal pain, urinary tract pain and urinary incontinence

13. DRUG INTERACTIONS

7.1 Somatostatin Analogs

Somatostatin and its analogs competitively bind to somatostatin receptors and may interfere with the efficacy of LUTATHERA. Discontinue long-acting somatostatin analogs at least 4 weeks and short-acting octreotide at least 24 hours prior to each LUTATHERA dose. Administer short- and long-acting octreotide during LUTATHERA treatment as recommended *[see Dosage and Administration (2.3)]*.

14. USE IN SPECIFIC POPULATIONS

a. Pregnancy

Risk Summary

Based on its mechanism of action, LUTATHERA can cause fetal harm. There are no available data on LUTATHERA use in pregnant women. No animal studies using lutetium Lu-177 dotatate have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including LUTATHERA, have the potential to cause fetal harm. Advise pregnant women of the risk to a fetus.

b. Lactation

Risk Summary

There are no data on the presence of lutetium Lu-177 dotatate in human milk, or its effects on the breastfed infant or milk production. No lactation studies in animals were conducted. Because of the potential risk for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with LUTATHERA and for 2.5 months after the final dose.

c. Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating LUTATHERA.

d. Contraception

Females

LUTATHERA can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the final dose of LUTATHERA.

Males

Based on its mechanism of action, advise males with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of LUTATHERA.

Infertility

The recommended cumulative dose of 29.6 GBq of LUTATHERA results in a radiation absorbed dose to the testis and ovaries within the range where temporary or permanent infertility can be expected following external beam radiotherapy.

e. Pediatric Use

The safety and effectiveness of LUTATHERA have not been established in pediatric patients.

f. Geriatric Use

Of the 1325 patients treated with LUTATHERA in clinical trials, 438 patients (33%) were 65 years and older. The response rate and number of patients with a serious adverse event were similar to that of younger subjects.

g. Renal Impairment

No dose adjustment is recommended for patients with mild to moderate renal impairment; however, patients with mild or moderate renal impairment may be at greater risk of toxicity. Perform more frequent assessments of renal function in patients with mild to moderate impairment. The safety of LUTATHERA in patients with severe renal impairment (creatinine clearance < 30 mL/min by Cockcroft-Gault) or end-stage renal disease has not been studied.

h. Hepatic Impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. The safety of LUTATHERA in patients with severe hepatic impairment (total bilirubin > 3 times upper limit of normal and any AST) has not been studied.

15 CLINICAL PHARMACOLOGY

a. Mechanism of Action

Lutetium Lu-177 dotatate binds to somatostatin receptors with highest affinity for subtype 2 receptors (SSRT2). Upon binding to somatostatin receptor expressing cells, including malignant somatostatin receptor-positive tumors, the compound is internalized. The beta emission from Lu-177 induces cellular damage by formation of free radicals in somatostatin receptor-positive cells and in neighboring cells.

b. Pharmacodynamics

Lutetium Lu-177 exposure-response relationships and the time course of pharmacodynamics response are unknown.

Cardiac Electrophysiology

The ability of LUTATHERA to prolong the QTc interval at the therapeutic dose was assessed in an open label study in 20 patients with somatostatin receptor-positive midgut carcinoid tumors. No large changes in the mean QTc interval (i.e., >20 ms) were detected.

c. Pharmacokinetics

The pharmacokinetics (PK) of lutetium Lu-177 dotatate have been characterized in patients with progressive, somatostatin receptor-positive neuroendocrine tumors. The mean blood exposure (AUC) of lutetium Lu-177 dotatate at the recommended dose is 41 ng.h/mL [coefficient of variation (CV) 36 %]. The mean maximum blood concentration (Cmax) for lutetium Lu-177 dotatate is 10 ng/mL (CV 50%), which generally occurred at the end of the LUTATHERA infusion.

d. Distribution

- The mean volume of distribution for Lu-177 dotatate is 460 L (CV 54%).
- Within 4 hours after administration, Lu-177 dotatate distributes in kidneys, tumor lesions, liver, spleen, and, in some patients, pituitary gland and thyroid.
- The co-administration of amino acids reduced the median radiation dose to the kidneys by 47% (34% to 59%) and increased the mean beta-phase blood clearance of lutetium Lu-177 dotatate by 36%.
- The non-radioactive form of lutetium dotatate is 43% bound to human plasma proteins.

e. Elimination

The mean clearance (CL) is 4.5 L/h (CV 31%) for lutetium Lu-177 dotatate. The mean (± standard deviation) effective blood elimination half-life is 3.5 (±1.4) hours and the mean terminal blood half-life is 71 (± 28) hours.

f. Metabolism

Lutetium Lu-177 dotatate does not undergo hepatic metabolism.

g. Excretion

Lutetium Lu-177 dotatate is primarily eliminated renally with cumulative excretion of 44% within 5 hours, 58% within 24 hours, and 65% within 48 hours following LUTATHERA administration. Prolonged elimination of lutetium Lu-177 dotatate in the urine is expected; however, based on the half-life of lutetium 177 and terminal half-life of lutetium Lu-177 dotatate, greater than 99% will be eliminated within 14 days after administration of LUTATHERA.

h. Drug Interaction Studies

The non-radioactive form of lutetium is not an inhibitor or inducer of cytochrome P450 (CYP) 1A2, 2B6, 2C9, 2C19 or 2D6 in vitro. It is not an inhibitor of P-glycoprotein, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, or OCT1 in vitro.

16. NONCLINICAL TOXICOLOGY

a. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and mutagenicity studies have not been conducted with Lutetium Lu-177 dotatate; however, radiation is a carcinogen and mutagen.

No animal studies were conducted to determine the effects of lutetium Lu-177 dotatate on fertility.

13.2 Animal Toxicology and/or Pharmacology

The primary target organ in animal studies using a non-radioactive form of lutetium Lu-177 dotatate (lutetium Lu 175 dotatate) was the pancreas, a high SSTR2 expressing organ. Pancreatic acinar apoptosis occurred at lutetium Lu 175 dotatate

doses ≥ 5 mg/kg in repeat dose toxicology studies in rats. Pancreatic acinar cell atrophy also occurred in repeat dose toxicology studies in dogs at doses ≥ 500 mg/kg. These findings were consistent with high uptake of the radiolabeled peptide in the pancreas in animal biodistribution studies.

17 CLINICAL STUDIES

14.1 Progressive, Well-differentiated Advanced or Metastatic Somatostatin Receptor-Positive Midgut Carcinoid Tumors

The efficacy of LUTATHERA in patients with progressive, well-differentiated, locally advanced/inoperable or metastatic somatostatin receptor-positive midgut carcinoid tumors was established in NETTER-1 (NCT01578239), a randomized, multicenter, open-label, active-controlled trial. Key eligibility criteria included Ki67 index ≤ 20%, Karnofsky performance status ≥ 60, confirmed presence of somatostatin receptors on all lesions (OctreoScan uptake ≥ normal liver), creatinine clearance ≥ 50 mL/min, no prior treatment with peptide receptor radionuclide therapy (PRRT), and no prior external radiation therapy to more than 25% of the bone marrow.

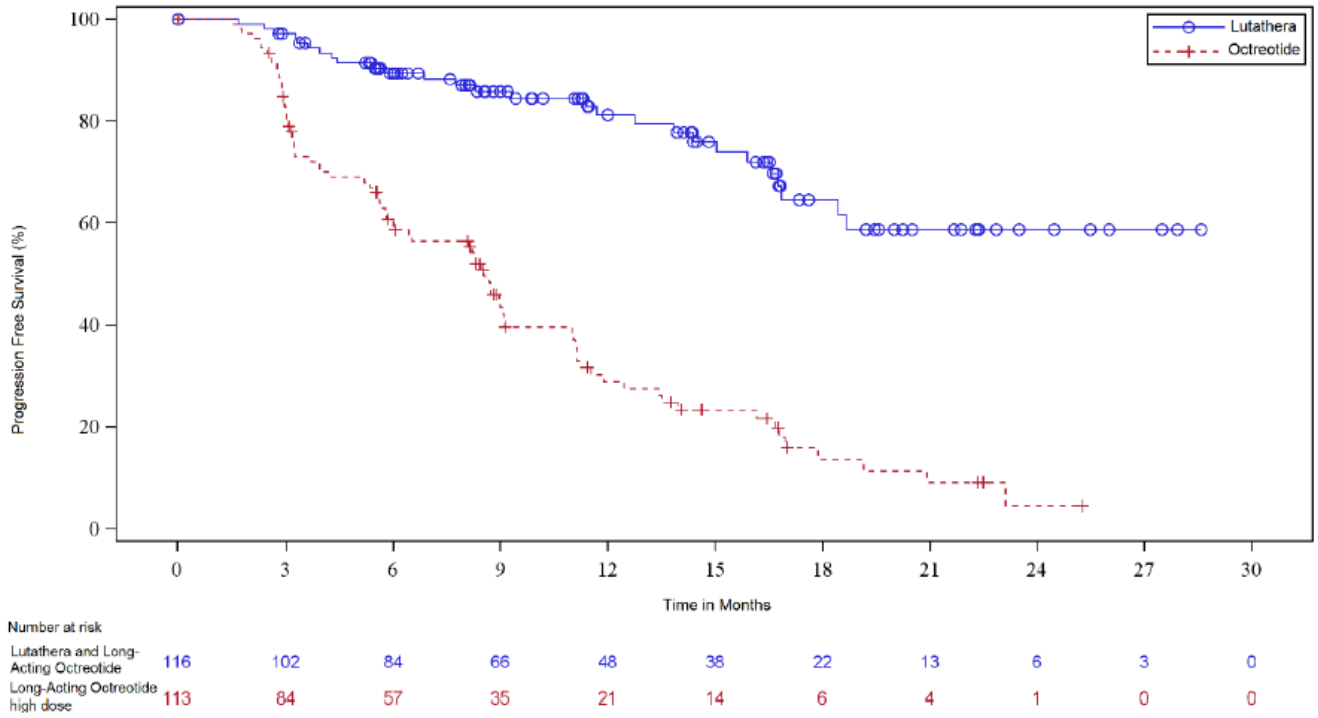
Two hundred twenty-nine (229) patients were randomized (1:1) to receive either LUTATHERA 7.4 GBq (200 mCi) every 8 weeks for up to 4 administrations (maximum cumulative dose of 29.6 GBq) or high-dose long-acting octreotide (defined as 60 mg by intramuscular injection every 4 weeks). Patients in the LUTATHERA arm also received long-acting octreotide 30 mg as an intramuscular injection 4 to 24 hours after each LUTATHERA dose and every 4 weeks after completion of LUTATHERA treatment until disease progression or until week 76 of the study. Patients in both arms could receive short-acting octreotide for symptom management; however, short-acting octreotide was withheld for at least 24 hours before each LUTATHERA dose. Randomization was stratified by OctreoScan tumor uptake score (Grade 2, 3 or 4) and the length of time that patients had been on the most recent constant dose of octreotide prior to randomization (≤ 6 or > 6 months). The major efficacy outcome measure was progression free survival (PFS) as determined by a blinded independent radiology committee (IRC) per RECIST v1.1. Additional efficacy outcome measures were overall response rate (ORR) by IRC, duration of response, and overall survival (OS).

Efficacy Results in NETTER-1

	LUTATHERA and Long-Acting Octreotide (30 mg) N=116	Long-Acting Octreotide (60 mg) N=113
PFS by IRC		
Events (%)	27 (23%)	78 (69%)
Progressive disease, n (%)	15 (13%)	61 (54%)
Death, n (%)	12 (10%)	17 (15%)
Median in months (95% CI)	NR[c] (NE, NE)	8.5 (5.8, 9.1)
Hazard ratio[a] (95% CI)	0.21 (0.13, 0.32)	
P-Value[b]	< 0.0001	
OS (Updated)		
Deaths (%)	27 (23%)	43 (38%)
Median in months (95% CI)	NR (31.0, NE)	27.4 (22.2, NE)
Hazard ratio[a,d] (95% CI)	0.52 (0.32, 0.84)	
ORR by IRC		
ORR, % (95% CI)	13% (7%,19%)	4% (0.1%, 7%)
Complete response rate, n (%)	1 (1%)	0
Partial response rate, n (%)	14 (12%)	4 (4%)
P-Value[e]	0.0148	
Duration of response, median in months (95% CI)	NR (2.8, NE)	1.9 (1.9, NE)

a: Hazard ratio based on the unstratified Cox model
b: Unstratified log rank test
c: Median follow-up 10.5 months at time of primary analysis of PFS (range: 0 to 29 months)
d: Interim analysis of OS not statistically significant based on pre-specified significance criteria
e: Fisher's Exact test
NR: Not reached; NE: Not evaluable

Figure 1. Kaplan-Meier Curves for Progression-Free Survival in NETTER-1



18. PATIENT COUNSELING INFORMATION

Radiation Risks

Advise patients to minimize radiation exposure to household contacts consistent with institutional good radiation safety practices and patient management procedures.

Myelosuppression

Advise patients to contact their healthcare provider for any signs or symptoms of myelosuppression or infection, such as fever, chills, dizziness, shortness of breath, or increased bleeding or bruising.

Secondary Myelodysplastic Syndrome and Acute Leukemia

Advise patients of the potential for secondary cancers, including myelodysplastic syndrome and acute leukemia.

Renal Toxicity

Advise patients to hydrate and urinate frequently during and after administration of LUTATHERA.

Hepatotoxicity

Advise patients of the need for periodic laboratory tests to monitor for hepatotoxicity..

Neuroendocrine Hormonal Crises

Advise patients to contact their health care provider for signs or symptoms that may occur following tumor-hormone release, including severe flushing, diarrhea, bronchospasm, and hypotension..

Embryo-Fetal Toxicity

Advise pregnant women and males and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.

Advise females of reproductive potential to use effective contraception during treatment with LUTATHERA and for 7 months after the final dose.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with LUTATHERA and for 4 months after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise females not to breastfeed during treatment with LUTATHERA and for 2.5 months after the final dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise female and male patients that LUTATHERA may impair fertility *[see Warnings and Precautions (5.8), Use in Specific Populations (8.3)]*.