NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement – SE5
Application Number(s)	NDA 208700-S031
Priority or Standard	Priority
Submit Date(s)	October 25, 2023
Received Date(s)	October 25, 2023
PDUFA Goal Date	April 25, 2024
Division/Office	Division of Oncology 2 / Office of Oncologic Drugs
Review Completion Date	*Electronic Stamp Date*
Established/Proper Name	lutetium Lu 177 dotatate
(Proposed) Trade Name	Lutathera
Pharmacologic Class	Radiopharmaceutical
Code name	n/a
Applicant	Advanced Accelerator Applications USA, Inc.
Dosage form	Injection; solution
Applicant proposed Dosing Regimen	7.4 GBq (200 mCi) every 8 weeks (± 1 week) for a total of 4 doses
Applicant Proposed Indication(s)/Population(s)	(b) (4) [redacted]
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult and pediatric patients 12 years and older with somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors.
Recommended Dosing Regimen	7.4 GBq (200 mCi) every 8 weeks (± 1 week) for a total of 4 doses

Table of Contents

Table of Tables

Table of Figures

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Lutetium Lu 177 dotatate (Lutathera) is a radiolabeled somatostatin analog with affinity for somatostatin receptor 2 (SSTR2), which is highly expressed in neuroendocrine tumors including gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Lutetium Lu 177 dotatate consists of the somatostatin peptide analog octreotate coupled to the metal-ion chelating moiety DOTA, and labeled with the beta-emitting radionucleotide lutetium-177. On binding to SSTR2, lutetium Lu 177 dotatate is internalized into tumor cells, where it delivers tumoricidal radiation.

Lutetium Lu 177 dotatate was granted FDA approval in January 2018 for the treatment of adult patients with SSTR-positive GEP-NETs. The approved dosage is 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses. The Applicant's proposed indication for this efficacy supplement is for the treatment of somatostatin receptor (SSTR)-positive GEP-NETs, including foregut, midgut, and hindgut neuroendocrine tumors in adults and pediatric patients 12 years and older.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support the traditional approval of lutetium Lu 177 dotatate for for the treatment pediatric patients 12 to < 18 years with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors. The recommendation for traditional approval is based on pharmacokinetic (PK), dosimetry and safety data from 9 adolescent patients enrolled in Study CAAA601A32201 (NETTER-P), an ongoing, open-label, multicenter, single-arm study to evaluate the safety and dosimetry of lutetium Lu 177 dotatate in adolescent patients with SSTR-positive GEP-NETs or pheochromocytoma/paraganglioma (PPGL).

The recommendation for traditional approval is also based on the extrapolation of efficacy from the adult indication, which was supported by a statistically significant and clinically meaningful improvement in progression-free survival (PFS) in patients randomized to the lutetium Lu 177 dotatate arm of NETTER-1, an international, randomized, open-label trial in patients with advanced/inoperable or metastatic, SSTR-positive midgut GEP-NETs. Extrapolation of the effectiveness of lutetium Lu 177 dotatate to pediatric patients aged 12 and older with SSTR-positive GEP-NETs is appropriate given the similarity in drug exposure between adult and adolescent patients, and that the biology and clinical characteristics of GEP-NETs are similar in adolescent and adult patients. Further, the mechanism of action of lutetium Lu 177 dotatate is expected to be the same in these populations. It would not be feasible to conduct a randomized trial of lutetium Lu 177 dotatate in adolescent patients given that GEP-NETs are exceedingly rare in the pediatric population.

The submitted evidence meets the statutory evidentiary standard for traditional approval. Pharmacokinetic data showed no clinically relevant differences in PK exposure between adolescents and adult patients treated at the approved dose. Dosimetry data was notable for a lower mean absorbed dose in a majority of organs in adolescents, but a higher mean absorbed dose to the kidney, adrenals, small intestines, and urinary bladder wall. Given these similarities and the acceptable safety profile observed in adolescents that is supported by the adult safety data, extrapolation of efficacy from the adult population is possible. Therefore, the review team recommends granting traditional approval to lutetium Lu 177 dotatate to pediatric patients 12 years and older with somatostatin receptor-positive GEP-NETs, including foregut, midgut, and hindgut neuroendocrine tumors.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a rare and heterogeneous group of neoplasms arising from neuroendocrine cells and their precursors. GEP-NETs are exceedingly rare in the pediatric population, with an incidence of approximately 2.8 per 1 million children (Kotagal et al, 2020). The behavior and prognosis of GEP-NETs varies depending on primary tumor location, grade and differentiation. The most common primary tumor location for pediatric GEP-NETs is the appendix, and these are typically cured with surgical resection. However, extra-appendiceal GEP-NETs are more likely to be higher-grade and metastatic, and may have an indolent course. The prognosis for metastatic GEP-NET is poor, with a 5-year overall survival (OS) of 35% for well-differentiated metastatic GEP-NETs (Diez et al, 2013).

There are currently no FDA-approved therapies for the treatment of pediatric GEP-NETs. Given the rarity of pediatric GEP-NETs, there are no pediatric-specific treatment guidelines and treatment of pediatric patients typically follows established adult guidelines. Surgical resection with close follow-up is recommended for locoregional disease (Gaiani et al, 2019). For unresectable GEP-NETs, somatostatin analogues lanredotide and octreotide are FDA-approved in the first-line setting and for symptomatic control of functional GEP-NETs, repectively. FDA-approved treatments for adults with progressive GEP-NETs include everolimus and lutetium Lu 177 dotatate. Sunitinib is approved for adult patients with pancreatic NETs (pNETs).

Lutetium Lu 177 dotatate is a radiolabeled somatostatin analog with affinity for somatostatin receptor 2 (SSTR), which is highly expressed on GEP-NETs. Lutetium Lu 177 dotatate was granted traditional approval in January 2018 for the treatment of adults with SSTR-positive GEP-NETs based on a statistically significant and clinically meaningful improvement in PFS for patients treated with lutetium Lu 177 dotatate with octreotide LAR compared to those treated with octreotide LAR alone [median PFS was not reached compared to 8.5 months (95% CI: 5.8, 9.1) , respectively; HR 0.21 (95% CI: 0.13, 0.32)].

NETTER-P is an ongoing, open-label, multicenter, single-arm study designed to evaluate the safety and dosimetry of lutetium Lu 177 dotatate in adolescent patients with SSTR-positive GEP-NETs or pheochromocytomas/paraganglionomas (PPGLs). The primary objectives for NETTER-P are target organ absorbed radiation doses in adolescents with SSTR-positive GEP-NETs and PPGL as a pooled cohort; and incidence of adverse events (AEs) and laboratory toxicities after the first administration of lutetium Lu 177 dotatate in adolescents with SSTR-positive GEP-NETs and PPGL as a pooled cohort. The dosage of lutetium Lu 177 dotatate studied in NETTER-P was 7.4 GBq as an IV infusion once every 8 weeks for a total of 4 doses (29.6 GBq) with a co-infusion of a commercially available amino acid, which is the same dosing regimen approved for adults.

NETTER-P was conducted as part of a pediatric Written Request (WR) under the Best Pharmaceuticals for Children Act (BPCA).

PK, dosimetry, safety and preliminary efficacy data from NETTER-P were available for 9 patients. No clinically relevant differences were observed in PK exposure between adolescents and adults; however, higher absorbed doses in the kidneys were observed in some patients compared to adults exposed to the same dose. Although the sample size was limited, population PK model fitting was generally acceptable and the kidney dosimetry model predicted the median probability exceeding the external beam radiation therapy (EBRT) thresholds reasonably well.

The most common (≥33%) adverse reactions observed in NETTER-P were headache, fatigue, lymphopenia, abdominal pain, epistaxis, nausea and neutropenia. Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, decreased leukocytes, decreased neutrophils and increased calcium. Serious adverse events (SAEs) including events of Grade 3 lower gastrointestinal hemorrhage, Grade 3 hypercalcemia, and Grade 3 catheter-related infection, occurred in 2 patients (22%).

Lutetium Lu 177 dotatate appears to have an acceptable safety profile in pediatric patients, consistent with the known safety profile in adults. Significant safety concerns in the pediatric population are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling. There were no new safety concerns identified during sNDA review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). Two postmarketing requirements (PMRs) to address safety in the adolescent population will be issued to assess 1) long-term renal toxicity and 2) secondary malignancies arising due to exposure to radiation.

The submitted evidence meets the statutory evidentiary standard for traditional approval. The similarities in exposure between adult and adolescent patients, as well as the observed safety profile in adolescents, allow for the extrapolation efficacy from the adult population with GEP-NETs. Given the rarity of pediatric GEP-NETs, a dedicated randomized trial in the pediatric population is not feasible. Based on the favorable risk-benefit assessment for this population with a high unmet medical need and a serious, life-threatening disease, traditional approval is recommended for the following indication:

Lutetium Lu 177 dotatate (Lutathera) is indicated for the treatment of adult and pediatric patients 12 years and older with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Gastropancreatic Neuroendocrine tumors (GEP-NETs) are a heterogeneous group of tumors arising from neuroendocrine cells and their precursors. • GEP-NETs are grouped by location and by whether the tumor is functional, i.e., whether they secrete peptide hormones that result in clinical symptoms. • Treatment of functional GEP-NETs requires management of clinical symptoms in addition to anti-cancer therapy. • GEP-NETs most commonly occur in the fifth decade of life or later, and are exceedingly rare in children. • GEP-NETs occurring in pediatric patients exhibit similar biology, clinical presentation and natural history as those occurring in adult patients. • The prognosis for metastatic GEP-NET is poor, with a 5-year overall survival (OS) of 35% for well-differentiated metastatic GEP-NETs (Diez et al, 2013).	Unresectable SSTR-positive GEP-NETs represent a serious and life-threatening condition. Pediatric patients with unresectable, SSTR positive GEP-NETs are a group of patients with a high unmet medical need. These patients would benefit from available therapies to treat their tumors and to control symptoms and co-morbid conditions associated with excess peptide hormone secretion.
Current Treatment Options	• There are currently no approved therapies for pediatric patients with GEP-NETs. Pediatric patients requiring systemic therapies are typically treated according to treatment paradigms used in adult patients. • Systemic therapies available for the treatment of GEP-NETs include somatostatin analogues, targeted therapies, and chemotherapy.	There are no FDA-approved therapies for pediatric patients with GEP-NETs. Extrapolation of efficacy of lutetium Lu 177 dotatate from the adult population represents a clinically meaningful advance for a very rare population with no treatment options and a high unmet medical need.
Benefit	• NETTER-P is an ongoing, open-label, multicenter, single-arm study to evaluate the safety and dosimetry of lutetium Lu 177 dotatate in adolescent patients with SSTR-positive, well-differentiated GEP-NETs or pheochromocytomas/paraganglionomas (PPGLs). • Data from 9 patients (4 GEP-NET, 5 PPGL) was included in the	The PK and dosimetry data from NETTER-P supporting similar exposures between adolescent and adult patients, in the context of the similar disease biology and mechanism of action of lutetium Lu 177 dotatate in pediatric

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	submission. PK and dosimetry data were adequate to allow for an assessment of the similarity of exposure between adults and adolescents. • Updated tumor response data was provided for 8 patients (4 GEP-NET, 4 PPGL).One patient with GEP-NET had a complete response by scintigraphy. Six patients (2 GEP-NET, 4 PPGL) had stable disease, and 1 patient with GEP-NET had progressive disease.	and adult patients with GEP-NETs, allow for extrapolation of efficacy from the adult population. It is expected that the clinical benefit to pediatric patients will be similar to that observed in adult patients enrolled in the NETTER-1 study.
Risk and Risk Management	• The safety dataset for this sNDA includes 9 adolescent patients with SSTR-positive GEP-NETs or PPGLs who received at least one dose of lutetium Lu 177 dotatate. • Warnings and Precautions for lutetium Lu 177 dotatate include risk from radiation exposure, myelosuppression, secondary myelodysplastic syndrome (MDS) and leukemia, renal toxicity, hepatotoxicity, hypersensitivity reactions, neuroendocrine hormonal crisis, embryo-fetal toxicity and risk of infertility. • The target organs for radiation toxicities are bone marrow and kidneys. • Lutetium Lu 177 dotatate is administered with an amino acid infusion to reduce renal uptake of radioactivity. • Serious adverse reactions occurred in 22% of patients who received lutetium Lu 177 dotatate in NETTER-P. There were no fatal adverse reactions. • The most common (≥33%) adverse reactions were headache, fatigue, lymphopenia, abdominal pain, epistaxis, nausea and neutropenia. Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, decreased leukocytes, decreased neutrophils and increased calcium. • Higher absorbed radiation doses in the kidneys were observed in adolescents than in adults. Dosimetry was similar across other target	• Safety concerns associated with Lutetium lu 177 dotatate in adolescents are adequately addressed by information in the Warnings and Precautions and Dosage and Administration sections of product labeling. • A statement regarding increased risk of radiation toxicities in pediatric patients was added to sections 5 and 8 in the label. Continued follow-up for evaluation of long-term effects is recommended. • Two postmarketing requirements (PMR) will be issued to assess long-term toxicities, specifically renal toxicity and the development of myelodysplastic syndrome and acute leukemia. Refer to section 13 of this review for the specifics of each PMR.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	organs. • Due to longer life expectancy, pediatric patients may have an increased risk of long-term radiation toxicities including secondary malignancies.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	The patient experience data that were submitted as part of the application include:			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1. Analysis of Condition

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogeneous group of neoplasms thought to arise from neuroendocrine cells and their precursors. GEP-NETs are rare tumors overall, and are particularly rare in childhood, with an annual incidence rate of approximately 2.8 per 1 million children (Kotagal et al, 2019; Farooqui et al, 2020). Further, most cases of pediatric GEP-NETs occur in adolescents. The 2019 World Health Organization (WHO) criteria classifies neuroendocrine neoplasms (NENs) based on location, differentiation and grade. Grading is based on mitotic rate and Ki-67 index and includes low grade, (G1, Ki-67 index 0-2%), intermediate grade (G2, Ki-67 index 3-20%) and high grade (G3, Ki-67 index >20%) NENs. Poorly differentiated NENs are classified as neuroendocrine carcinomas (NECs) and are highly aggressive with a poor prognosis (Popa et al, 2021). As in adult patients, the behavior and prognosis of GEP-NETs in adolescent patients varies depending on primary tumor location, grade and differentiation. GEP-NETs are also categorized as functional or non-functional. Functional GEP-NETs, such as gastrinomas and carcinoids, are characterized by excess peptide hormone secretion which is often associated with clinical symptoms such as flushing, diarrhea, tachycardia and wheezing. Patients with functional GEP-NETs may present earlier in the disease course due to the symptoms associated with these tumors (Kotagal et al, 2019).

Pediatric GEP-NETs most commonly occur in the appendix and prognosis is excellent with surgical treatment. Extra-appendiceal GEP-NETs are more rare and are more likely to be higher-grade and metastatic (Gaiani et al, 2019). GEP-NETs may have an indolent course and present with non-specific symptoms, resulting in delays in diagnosis until metastatic disease is present, particularly in the pediatric population where GEP-NETs are rarely encountered. The prognosis for metastatic GEP-NET is poor, with 5-year overall survival (OS) of 35% for moderate or well-differentiated metastatic GEP-NETs (Diez et al, 2013).

2.2. Analysis of Current Treatment Options

There are no FDA-approved therapies for pediatric patients with GEP-NETs, and no pediatric-specific treatment guidelines. Consequently, pediatric patients requiring systemic therapy are often treated with agents approved for the treatment of GEP-NETs in adults. Systemic treatment options for unresectable or metastatic GEP-NET in adults include somatostatin analogues, targeted therapies, chemotherapy and peptide receptor radionucleotide therapy (PRRT) (Table 1). Somatostatin analogues lanredotide andoctreotide are FDA-approved in the first-line setting and for control of symptoms associated with functional GEP-NETs, respectively. Targeted therapies for progressive GEP-NETs include the mTOR inhibitor everolimus and the multi-tyrosine kinase inhibitor sunitinib, which is approved for progressive pancreatic neuroendocrine tumors (pNET). Chemotherapy regimens which have shown anti-

tumor activity in GEP-NETs include capecitabine with temozolomide, streptozocin with 5-fluorouracil or doxorubicin, and dacarbazine (Zappi et al, 2023). Lutetium Lu 177 dotatate is an option for PRRT which was granted FDA approval in 2018.

Table 1: Summary of FDA approved treatments for GEP-NETs in Adults (adapted from original NDA review)

Product Name	Pharmacologic class	Relevant Indication	Year of Approval	Efficacy Information
Streptozocin (Zanosar)	Alkylating agent	Metastatic pancreatic islet cell cancer	1982	Streptozocin and doxorubicin resulted in RR 69% Median OS 2.2 years
Octreotide acetate (Sandostatin)	Somatostatin analogue	Symptomatic treatment of metastatic carcinoid tumors	1988	Similar control of symptoms and reduction of urinary 5-HIAA levels among 67 patients treated with Sandostatin LAR and 26 patients with Sandostatin injection
Lanreotide acetate (Somatuline Depot)	Somatostatin analogue	Metastatic, well-differentiated, non-functional GEP-NETs	2014	Results of a randomized, double-blind, placebo-controlled trial (CLARINET, N=204) demonstrated a statistically significant improvement in PFS [median >22.1 vs 16.6 months, HR 0.47 (95% CI: 0.30, 0.73); p <0.001].
Everolimus (Afinitor)	mTOR inhibitor	Progressive pNET and well-differentiated, non-functional NET of GI or lung origin that is unresectable, locally advanced or metastatic	2016	Results of a randomized, double-blind, placebo-controlled trial (RADIANT-4, N=302) showed a statistically significant improvement in PFS [median 11.0 vs 3.9 months, HR 0.48 (95% CI: 0.35, 0.67); p <0.001].
Sunitinib (Sutent)	mTKI	Well-differentiated, progressive pNET that is unresectable or metastatic	2011	Results of a randomized, double-blind, placebo-controlled trial (Study A6181111, N=171) demonstrated a statistically significant improvement in PFS [median 10.2 vs 5.4 months, HR 0.43 (95% CI: 0.27, 0.67); p< 0.001].
Lutetium Lu 177 dotatate (Lutathera)	Radiolabeled somatostatin analogue	SSTR-positive GEP-NETs	2018	Results of a randomized, open-label, active-controlled trial (NETTER-1, N=229) demonstrated a statistically significant improvement in PFS for patients randomized to Lutetium Lu 177 dotatate vs octreotide [median NR vs. 8.5 months, HR 0.21 (95% CI: 0.13, 0.32); p< 0.0001].

pNET: pancreatic neuroendocrine tumor, PFS: progression free survival, HR: hazard ratio, CI: confidence interval, SSTR: somatostatin receptor

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

On January 16, 2018, Lutetium Lu 177 dotatate was granted tradiational approval for the treatment of SSTR-positive GEP-NETs. Please refer to the original NDA review dated January 26, 2018 for a full regulatory history preceding the original approval.

On October 26, 2020, FDA issued a Written Request (WR) to obtain pediatric information on Lutetium Lu 177 dotatate. The sole study included in the WR is Study CAAA601A32201 (NETTER-P), a multi-center, single-arm study of Lutathera in pediatric patients from 12 to <18 years of age with SSTR-positive GEP-NETs and pheochromocytoma/paraganglionoma (PPGL). The co-primary objectives were to evaluate organ abdorbed radiation doses and to evaluate the safety and tolerability of Lutetium Lu 177 dotatate in adolescents with GEP-NETs to support extrapolation from the adult indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

- April 27, 2020: FDA issued Written Response Only (WRO) meeting responses to address questions regarding development of lutetium Lu 177 dotatate in adolescent patients with SSTR-positive GEP-NETs.
- June 29, 2020: Applicant submitted the initial Proposed Pediatric Study Request (PPSR) and responded to FDA comments provided in the written response.
- September 1, 2020: FDA requested Applicant revise the PPSR to include pediatric patients with pheochromocytomas and paraganglionomas (PPGL).
- September 29, 2020: Teleconference between FDA and Applicant to discuss the inclusion of patients with PPGL in the pediatric study.
- October 13, 2020: Applicant submitted updated PPSR to IND in the format of a revised draft WR which included an exploratory PPGL cohort.
- October 26, 2020: FDA issued the WR for lutetium Lu 177 dotatate in patients 1 year of age and older.
- November 6, 2020: Applicant submitted proposal to amend the WR to study patients aged 12 years and older, from 1 year and older.
- December 7, 2020: FDA issued a rescinded WR due to potential safety concerns associated with lutetium Lu 177 dotatate in patients younger than 12 years of age due to the lack of pharmacokinetic data and accurate dosing strategies, and reissued the WR with revised age eligibility for study participants (12 years of age and older).
- January 27, 2021: FDA issued WR Amendment 1 to correct template/typographical errors in the initial WR.
- February 28, 2023: Applicant submitted a request to amend the WR due to ongoing recruitment challenges for the NETTER-P study. Applicant proposed that the primary analysis include 5 patients pooled across GEP-NET and PPGL indications (and at least 2 GEP-

NET patients) instead of the 8 GEP-NET patients originally stipulated.

- May 1, 2023: The Applicant's proposal to amend the WR was discussed with the Oncology Center of Excellence Pediatric Review Committee (OCE PeRC). Representatives from OCE PeRC, DO2, and the Office of Clinical Pharmacology met with members of the Office of Regulatory Policy and the Division of Pediatric and Maternal Health. The consensus was that the WR should not be amended to accept a minimum of 5 patients in the absence of scientific justification to support that 5 patients would be sufficient to adequately characterize PK and dosimetry.
- May 19, 2023: FDA held an informal teleconference with the Applicant to discuss the proposed changes to the WR. FDA agreed to amend the WR to pool analyses of PK, dosimetry and safety across disease types. FDA stated that the Applicant could submit mature data for the 5 treated patients and partial data for any additional patients if the Applicant considered these data to be sufficient to adequately characterize PK and dosimetry. FDA cautioned that whether the terms of the WR have been met will be dependent on FDA review of the data.
- June 27, 2023: FDA issued WR Amendment 2 with revised objectives to reflect the pooled analysis of data from GEP-NET and PPGL patients. The Amended WR stipulated that 8 patients be enrolled across tumor types.
- March 13, 2024: Meeting of the Pediatric Exclusivity Board to discuss whether pediatric exclusivity should be granted based on data submitted to fulfill the WR. At the conclusion of the meeting the Board determined that an additional meeting was needed.
- April 5, 2024: A second meeting of the Pediatric Excusivity board was held. The Board determined that the Applicant had fairly responded to the WR and voted to grant pediatric exclusivity.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No sites were inspected during the review of this supplemental application.

4.2. Product Quality

Not applicable.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

Please refer to the original NDA review dated January 26, 2018 for a full nonclinical pharmacology/toxicology review. No new additional nonclinical data were reviewed as part of this submission.

6 Clinical Pharmacology

6.1. Executive Summary

Lutathera® (lutetium Lu 177 dotatate) is a radiolabeled somatostatin analog approved for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults. With the current Supplement, the Applicant seeks approval of Lutathera in pediatric patients ≥ 12 years of age for the same indication as approved in adults.

The proposed recommended dosage is the same as that approved in adults: 7.4 gigabecquerels (GBq) as an intravenous (IV) infusion once every 8 weeks for a total of 4 doses (29.6 GBq) with a co-infusion of a commercially available amino acid.

- Supplement 31 included the pediatric study report for Study CAAA601A32201 (NETTER-P) to fulfill Written Request Amendment 2, which requested conduct of a clinical trial to provide evidence for the safe and effective use of Lutathera in adolescent patients with GEP-NET (≥12 years of age). The Applicant fairly responded to the terms of Written Request Amendment 2 by enrolling at least 8 adolescents across GEP-NETs and PPGLs, including a minimum of 3 adolescents with GEP-NETs, to support the efficacy in adolescent patients based on similar exposure and dosimetry in adolescent patients with somatostatin receptor-positive GEP-NETs and PPGL compared to those in adults.

The clinical pharmacology review focused on:

- Comparison of exposure and dosimetry data from adolescents enrolled in NETTER-P to that of adults, and adequacy of the population PK model to identify covariates that affect exposure and dosimetry.
- Adequacy of the available PK and dosimetry data to support extrapolation of the efficacy of lutetium Lu 177 dotatate in adults to adolescent patients aged ≥12 years with GEP-NETs.
- Appropriateness of the Applicant's proposed recommended dosage in adolescents with GEP-NETs.

Based on the data from 9 adolescent patients, the clinical pharmacology analyses showed no clinically relevant differences in PK exposure between adolescents and adults but higher absorbed doses in the kidneys of adolescents compared to adults at the proposed dose. Population PK model fitting was found to be generally acceptable, with no significant covariates effects identified. The kidney dosimetry model predicted the median probability of exceeding the EBRT thresholds reasonably well, with the adolescent patient population estimated to have a higher probability exceeding the threshold for kidney absorbed dose compared to adult patients at the approved dosage.

Overall, the clinical pharmacology analyses and conclusions were limited by the the small sample size of adolescent patients with PK data, the different PK sampling schedule between adolescent and adult patients, large variability of kidney dosimetry in adults at the same approved dose and absence of PK data at doses below 7.4 GBq in both adults and adolescents. Therefore, a combined approach that includes the available clinical pharmacology data and additional clinical considerations (see Clinical review), supported the FDA's conclusion that the current approved Lutathera dosage, and efficacy in adults, can be extrapolated to provide an optimized benefit-risk profile in pediatric patients ≥12 years of age with GEP-NETs.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Lutetium Lu 177 dotatate, a radiolabeled somatostatin analog, binds to somatostatin receptors with the highest affinity for subtype 2 somatostatin receptors (SSTR2). Upon binding to somatostatin receptor expressing cells, including malignant somatostatin receptor-positive tumors, the compound is internalized. The beta-minus emission from lutetium-177 induces cellular damage by formation of free radicals in somatostatin receptor-positive cells and in neighboring cells.

The PK of lutetium Lu 177 dotatate was previously reviewed and described in the clinical pharmacology reviews under the original NDA 208700. The current submission provides assessments of PK in adolescent patients (≥12 years of age).

PK data were collected from 9 adolescent patients 13 to 16 years of age with somatostatin receptor-positive GEP-NET or PPGL enrolled in NETTER-P. Following a single dose of lutetium Lu 177 dotatate 7.4 GBq, the geometric mean C_{max} of 12 ng/mL (CV 33%), occurred at the end of the LUTATHERA infusion, with a geometric mean $AUC_{0\text{-last}}$ of 41 ng·h/mL (CV 12%) (See Table 2).

6.2.2. General Dosing and Therapeutic Individualization

The proposed indication and dosage of lutetium Lu 177 dotatate for pediatric patients ≥12 years of age with somatostatin receptor-positive GEP-NETs, including foregut, midgut, and hindgut neuroendocrine tumors, are the same as the approved dosage for adult patients. Per the Applicant, the proposed dosage for adolescent patients was supported by similar PK and dosimetry of lutetium Lu 177 dotatate between adolescent and adult patients using population PK and dosimetry modeling for kidney and bone marrow. Per the Applicant, model-predicted kidney and blood dosimetry values in adolescents were comparable to adults. Considering the similar course of GEP-NETs in adults and adolescents, with the use of the same dose regimen as in adults, adolescents are expected to derive the same benefit.

FDA analysis showed that the C_{max} of lutetium Lu 177 dotatate could be up to 30% higher in adolescent patients compared to that of adult patients; however, this difference is not clinically relevant and the conclusions are limited by the small PK sample size. The AUC of lutetium Lu 177 dotatate derived from NETTER-P may over- or under-estimate the AUC from NETTER-1 in adult patients due to differences in PK sampling schedules between adolescent and adult patients. The predicted exposure of lutetium Lu 177 dotatate between adolescent and adult patients by a population PK model is smaller than the observed exposure data as shown in Table 2.

Table 2 Observed and population model predicted exposure of lutetium Lu 177 dotatate in adolescent and adult patients

Study	$AUC_{0\text{-last}}$ (ng*h/mL)	C_{max} (ng/mL)
Observed geomean (CV%)		
NETTER-P (n=9)	41 (24)	12 (33)
NETTER-1 (n=20)	30 (50)	9.0 (73)
Predicted geomean (CV%)		
NETTER-P (n=9)	32 (10)	10 (5)
NETTER-1 (n=20)	31 (41)	6.8 (49)

Source: FDA analysis

The kidney dosimetry data showed high variabilities in both adult and adolescent patients and were mainly collected at the dose level of 7.4 GBq with very limited data at doses below 7.4 GBq as shown in Figure 1 .

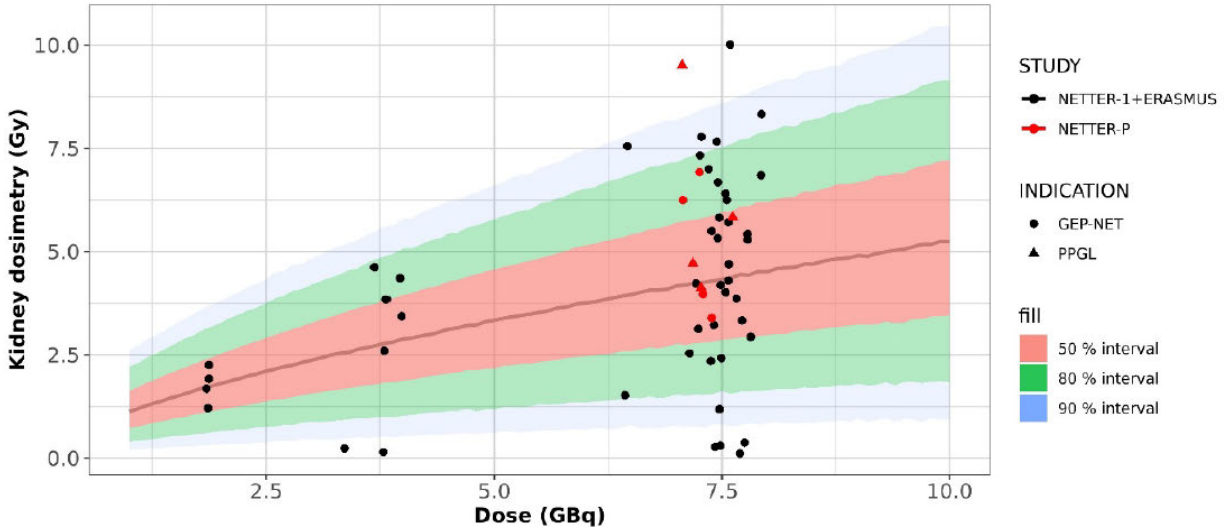


Figure 1 Kidney dosimetry with dose

Source: Sponsor's population pharmacokinetics and dosimetry modeling report for adolescents Figure 7-17, submitted on January 19th, 2024.

Of note, there was a trend toward higher kidney dosimetry in adolescent patients compared to adult patients (Figure 2, Table 3). However, this should be interpreted with caution, as the samples available from adolescents were limited.

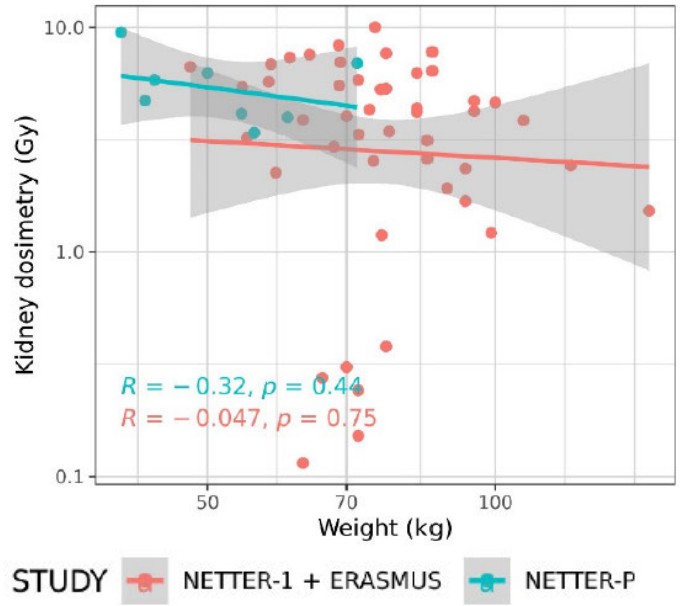


Figure 2 Observed kidney dosimetry in adults and adolescents

Source: Sponsor's population pharmacokinetics and dosimetry modeling report for adolescents Figure 7-14, submitted on January 19th, 2024.

Table 3 Percentage of calculated absorbed dose for 4 × 7.4 GBq for observed dosimetry in kidney exceeding the predefined threshold (23 Gy used in NETTER-1 and 29 Gy used in NETTER-P) in adolescent and adult patients

Kidney dosimetry	> 29 Gy	> 23 Gy
Adult (n=47) NETTER-1+ERASMUS	6 (13%)	12 (26%)
Adolescent (n=9) NETTER-P	2 (22%)	5 (56%)

Source: FDA analysis

Dose and creatinine clearance were used to predict the kidney and bone marrow dosimetry; however, these parameters demonstrated poor prediction performance in capturing variability of kidney dosimetry data. The model predicted kidney dosimetry (> 29 Gy) is higher in adolescents than that in adults, which is consistent with observed data.

Table 4 Predicted probabilities of dosimetry in kidney and bone marrow exceeding the predefined threshold based on dose-dosimetry model in adolescent and adult patients

Predicted	Model	Kidney (Probability (%) >29 Gy)	Bone Marrow (Probability (%) >2 Gy)
Adults (GEP-NET)	Adult Dose-dosimetry model	10.2 (5.2, 16.0)	12.4 (7.6, 17.8)
Adolescent (GEP-NET and PPGL)	Pooled Dose-dosimetry model	21.0 (6.3, 40.3)	2.6 (0.0, 7.1)
Pooled adult GEP-NET and adolescents GEP-NET and PPGL	Pooled Dose-dosimetry model	11.8 (6.2, 17.8)	10.0 (5.2, 15.2)

Source: Applicant response to FDA IR Table 2-5, submitted on February 20th, 2024

Therapeutic Individualization

No dosage adjustment is recommened for pediatric patients (≥12 years of age) at this time given that no significant covariates including body weight and age are identified to have effects on the PK of lutetium Lu 177 dotatate, with the current limited samples size in the population PK model (i.e., n=20 for adults and 9 for adolescents).

Outstanding Issues

None from a clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Office of Clinical Pharmacology recommends the following labeling concepts in the final package insert:

Include in Section 12.3 Specific Populations: Pediatric Patients
There was no clinically relevant differences in exposure of lutetium Lu 177 dotatate in pediatric patients 12 years and older compared to that of adult patients.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Pharmacokinetic data showed no clinically relevant differences in PK exposure between adolescents and adult patients treated at the approved dose. Therefore, evidence of effectiveness is extrapolated from clinical data supporting the original approval of lutetium Lu 177 dotatate. Tumor response data was provided for 8 patients; of these 1 patient with GEP-NET had a complete response by scintigraphy, 6 patients (2 GEP-NET, 4 PPGL) had stable disease, and 1 patient with GEP-NET had progressive disease.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. Based on data from 9 adolescent patients, FDA analyses showed similar PK exposure but higher kidney absorbed doses in adolescents compared to adults following the same flat dose approved for adult patients.

Overall, the clinical pharmacology analyses and conclusions were limited by the small sample size of adolescent patients with PK data, the different PK sampling schedule between adolescent and adult patients, large variability of kidney dosimetry in adults at the same approved dose and absence of PK data at doses below 7.4 GBq in both adults and adolescents. Therefore, a combined approach, that includes the limited clinical pharmacology data and additional clinical considerations (see Clinical review), was used to support FDA's conclusion that the current approved Lutathera dosage provides an optimized benefit-risk profile in pediatric patients ≥12 years of age with GEP-NETs.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

None. See more details in the clinical pharmacology review under the original NDA 208700.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 5: Clinical Study included in the sNDA

Study ID	Study Title and Description	Regimen/Schedule/Route	Study Objectives	Treatment Duration (median weeks)	Number of Treated Patients by Tumor Type
Study CAAA601A32201 (NETTER-P)	A multicenter open-label study to evaluate safety and dosimetry of Lutathera in adolescent patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine (GEP-NET) tumors, pheochromocytoma and paraganglionomas	Lutathera 7.4 GBq (200 mCi) IV every 8 ± 1 weeks for 4 doses	Primary objectives: • Evaluate organ absorbed radiation doses from PRRT with Lutathera in adolescent patients with SSTR-positive GEP-NETs and PPGLs as a pooled cohort • Evaluate safety and tolerability of Lutathera in adolescents with SSTR positive GEP-NETs and PPGL as a pooled cohort	16.3 weeks (range: 8-34.9 weeks).	GEP-NET: 4 PPGL: 5

7.2. Review Strategy

FDA reviewed a single clinical trial, Study CAAA601A32201 (NETTER-P) as the source of clinical data for the supplemental application.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

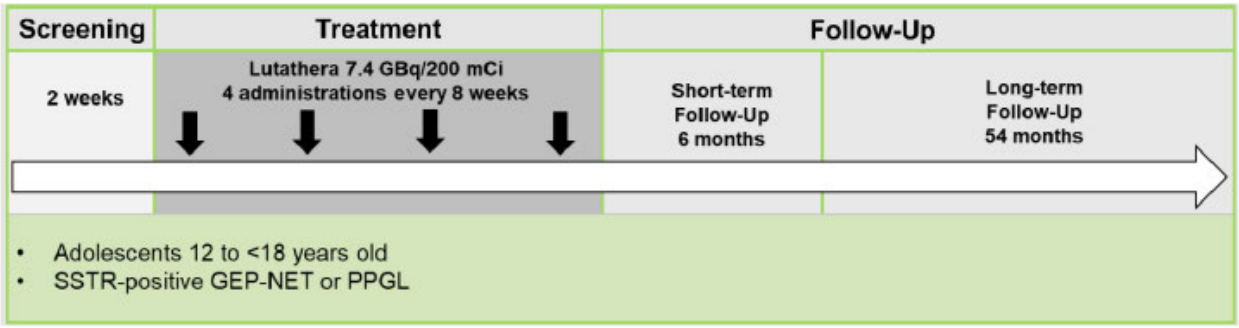
8.1.1. NETTER-P (Study CAAA601A32201)

Trial Design

NETTER-P is an ongoing, open-label, multicenter, single-arm study to evaluate the safety and dosimetry of Lutetium Lu 177 dotatate in adolescent patients with SSTR-positive GEP-NETs or PPGLs. Patients were between 12 and <18 years of age with metastatic or locally advanced SSTR-positve GEP-NET (Grade 1 or Grade 2, well-differentiated) or PPGL.

Treatment with Lutetium Lu 177 dotatate 7.4 GBq (200 mCi) per dose was to be administered once every 8 ± 1 weeks for 4 doses. After completion of treatment, patients enter a short-term follow-up phase (until 6 months after the last dose of Lutetium Lu 177 dotatate) and then a long-term follow-up phase (until 54 months after the last dose of Lutetium Lu 177 dotatate).

Figure 3: NETTER-P Study Design (Source: NETTER-P Study Protocol)



Study Endpoints

The primary endpoints were target organ absorbed radiation doses in adolescents with SSTR-positive GEP-NETs and PPGL as a pooled cohort; and incidence of adverse events (AEs) and laboratory toxicities after the first administration of lutetium 177 Lu dotatate in adolescents with SSTR-positive GEP-NETs and PPGL as a pooled cohort.

Secondary endpoints were incidence of AEs and laboratory toxicities until 6 months and until 5 years after the last dose of lutetium 177 Lu dotatate in adolescents with SSTR-positive GEP-NETs and PPGL as a pooled cohort; and calculated organ absorbed doses and PK parameters based on imaging/blood radioactivity concentration data from adolescent patients with SSTR-positive GEP-NETs and PPGL as a pooled cohort compared to the predicted distribution/organ absorbed doses.

Exploratory endpoints were target organ absorbed radiation doses in adolescents with SSTR-positive GEP-NETs and PPGL as separate cohorts, and incidence of adverse events (AEs) and laboratory toxicities after the first administration of lutetium 177 Lu dotatate in adolescents with SSTR-positive GEP-NETs and PPGL as separate cohorts, incidence of AEs and laboratory toxicities until 6 months and until 5 years after the last dose of lutetium 177 Lu dotatate in adolescents with SSTR-positive GEP-NETs and PPGL as separate cohorts, and ORR, PFS and OS in adolescents with SSTR-positive GEP-NETs and PPGL as separate cohorts.

The reviewers note that time-to-event endpoints such as PFS and OS are not interpretable in a single-arm study.

Statistical Analysis Plan (Source: CSR Appendix 16.1.9 Documentation of statistical methods)

The safety analysis was to be conducted on the safety analysis set which consisted of all patients who received at least one dose of Lutetium Lu 177 dotatate. The safety analysis set is identical to the full analysis set. The dosimetry analysis set consisted of all patients with at least one valid dosimetry measurement and was used for summaries, listings of dosimetry data and modeling. The PK analysis set consisted of all patients with at least one valid PK measurement and was used for listings of PK data and modeling. No statistical hypotheses were tested.

For the primary endpoint target organ absorbed radiation doses, the analysis consisted of descriptive summaries and graphical representations of the absorbed radiation doses in target organs. For the safety primary endpoint, adverse events and laboratory toxicities occurring during the first cycle of treatment were summarized descriptively. AE and SAE summaries were provided for all-causality AEs and those suspected to be related to the study drug by SOC, PT, and severity. Summaries of hematology and biochemistry laboratory data by laboratory parameter include worst post-baseline CTC grade and shift tables.

For the safety secondary endpoints, AE summaries included all AEs occurring during the on-treatment period, and for SAEs and AESIs occurring during the short-term and long-term follow-up phases. Summaries of hematology and biochemistry laboratory data by laboratory parameter include worst post-baseline CTC grade and shift tables presented separately for the on-treatment, short-term follow-up and long-term follow-up phases.

Analyses of exploratory efficacy endpoints were to be based on the full analysis set. Objective response rate (ORR) was to be assessed using RECIST v1.1. Progression Free Survival (PFS) is defined as the time from the date of start of treatment to the date of the first documented/confirmed progression or death due to any cause. Overall Survival (OS) is defined as the time from date of start of treatment to date of death due to any cause. Of note, the Applicant did not provide efficacy summaries due to insufficient/immature data. Instead, the Applicant provided response data as a patient listing with best overall response at each imaging assessment.

Protocol Amendments (Source: CSR Appendix 16.1.1 Protocol and protocol amendments)

The original study protocol for NETTER-P (Version number 00) was submitted to IND 077219 on November 4, 2021. Amendments to the original protocol are summarized below. These amendments did not have an impact on the integrity of the trial or interpretation of the results.

NETTER-P Protocol Amendment 01: May 11, 2022

The primary purpose of Amendment 01 was to modify contraception requirements to align with version 17 of the Investigator's Brochure and current guidelines related to contraception and pregnancy testing in clinical trials, specifically the Sponsor Guideline on Prevention of Pregnancies in Participants in Clinical Trials and the Clinical Trials Facilitation and Coordination Group guideline. Based on these guidelines, the recommended duration of contraceptive use for females of childbearing potential was revised to 7 months from 6 months from the last study treatment, and the recommended duration condom use for male patients with female partners of childbearing potential or pregnant female partners was specified to be 4 months. The protocol was also revised so that female and male patients must be informed of the potential for gonadal toxicity with the study treatment. The protocol was also revised to add recommendations for genetic consultation if the patient wishes to have children after treatment as well as a discussion of cryopreservation of sperm or eggs as an option prior to starting the study treatment.

Additionally, in this amendment, the protocol was revised with the following changes:

- Recommendation added to monitor vital signs during the infusion
- Body temperature added to the vital sign measurements
- Specifying the sterile condition of the amino acid solution
- Correction of an error in the Cockcroft-Gault formula for calculation of creatinine clearance
- Providing guidance to document if the patient has withdrawn consent for the use of data in addition to a study discontinuation
- Adding details of data protection under Ethical Considerations and Administrative procedures
- Infusion rate of lutetium Lu 177 dotatate updated from "400 mL/hr" to "up to 400 mL/hr" to align with USPI
- Editorial changes

NETTER-P Protocol Amendment 02: May 24, 2023

The primary purpose of Amendment 02 was to revise the protocol to include an interim analysis of dosimetry and safety data when at least 5 patients (including at least 2 patients with GEP-NET) have received at least one dose of lutetium Lu 177 dotatate. This interim analysis was added due to initial slow accrual to NETTER-P. For this interim analysis of safety, dosimetry and PK, patients with GEP-NETs and PPGLs were to be analyzed as a pooled cohort goven that results were not expected to differ between disease indications. The Applicant discussed the proposal for an interim analysis with DO2 prior to submission of the amended protocol.

Additionally, based on the recommendation of the Data and Safety Monitoring Board (DSMB), monitoring for microproteinuria during the course of the study treatment was added to the schedule of assessments in the protocol in order to detect early manifestations of renal toxicity.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's statement that Study CAAA601A32201 (NETTER-P) was conducted in accordance with Good Clinical Practice (GCP) guidelines was reviewed in the CSR.

Financial Disclosure

Financial disclosure information was collected for the Investigators (Principal and Sub-investigators) participating in NETTER-P.

The Applicant submitted a list of investigators and FDA forms 3454 and 3455 appeared to adequately discolose the financial interests/arrangements of the clinical investigators. The financial disclosure data does not raise concerns about the integrity of the data.

Patient Disposition

The patient disposition for the NETTER-P full analysis set is summarized in Table 6.

As of the August 21, 2023 data cutoff, 4 (44.4%) patients had completed treatment, 4 (44.4%) patients had treatment ongoing, and 1 (11.1%) of patients had discontinued treatment. The reason for discontinuation was physician decision.

Table 6: NETTER-P Patient Disposition, DCO August 21, 2023, Source: ADSL

	GEP-NET, n (%)	PPGL, n (%)	All, N (%)
Patients treated	4 (100)	5 (100)	9 (100)
Treatment complete	2 (50)	2 (40)	4 (44)
Treatment ongoing	2 (50)	2 (40)	4 (44)
Treatment discontinued	0 (0)	1 (20)	1 (11)
Primary reason for treatment discontinuation			
Physician decision	0 (0)	1 (20)	1 (11)

	GEP-NET, n (%)	PPGL, n (%)	All, N (%)
Patients in short-term follow up	2 (50)	3 (60)	5 (56)
Patients in long-term follow up	0 (0)	0 (0)	0 (0)

Protocol Violations/Deviations (Source: CSR Appendix 16.2.2 Protocol deviations)

In the full analysis set, 4 patients (2 GEP-NET, 2 PPGL) had at least one protocol deviation as of the May 8, 2023 data cutoff. Four protocol deviations were major protocol deviations and 11 were minor. The most frequent (46.7%) protocol deviations were study procedure-related, followed by investigational product (IP) administration-related protocol deviations (20%), laboratory assessment-related protocol deviations (13.3%), and safety and visit schedule-related protocol deviations (6.7% each). No protocol deviations were related to the COVID-19 pandemic.

Overall, the protocol deviations were not considered to have a significant impact on the efficacy or safety conclusions of the study.

Table of Demographic Characteristics

Considering the overall small sample size, the demographics of the population in NETTER-P generally reflect the expected U.S. population (Table 7). Of the full analysis population, 3 (33%) patients were enrolled in the U.S. The Applicant provided an appropriate rationale for applicability of foreign data to the U.S. population, specifically the extreme rarity of pediatric GEP-NETs and similar treatment approaches in the U.S. and European Union.

Table 7: Demographic Characteristics, Data Cut Off August 21, 2023 (Source: ADSL)

	GEP-NET (n=4)	PPGL (n=5)	All (N=9)
Sex, n (%)			
Male	2 (50)	2 (40)	4 (44)
Female	2 (50)	3 (60)	5 (56)
Race, n (%)			
White	2 (50)	2 (40)	4 (44)
Black	1 (25)	0 (0)	1 (11)
Asian	0 (0)	1 (20)	1 (11)
Other	0 (0)	1 (20)	1 (11)
Not reported	1 (25)	1 (20)	2 (22)
Ethnicity, n (%)			
Not Hispanic or Latino	3 (75)	3 (60)	6 (67)
Not reported	1 (25)	2 (40)	3 (33)
Age, years			
Median	15.5	14	15
Range	15-16	13-16	13-16
Country, n (%)			
USA	1 (25)	2 (40)	3 (33)
France	1 (25)	1 (20)	2 (22)
UK	0 (0)	0 (0)	1 (11)
Poland	1 (25)	1 (20)	2 (22)
Spain	1 (25)	0 (0)	1 (11)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline characteristics for pediatric GEP-NET patients (Table 8) were generally similar to those of adult GEP-NET patients enrolled in NETTER-1, specifically with respect to tumor grade and presence of metastatic disease. See original NDA review for more details.

Table 8: Baseline Disease Characteristics, Data Cut Off August 21, 2023 (Source: Adapted from Safety Update, Listing 2.3)

	GEP-NET (N=4)	PPGL (N=5)
Primary tumor site, n (%)		
Adrenal	0 (0)	5 (100)
Pancreas	2 (50)	0 (0)
Stomach	1 (25)	0 (0)
Rectum	1 (25)	0 (0)
Metastatic (Yes), n (%)	4 (100)	5 (100)

	GEP-NET (N=4)	PPGL (N=5)
Functional (Yes), n (%)	2 (50)	NA
Grade, n (%)		
G1	2 (50)	NA
G2	2 (50)	NA
Tumor Type		
Pheochromocytoma	NA	3 (60)
Paraganglionoma	NA	2 (40)
Number of prior lines of systemic therapy, n (%)		
0	0 (0)	5 (100)
1	3 (75)	0 (0)
2	1 (25)	0 (0)
Type of prior systemic therapy, n (%)[a]		
Lanreotide	3 (75)	NA
Temozolomide/capecitabine	2 (50)	NA
Everolimus	1 (25)	NA
Sunitinib	1 (25)	NA
Prior radiotherapy (Yes), n (%)	NA	1 (20)
Prior cancer-related surgery (Yes), n (%)	4 (100)	4 (80)

[a] Patients may be counted in more than 1 row.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use (Source: Safety Update Tables, Listings, Figures; Listing 2.2-1, 2.2-2, 2.2-3)

The most frequently used therapeutic classes of concomitant medications included serotonin 5-HT_3 antagonists (100%), non-opioid analgesics (56%), and corticosteroids (44%). See Section 8.2.2 for summary of exposure.

Efficacy Results – Primary Endpoint

All efficacy endpoints in NETTER-P were exploratory. Please see Efficacy Results – Secondary and other relevant endpoints for a discussion of available efficacy data.

Data Quality and Integrity

The Applicant has provided all the datasets and supporting documentation as requested. There do not appear to be any data quality or integrity concerns.

Efficacy Results – Secondary and other relevant endpoints

Exploratory efficacy endpoints in NETTER-P included ORR, PFS and OS. The Applicant did not perform efficacy analyses due to immaturity of the data. The Applicant provided a listing of tumor assessments and responses based on local radiology review (Safety Update Tables, Listings, Figures; Listing 9-1). As of the August 21, 2023 data cutoff date, four patients had post-baseline tumor assessments and no patient had an objective response. Three of 4 evaluable patients (1 GEP-NET, 2 PPGL) had stable disease, and 1 patient with GEP-NET had progressive disease. PFS and OS are not interpretable in this single-arm study.

Given the immaturity of the available efficacy data at the time of sNDA submission, FDA requested an update on tumor assessments for the 9 treated patients on February 28, 2024. On March 6, 2024, the Applicant responded with the requested information. As of March 6, 2024, 8 patients had post-baseline tumor assessments available. Of these 8 patients, 1 patient had a complete response (CR) as assessed by scintigraphy, 6 patients had stable disease (SD) and 1 patient had progressive disease (PD). The responder was a patient with GEP-NET and evaluable disease who had an investigator-assessed complete response by scintigraphy approximately 41 weeks after the first dose of lutetium Lu 177 dotatate. Of the 6 patients with stable disease, 3 patients (1 GEP-NET, 2 PPGL) had SD at Week 25 after the fourth dose of lutetium Lu 177 dotatate, or 48, 48, and 51 weeks after the first dose of lutetium Lu 177 dotatate. The remaining 3 patients (1 GEP-NET, 2 PPGL) had completed all 4 doses of lutetium Lu 177 dotatate and had stable disease at the Cycle 4, Week 1 assessment, approximately 41 weeks after the first dose. One patient discontinued the study after Cycle 1 and does not have tumor response data available.

Dose/Dose Response

Refer to the Clinical Pharmacology review for dose-response analyses.

Durability of Response

As there were no confirmed objective responses in NETTER-P, this section is not applicable.

Persistence of Effect

See durability of response, above.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Not applicable.

Additional Analyses Conducted on the Individual Trial

Not applicable.

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

This section is not applicable to this review as there was one clinical trial that supported the application. Please refer to the original NDA review dated January 26, 2018 for discussion of the assessment of efficacy across trials for lutetium Lu 177 dotatate in adult patients with GEP-NETs.

Primary Endpoints

Not applicable, see above.

Secondary and Other Endpoints

Not applicable, see above.

Subpopulations

The small sample size and immaturity of the efficacy data submitted for NETTER-P does not allow for meaningful analysis of efficacy between subpopulations.

Additional Efficacy Considerations

Not applicable, see above.

8.1.4. Integrated Assessment of Effectiveness

The primary objectives of NETTER-P were to characterize PK and dosimetry of Lutetium Lu 177 dotatate in adolescent patients with GEP-NETs and PPGL to support extrapolation of exposure from the adult indication. As noted above, efficacy was an exploratory objective in NETTER-P. While the Applicant provided the results of tumor assessments for 8 patients in the full analysis set, including 4 patients with GEP-NETs, the small sample size, single-arm design, and immaturity of the tumor response data do not allow for a meaningful analysis of efficacy based on imaging data from NETTER-P alone, although one patient (11%) with GEP-NET had an investigator-assessed complete response by scintigraphy. Furthermore, the expected response rate from treatment with lutetium Lu 177 dotatate is low based on the observed ORR of 13% (95% CI 7, 19) in adult patients enrolled on NETTER-1. Thus, FDA relied on PK and dosimetry data for extrapolation of the exposure of lutetium Lu 177 dotatate in adolescent patients and thereby its effectiveness in the context of the data from NETTER-1 which supported the original approval.

Additional support for the indication in pediatric patients comes from a review of the published literature performed by the Applicant, which resulted in case reports of 4 pediatric patients with GEP-NET between 8 and 13 years of age who were treated with 4-5 cycles of lutetium Lu 177 dotatate. Three of the 4 patients had a decrease in tumor size on imaging accompanied by improvement in clinical symptoms, and the fourth had stable disease for 4 years after

treatment with lutetium Lu 177 dotatate. The majority of adverse events were hematologic toxicities; no renal toxicity was reported (Foster et al 2021, Parelkar et al 2020, Potter et al 2018, Yesil et al 2016).

8.2. Review of Safety

8.2.1. Safety Review Approach

The overall safety population is comprised of 9 adolescent patients with SSTR-positive GEP-NETs or PPGLs who received at least one dose of lutetium Lu 177 dotatate in study NETTER-P based on the August 21, 2023 data cut-off.

8.2.2. Review of the Safety Database

Overall Exposure

The dosing regimen for lutetium Lu 177 dotatate was 7.4 GBq (200 mCi) every 8 ± 1 weeks for a total of 4 doses. As of August 21, 2023, the median number of doses of lutetium Lu 177 dotatate administered was 2, with 4 patients receiving 4 doses, 2 patients receiving 2 doses and 3 patients receiving 1 dose.

The median duration of exposure was 16.3 weeks (range: 8-34.9 weeks). Of note, 44% of patients in the safety population remain on treatment as of the data cutoff. One patient (11%) discontinued treatment due to physician decision. See clinical pharmacology review and Division of Imaging and Radiation Medicine consult for additional details.

Adequacy of the safety database:

The design of NETTER-P, including the frequency of assessments collected, the number of patients treated, and the extent of exposure to lutetium Lu 177 dotatate, was adequate to characterize the safety of lutetium Lu 177 dotatate in adolescent patients with SSTR-positve GEP-NETs. The safety population studied in NETTER-P adequately represents the target population, including demographics, disease and other baseline characteristics.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant has provided all datasets and supporting documentation as requested during the course of the review. There were no data quality or integrity concerns impacting FDA's review.

Categorization of Adverse Events

The reported verbatim AE term was assigned a preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0 and categorized by System Organ Class (SOC). Treatment-emergent adverse events (TEAEs) were defined as those with onset (or worsening)

after administration of the first dose of study drug. The analyses described in this submission were based on TEAEs, unless otherwise specified, and are denoted as "AEs" in this review.

The severity of each AE was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. AEs were summarized by presenting the number and percentage of participants having at least 1 AE by SOC and by (PT), maximum severity grade, and relationship to the study drug as assessed by the investigator.

Routine Clinical Tests

Laboratory assessments were performed at baseline prior to lutetium Lu 177 dotatate dosing, at regularly scheduled intervals and when medically necessary during drug administration. Additionally, vital sign measurements, physical exams, performance status, ECG tracings and pregnancy testing were collected to allow for adequate safety mornitoring.

8.2.4. Safety Results

Deaths

No deaths have been reported as of the August 21, 2023 data cut off. Due to the limited safety follow-up data available for patients in NETTER-P at the time of the August 21, 2023 data cut off, FDA requested an additional update on deaths in NETTER-P during the review cycle. As of April 1, 2024, no additional deaths due to AEs have been reported.

Serious Adverse Events

Serious adverse events (SAEs) were reported in 1 (11%) patient with GEP-NET. This patient is a 15 year old male with metastatic GEP-NET (abdomen, liver, lung, lymph nodes and mediastinum) who had SAEs of Grade 3 lower gastrointestinal hemorrhage and Grade 3 hypercalcemia. Per the Applicant's narrative, the patient developed a Grade 3 lower gastrointestinal hemorrhage on Cycle 1, day 11 in the setting of colitis, which was confirmed with an abdominal CT scan. The etiology of the colitis was not known but the patient had a history of bacterial overgrowth in the gastrointestinal tract which may be a confounding factor. Treatment included paracetamol, oxycodone and sodium chloride. The event resolved on Cycle 1, day 12 and the patient went on to complete his treatment course. On study day 210, 38 days after receiving the fourth dose of lutetium Lu 177 dotatate, the same patient developed Grade 3 hypercalcemia requiring hospitalization. He was treated with zoledronic acid and paracetamol and hypercalcemia improved to Grade 2 the following day. Confounding factors include a history of multiple endocrine and electrolyte disorders including Cushing's syndrome, diabetes, hyperthyroidism, hypokalemia and adrenal insufficiency. Relevant concomitant medications included calcium chloride and calcium carbonate.

Due to the limited safety follow-up data available for patients in NETTER-P at the time of the August 21, 2023 data cut off, FDA requested an additional update on SAEs reported in NETTER-P during the review cycle. As of April 1, 2024, there was one additional SAE of Grade 3 catheter-

related infection reported. The outcome was recovered/resolved and no action was taken with lutetium Lu 177 dotatate.

Dropouts and/or Discontinuations Due to Adverse Effects

No AEs leading to discontinuation have been reported as of the August 21, 2023 data cut off. Due to the limited safety follow-up data available for patients in NETTER-P at the time of the August 21, 2023 data cut off, FDA requested an additional update on discontinuations reported in NETTER-P during the review cycle. As of April 1, 2024, there were no discontinuations due to AEs.

Significant Adverse Events

AEs leading to dose modification were reported in 1 (11%) patient. The patient had an AE of Grade 3 neutropenia during Cycle 3 which resulted in a dose reduction of Lutetium Lu 177 dotatate by 50%, consistent with dose modification guidelines described in the protocol for Cycle 4.

AEs leading to interruption of lutetium Lu 177 dotatate infusion occurred in 2 (22%) patients. One patient had a Grade 1 infusion related reaction which resolved the same day with no additional therapy. One patient had an AE of Grade 1 headache which resolved the same day and did not require additional treatment. In both cases, the infusion was resumed at the same dose.

Adverse events of special interest (AESIs) were reported in 6 (67%) patients. The Applicant considered secondary malignancies, hematotoxicities, nephrotoxicities, endocrine disorders, bone development disorders, and cardiovascular and electrolyte disorders as AESIs in NETTER-P. The small number of patients in NETTER-P and limited follow-up does not allow for analysis of long-term toxicities such as secondary malignancies, endocrine disorders and bone development disorders.

Hematotoxicities occurred in 5 (56%) patients in NETTER-P, and Grade 3 hematotoxicities occurred in 3 (33%) patients. For FDA's analysis, the reported PTs anemia, leukopenia, lymphocyte count decreased, lymphopenia, neutropenia, neutrophil count decreased and white blood cell count decreased were categorized as hematotoxicities (see Table 9). One patient required a dose reduction in Lutetium Lu 177 dotatate due to Grade 3 neutropenia. Abnormalities in hematologic laboratory parameters were common in NETTER-P (see Table 10).

AESIs under the category of nephrotoxicities were reported in 1 (11%) patient (Grade 3 portal vein thrombosis) based on the Applicant's Case Retreiving Strategy; however, after review of the narrative provided for this patient, FDA determined that this was not associated with nephrotoxicity. Three (33%) patients had Grade 1 increases in creatinine, however these were not reported as AEs.

One AESI related to cardiovascular and electrolyte disorders was reported (loss of consciousness, Grade 1).

Due to the limited safety follow-up data available for patients in NETTER-P at the time of the August 21, 2023 data cut off, FDA requested an additional update on AESIs reported in NETTER-P during the review cycle. As of April 1, 2024, 3 patients had additional AESIs. All AESIs since the August 21, 2023 data cut off were categorized as hematotoxicities and included lymphopenia (Grade 3, 3 patients), neutropenia (Grade 3, 2 patients) and leukopenia (Grade 3, 1 patient).

Treatment Emergent Adverse Events and Adverse Reactions

In NETTER-P, treatment-emergent AEs (TEAEs) occurred in 9 (100%) patients. Grade 3 TEAEs occurred in 3 (33%) patients, and no patient had a Grade 4 or Grade 5 TEAE. The most common (≥33%) TEAEs were consistent with the known safety profile of Lutetium Lu 177 dotatate and included headache, fatigue, lymphopenia, abdominal pain, epistaxis, nausea and neutropenia.

Table 9 summarizes the TEAEs that occurred in ≥10% of patients in NETTER-P.

Table 9: Treatment Emergent Adverse Events **(≥10%)** in NETTER-P Safety Set, Data Cut Off August 21, 2023 (Source: ADAE)

Adverse Event	NETTER-P (n=9)	
	Grades 1-4[a] (%)	Grades 3-4 (%)
Nervous System Disorders		
Headache	56	0
Dizziness	22	0
Hypersomnia	11	0
Loss of consciousness	11	0
General Disorders and Administration Site Conditions		
Fatigue[b]	44	0
Influenza like illness	11	0
Blood and Lymphatic System Disorders		
Lymphopenia[c]	44	22
Neutropenia[d]	33	22
Anemia	22	11
Leukopenia	22	0
Gastrointestinal Disorders		
Abdominal pain[f]	33	0
Nausea	33	0
Diarrhea[g]	22	0
Abdominal distension	11	0

Adverse Event	NETTER-P (n=9)	
Flatulence	11	0
Vomiting	11	0
Vascular Disorders		
Epistaxis	33	0
Lower gastrointestinal hemorrhage	11	11
Portal vein thrombosis	11	11
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[h]	22	0
Muscle spasms	11	0
Ear and labyrinth disorders		
Tinnitus	11	0
Eye disorders		
Photophobia	11	0
Infections and Infestations		
Upper respiratory tract infection	11	0
Injury, poisoning and procedural complications		
Infusion related reaction	11	0
Investigations		
Weight decreased	11	0
Metabolism and nutrition disorders		
Hypercalcemia	11	11
Hyperuricemia	11	0
Hypophosphatemia	11	0
Psychiatric disorders		
Insomnia	11	0
Phonophobia	11	0
Renal and urinary disorders		
Urinary incontinence	11	0
Skin and subcutaneous tissue disorders		
Dry skin	11	0
Eczema	11	0
Pityriasis	11	0

a. Grades per National Cancer Institute CTCAE v5.0.
b. Fatigue includes fatigue, asthenia.
c. Lymphopenia includes lymphocyte count decreased, lymphopenia.
d. Neutropenia includes neutrophil count decreased, neutropenia.
e. Leukopenia includes leukopenia, white blood cell count decreased.
f. Abdominal pain includes abdominal pain, abdominal pain upper.
g. Diarrhea includes diarrhea, colitis.
h. Musculoskeletal pain includes back pain, arthralgia.

Laboratory Findings

Laboratory abnormalities occurring in NETTER-P were consistent with the known safety profile

of lutetium Lu 177 dotatate. The most common (≥33%) laboratory abnormalities were decreased lymphocyte count, anemia, decreased white blood cell count, decreased neutrophil count, hypomagnesemia, and increased creatinine.

Table 10 summarizes the laboratory abnormalities that occurred in ≥10% of patients in NETTER-P.

Table 10: Post-Baseline Laboratory Abnormalities **(≥10%)** in NETTER-P Safety Set, Data Cut Off August 21, 2023, (Source: ADLB; Safety Update Listings 5-1, 5-2, 5-3, 5-4)

	NETTER-P (N=9)	
Laboratory Abnormality	Grades 1-4[a] (%)	Grades 3-4 (%)
Chemistry		
Decreased magnesium	44	0
Increased creatinine	33	0
Increased alkaline phosphatase	22	0
Increased bilirubin	22	0
Increased potassium	22	0
Decreased sodium	22	0
Decreased albumin	11	0
Increased calcium	11	11
Increased GGT	11	0
Increased LDH	11	0
Decreased potassium	11	0
Hematology		
Decreased lymphocytes	100	33
Decreased hemoglobin	78	0
Decreased leukocytes	67	11
Decreased neutrophils	44	22
Decreased platelets	22	0

a. Grades per National Cancer Institute CTCAE v5.0.

Vital Signs

No new significant findings were identified in FDA's evaluation of the vital signs dataset. In the overall safety population (n=9), the median weight was 54.2 kg (range 39.5 to 75). The median temperature was 36.6 degrees Celsius (range 35.7 to 37). The median heart rate was 79.5 beats per minute (range 59-124). The median systolic blood pressure was 120 mmHg (range 89-140). The median diastolic blood pressure was 73 mmHg (range 46-91).

Electrocardiograms (ECGs)

ECG assessments were conducted at baseline, immediately after each lutetium Lu 177 dotatate/amino acid infusion, at the end of treatment visit and as clinically indicated. ECGs were performed in triplicate.

QT

Per the Applicant's review of ECG assessments, there were no QT/QTcF values ≥450 msec. QT increases of >30 ms to ≤60 ms were reported in 2 patients and a QTcF increase of >30 ms to ≤60 ms was reported in 1 patient. These QT increases were not considered clinically significant and were not reported as AEs during the study.

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

Not applicable.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

The small sample size of the safety population precluded interpretable comparisons between demographic subgroups.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No new information related to human carcinogenicity is provided in the current submission.

Human Reproduction and Pregnancy

Embryo-fetal toxicity is currently included in the Warnings and Precautions section of the label. Female patients who were known to be pregnant or breastfeeding were excluded from NETTER-P. Birth control measures during treatment and and ongoing pregnancy screening were

enforced to ensure that no fetus was exposed to lutetium Lu 177 dotatate. No pregnancies of female subjects or female partners of male subjects were reported on NETTER-P as of the August 21, 2023 data cut off.

Pediatrics and Assessment of Effects on Growth

While NETTER-P is designed to assess growth and development, reproductive and endocrine function for each patient, the limited follow-up for the patients in the full analysis set precludes a meaningful assessment of the long-term effect of lutetium Lu 177 dotatate on pediatric growth and development.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Safety PMRs

FDA issued 2 safety PMRs with the initial approval of lutetium 177 Lu dotatate in January 2018:

1. PMR 3326-01: Submit cumulative, integrated safety analyses after 5 and after 10 years of follow-up from an adequate number of patients enrolled in clinical trials to identify and characterize the risk of renal failure with Lutathera; include incidence rates, time to onset, predisposing factors and outcomes. These safety evaluations should be adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modifications and monitoring recommendations.

2. PMR 3326-02: Submit cumulative, integrated safety analyses after 5 and after 10 years of follow-up from an adequate number of patients enrolled in clinical trials to identify and characterize the risks of myelodysplastic syndrome and acute leukemia with Lutathera; include incidence rates, time to onset, predisposing factors and outcomes. These safety evaluations should be adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modifications and monitoring recommendations.

The Applicant submitted an interim safety report on December 15, 2023 for Study CAAA601A12402, titled “An International, Non-Interventional, Post-Authorization Long-Term Safety Study of Lutathera®, in Patients with Unresectable or Metastatic, Well-Differentiated, Somatostatin Receptor Positive, Gastroenteropancreatic Neuroendocrine Tumors (SALUS study) to address the above PMRs. The full analysis set for the interim report included 867 patients. Second primary malignancies were reported in 23 patients (2.7%, 95% CI: 1.74, 3.89). Among patients with second primary malignancies, 15 had at least one solid tumor event and 8

patients had at least one hematological event, including 5 patients who developed MDS. No patient developed leukemia. Renal dysfunction was reported in 15% of patients, with 4% of patients developing Grade ≥3 renal dysfunction. The final report submission is expected in December 2025.

Expectations on Safety in the Postmarket Setting

Given the similar disease biology, presentation and course of GEP-NETs in the pediatric and adult populations, similar mechanism of action of Lutetium Lu 177 dotatate, and similar short-term toxicities observed in the adult and pediatric populations, it is expected that the toxicity profile will be similar between pediatric and adult patients in the postmarket setting. See Section 13 for postmarketing requirements in pediatric patients.

8.2.11. Integrated Assessment of Safety

The AEs observed in NETTER-P were generally consistent with the known safety profile of lutetium Lu 177 dotatate from adult studies. Given the small sample size and limited follow-up for patients in NETTER-P, the Applicant performed a literature search and a global safety database search to provide additional safety information. The literature search included case resports, clinical studies and review articles describing the use of lutetium Lu 177 dotatate and yttrium Y 90 dotatoc, a similar radiolabeled somatostatin analogue, in pediatric patients with SSTR-positive tumors. Hematotoxicities were the most commonly reported toxicities in pediatric patients in the published literature. Low-grade creatinine increases were also reported in pediatric patients. Grade 3-4 nephrotoxicity was occasionally reported in articles presenting aggregate data from pediatric and adult patients; it was not clear whether these toxicities occurred in pediatric or adult patients. Limited follow-up data up to 5 years were available from a small number of studies the published literature, however there were no reports of myelodysplastic syndrome or secondary malignancies in pediatric patients. The Applicant's search of a global safety database (data lock date April 30, 2023) yielded 15 cases excluding those from patients enrolled on NETTER-P. AEs in these safety reports included disease progression, infusion related reaction, fatigue, pyrexia, and oropharyngeal pain. There were 6 cases of pediatric off-label use of lutetium Lu 177 dotatate without AEs reported. Overall, the AEs reported in the literature were similar to those observed in NETTER-P and in the adult population.

8.3. Statistical Issues

There were no major statistical issues identified during the review of this application, and no formal hypotheses were tested in NETTER-P. Exploratory endpoints of PFS and OS were considered descriptive as time-to-event endpoints are not interpretable in a single-arm study.

8.4. Conclusions and Recommendations

The recommendation for traditional approval of lutetium Lu 177 dotatate for the

treatment of pediatric patients 12 to <18 years with SSTR-positive GEP-NETs, including foregut, midgut and hindgut tumors is based on data from 9 pediatric patients in Study NETTER-P. Despite limited efficacy data available from the pediatric patients, the PK data submitted demonstrated reasonably similar exposures with no clinically relevant differences between the adult and adolescent populations. Dosimetry data was notable for a lower mean absorbed dose in a majority of organs in adolescents, but a higher mean absorbed dose to the kidney, adrenals, small intestines, and urinary bladder wall.

According to FDA Guidance for Industry, the extrapolation of effectiveness from adult populations to pediatric populations may be appropriate if the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients. Extrapolation of effectiveness assumes that an appropriate pediatric dose can be established through several means, including the achievement of a similar exposure in children as in adults (FDA Guidance for Industry, July 2020). A statistically significant and clinically meaningful improvement in PFS was observed in adult patients treated with lutetium Lu 177 dotatate compared to patients treated with long-acting octreotide in NETTER-1. Given the overall similarities in disease course across adolescent and adult GEP-NETs and the mechanism of the drug, it is expected that lutetium 177 Lu dotatate will be similarly effective in the pediatric population. In addition, there was one investigator-assessed complete response among the 9 adolescent patients enrolled in NETTER-P as of March 6, 2024. The relatively low ORR is consistent with the ORRs observed in the NETTER-1 study at 13% (95% CI: 7%, 19%).

FDA review of the safety data from NETTER-P did not reveal new safety signals in the pediatric population. The most common (≥33%) TEAEs were consistent with the known safety profile of Lutetium Lu 177 dotatate and included headache, fatigue, lymphopenia, abdominal pain, epistaxis, nausea and neutropenia. Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, decreased leukocytes, decreased neutrophils and increased calcium. Analysis of the dosimetry data showed higher absorbed radiation doses to the kidney than were observed in adult patients; however, there were no severe acute renal toxicities reported in NETTER-P. A PMR will be issued to assess long-term renal toxicity in pediatric patients. Similarly, while pediatric patients are at higher risk of other long-term radiation toxicities including secondary malignancies, the limited follow-up for patients in NETTER-P did not allow for an assessment of this risk. As such, a PMR will be issued to assess the risk of myelodysplastic syndrome and leukemia in pediatric patients.

The benefit:risk profile for this indication is favorable, with the results of NETTER-P providing substantial evidence of effectiveness of lutetium Lu 177 dotatate for the treatment of adolescent patients with SSTR-positive GEP-NETs. Although the number of patients studied was small, pediatric GEP-NETs are exceedingly rare, the toxicity data observed in the adolescent patients was consistent with the known safety profile of the drug and the PK and dosimetry data were relatively similar between adults and adolescents. Therefore, extrapolation of efficacy of lutetium Lu 177 dotatate from the adult population is acceptable. Based on the favorable risk-benefit assessment for this population with a high unmet medical need and a

serious, life-threatening disease, traditional approval is recommended for the following indication:

> Lutetium Lu 177 dotatate (Lutathera) is indicated for the treatment of adult and pediatric patients 12 years and older with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors.

9 Advisory Committee Meeting and Other External Consultations

Not applicable. The review team did not refer this application to an advisory committee as no significant efficacy or safety issues were identified during the review which required external input for the proposed indication.

10 Pediatrics

The study supporting this sNDA (NETTER-P) was a pediatric study. As such, the label will be updated with information for use in the pediatric population as described throughout the review above.

This submission included a request for Pediatric Exclusivity Determination The Pediatric Exclusvity Board determined that the Applicant fairly responed to the terms of the Written Reqeust and exclusivity will be granted.

This application is exempt from the requirements under the Pediatric Research Equity Act. Lutetium Lu 177 Dotatate (Lutathera) received orphan designation for the treatment of patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in January 2009.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases. The table below summarizes high level key changes.

Label Section	Applicant Proposal	FDA Revision (agreed text)
1 INDICATIONS AND USAGE	(b) (4)	Editorial revision: LUTATHERA is indicated for the treatment of ***adult and pediatric patients 12 years and older*** with somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors.
2.5 Preparation and Administration		Inclusion of instructions to prevent and mitigate extravsation: Administration Instructions •*Prior to administration, flush the intravenous catheter used for LUTATHERA administration with ≥ 10 mL of 0.9% Sodium Chloride Injection, USP to ensure patency and to minimize the risk of extravasation. Manage cases of extravasation as per institutional guidelines.*
2.6 Radiation Dosimetry	***The maximum penetration of lutetium-177 in tissue is 2.2 mm and the mean penetration is 0.67 mm.*** The mean and standard deviation (SD) of the estimated radiation absorbed doses for adults receiving	FDA accepts these revisions.

	LUTATHERA are shown in Table 3. (b) (4) [redacted] ***The mean and SD of the estimated radiation absorbed doses for pediatric patients 12 years and older receiving LUTATHERA are shown in Table 4.*** New table added: Table 4. Estimated Radiation Absorbed Dose for LUTATHERA in Pediatric Patients 12 Years and Older in NETTER-P	
6.1 Clinical Trials Experience	Pediatric population (b) (4) [redacted]	Revisions for clarity. Added details specific to this broadened indication. Pediatric Population ***NETTER-P*** ***Safety data are available from 9 pediatric patients in NETTER-P (NCT04711135), an international, multi-center, single-arm, open-label trial of patients with somatostatin receptor-positive tumors, including 4 patients with GEP-NETs. Patients received LUTATHERA 7.4 GBq (200 mCi) administered every 8 weeks concurrently with the recommended amino acid solution. Adverse reactions observed in NETTER-P were similar to those observed in adults treated with LUTATHERA.***
8.4 Pediatric Use Somatostatin Receptor-Positive Gastroenteropancreatic		Revised for clarity and brevity. Removed (b) (4) [redacted] statement, as not informative to healthcare providers,

Neuroendocrine Tumors	(b) (4)	Use of LUTATHERA for this indication is supported by evidence from an adequate and well-controlled study of LUTATHERA in adults with additional safety, pharmacokinetic, and dosimetry data in pediatric patients aged 12 years and older with somatostatin receptor-positive tumors, including 4 pediatric patients with GEP-NETs *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)].* Removed (b) (4) FDA added the following: The risks of radiation exposure associated with LUTATHERA are greater in pediatric patients than in adult patients due to longer life expectancy. Continued follow-up is recommended for evaluation of long-term effects. There was no clinically relevant difference in lutetium Lu 177 dotatate exposure in pediatric patients aged 13 to 16 years versus adult patients *[see Clinical Pharmacology (12.3)]*.
12.3 Pharmacokinetics	Special populations Pediatric patients (b) (4)	Revised for brevity. Special populations Pediatric patients There were no clinically relevant differences in exposure of lutetium Lu 177 dotatate in

	(b) (4)	pediatric patients 12 years and older compared to that of adult patients.

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable to this submission.

13 Postmarketing Requirements and Commitment

FDA has issued 2 safety post marketing requirements for Lutetium Lu 177 dotatate in adolescent patients (age 12 to 17 years):

- Conduct cumulative, integrated safety analyses after 5 and after 10 years of follow-up from pediatric patients ages 12 to 17 enrolled in clinical trials to further characterize the known serious risk of renal failure with Lutetium Lu 177 dotatate; include incidence rates, time to onset, predisposing factors and outcomes. These safety evaluations should adequately characterize the serious risk of renal failure in patient populations at highest risk and provide evidence-based dose modifications and monitoring recommendations as appropriate.

- Conduct cumulative, integrated safety analyses after 5 and after 10 years of follow-up from pediatric patients ages 12 to 17 enrolled in clinical trials to further characterize the known serious risks of myelodysplastic syndrome (MDS) and acute leukemia with Lutetium Lu 177 dotatate; include incidence rates, time to onset, predisposing factors and outcomes. These safety evaluations should adequately characterize the serious risks of MDS and acute leukemia in patient populations at highest risk and provide evidence-based dose modifications and monitoring recommendations as appropriate.

Appendices

13.1. References

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13.2. Financial Disclosure

No disclosable financial information was reported by any of the clinical investigators provided in the Applicant's listing, and no clinical investigators are full or part-time employees of Advanced Accelerator Applications or Novartis. As study NETTER-P is ongoing, the Applicant is continuing collection of financial disclosures. The information below is current as of August 31, 2023.

Covered Clinical Study (Name and/or Number): NETTER-P

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 62		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/a		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

N/A

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

13.4.1. Population PK Analysis

13.4.2. Executive Summary

A PopPK model was developed to support the dose rationale for pediatric patients based on pharmacokinetic (PK) predictions from a total of 9 adolescents (including 4 participants with GEP-NET and 5 participants with PPGL), which were included in this NDA. These activities included the following objectives:

- Confirm comparable exposure between adults and adolescents;
- Provide support for the proposed flat dosing in adolescents

Method: Monolix was used to develop the popPK model using data from adolescent patients enrolled in NETTER-P collected after one cycle of intravenous infusion of [177Lu] Lu-DOTA-TATE. A two-compartment, zero order input with first-order elimination, and parameterized in terms of clearance and volume model was used to describe the PK data. The impact of demographic covariates (e.g., age, weight, gender, body surface area (BSA), and creatinine clearance (CLcrCLcr)) were assessed using stepwise covariate model-selection (SCM) approach, and were finalized by horseshoe prior approach. The final model was qualified by numerical and graphical goodness of fit (GOF) checks, including visual predictive checks (VPCs).

Results: Population PK dataset contained 45 PK observations from 9 adolescent patients from NETTER-P. The observed PK data was best described by a two-compartment, zero order input with first-order elimination, parameterized in terms of clearance and volume, with the addition of random effects on clearance (CL) and no covariate effects after intravenous infusion administration. For a typical subject with CLcr = 123 mL/min, the clearance was estimated to be 6.1 L/h and the central volume of distribution (V1) was estimated to be 18 L. The intercompartmental clearance (Q2) and peripheral volume of distribution (V2) were estimated at 2.6 L/h and 96 L, respectively. The popPK parameters estimated for adolescents were within the range of popPK parameters estimated for adults.

Conclusions:

- The review team found model fitting is generally acceptable, although there were some deviations between observed and predicted parameters at lower and higher drug concentrations.

- No significant covariates effects were identified in the final model. However, the covariate analysis is limited by the small sample size included in the popPK analysis.
- Based on the popPK modeling, similar [^{177}Lu] Lu-DOTA-TATE exposure (i.e., AUC, Cmax) between adults and adolescents was observed, while the observed PK exposure in adolescents was slightly higher compared to those in adults.

13.4.3. PPK Assessment Summary

The adolescent population PK was best described by a two-compartment, zero order input with first-order elimination, parameterized in terms of clearance and volume, with the addition of random effects on clearance and no covariate effects after intravenous infusion administration. Based on the final popPK model, the exposure was comparable across GEP-NET and PPGL patients in NETTER-P. Similar PK exposure metrics (including the variability) between adults and adolescents were also confirmed.

General Information		
Objectives of PPK Analysis		• Confirm comparable exposure between adults and adolescents; • Provide support for the proposed recommended dosage in adolescents
Studies Included		NETTER-P, NETTER-1
Dose(s) Included		7.4 GBq (multiple dose)
Population Included		Participants with GEP-NET or PPGL
Population characteristics	Pediatrics	Age median (range): 15 yrs (13-16) Weight median (range): 53 kg (40,71) Male: 4 (44%); Female: 5 (56%) GEP-NET: 4 (44%); PPGL: 5 (56%)
	Adults	Age median (range): 58 yrs (29, 73) Weight median (range): 76 kg (48, 145) Male: 11 (55%); Female: 9 (45%) GEP-NET: 20 (100%)
No. of Patients and PK Samples		9 adolescent participants; 45 PK samples 20 adult participants; sparse sampling
Sampling Schedule		NETTER-P: Pre-dose, end of infusion, 120min ± 30min, 6h ± 30min, 24h ± 2h, 72h ± 2h
Covariates Evaluated	Static	Age, weight, gender, height, body surface area (BSA), indication
	Time-varying	Creatinine clearance

Final Model	Summary	Acceptability [FDA's comments]
Software and Version	Monolix (Suite 2021 R2) Simulx (2021 R2)	Yes
Model Structure	Two-compartment, zero order input with first-order elimination, parameterized in terms of clearance and volume model	Yes
Model Parameter Estimates	Table 1Table 11	Yes
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	In the final model, all parameters were estimated with sufficient precision with RSE < 34%. IIV (%RSE) was 33.12% (CL). Residual variability was described by an addition error model with estimate of 11.87% RSE (CL).	Yes
GOF, VPC	Diagnostic GOF plots from final model are in figures below. VPCs are in figures below.	Yes, acceptable model fittings with some deviations at higher and lower drug concentrations.
Significant Covariates and Clinical Relevance	No covariates	The covariate effects cannot be identified due to limited data.
Analysis based on Simulation (optional)	Predicted exposures provided in Table 12 below.	Full PK profiles were predicted based on individual parameters estimated by the final popPK model, which were then compared with the observed exposures characterized by NCA analysis. There were no clinically relevant differences in exposure of lutetium Lu 177 dotatate in pediatric patients 12 years and older compared to that of adult patients.

Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	The pharmacokinetics (PK) of lutetium Lu 177 dotatate have been characterized in patients with progressive, somatostatin receptor-positive neuroendocrine tumors. The mean blood exposure (area under the curve) 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. <u>Distribution</u> The mean volume of distribution (Vz) for lutetium Lu 177 dotatate is 460 L (CV 54%). The non-radioactive lutetium Lu 175 dotatate is 43% bound to human plasma proteins. Within 4 hours after administration, lutetium 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%.	Generally acceptable. FDA revised the section about pediatric patients in the labeling. <u>Specific populations</u> *Pediatric patients* There were no clinically relevant differences in exposure of lutetium Lu 177 dotatate in pediatric patients 12 years and older compared to that of adult patients.

	Elimination The mean clearance (CL) is 4.5 L/h (CV 31%) and the mean terminal half-life is 71 (±28) hours for lutetium 177 dotatate. Metabolism Lutetium Lu 177 dotatate does not undergo hepatic metabolism. 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% of the administered radioactivity will be eliminated within 14 days after administration of LUTATHERA [see Warnings and Precautions (5.1)]. Specific populations *Pediatric patients* (b) (4)	

	(b) (4) Drug Interaction Studies In Vitro Studies CYP450 enzymes: The non-radioactive lutetium Lu 175 dotatate is not an inhibitor or inducer of cytochrome P450 (CYP) 1A2, 2B6, 2C9, 2C19 or 2D6 in vitro. Transporters: The non-radioactive lutetium Lu 175 dotatate is not an inhibitor of P-glycoprotein, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, or OATP1B3 in vitro.	

Table 11: Parameter Estimates of the Final PopPK Model

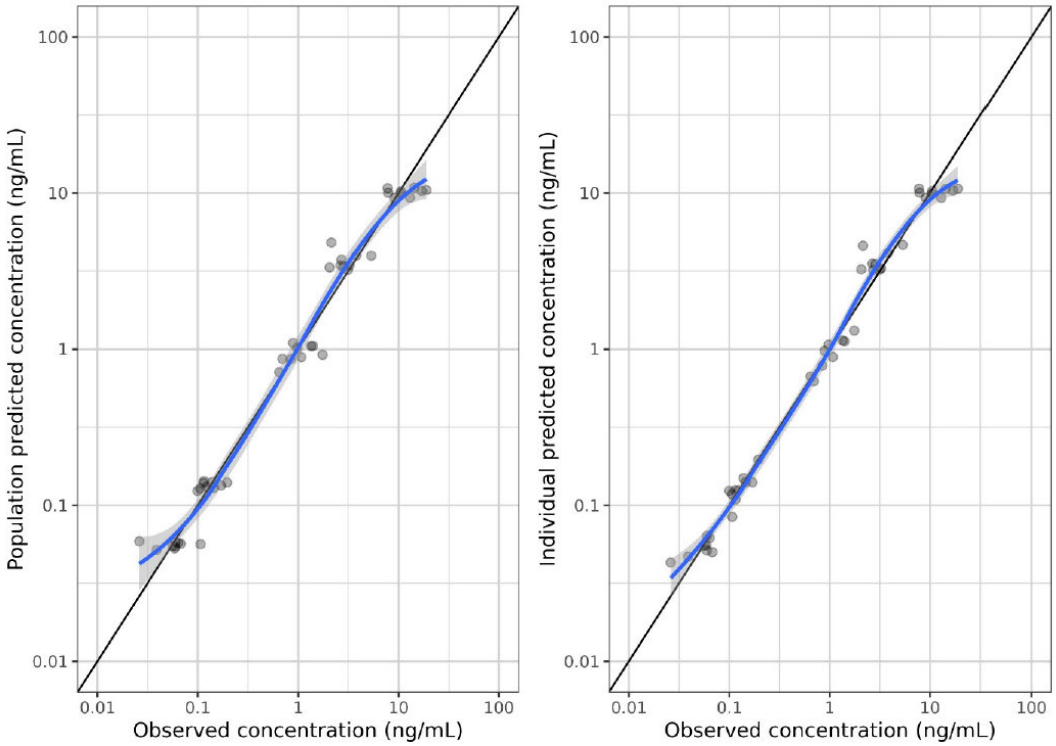
Parameter	Parameter estimate	RSE (%)
Cl (L/h)	6.14	5.79
V1 (L)	18.07	8.36
Q2 (L/h)	2.62	10.43
V2 (L)	96.03	16.83
ω_{Cl}	0.12	33.12
Constant residual error	0.27	11.84

%RSE: %Relative standard error as defined by SE/estimate * 100%

$\omega_{parameter}$: standard deviation for the random effects (parameter)

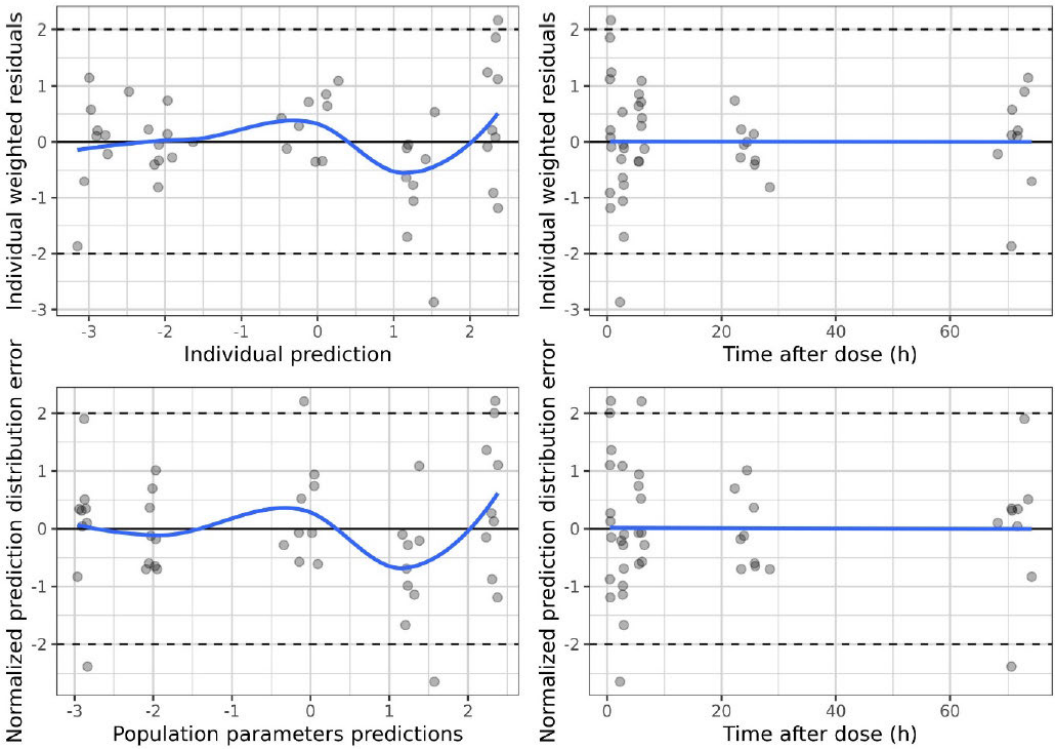
Cl: clearance from the central compartment, V1: volume of distribution of the central compartment, V2: volume of distribution of the peripheral compartment, Q2: intercompartmental clearance

Figure 4: Observed versus Individual and Population Predicted Concentrations – Final PoPK Model



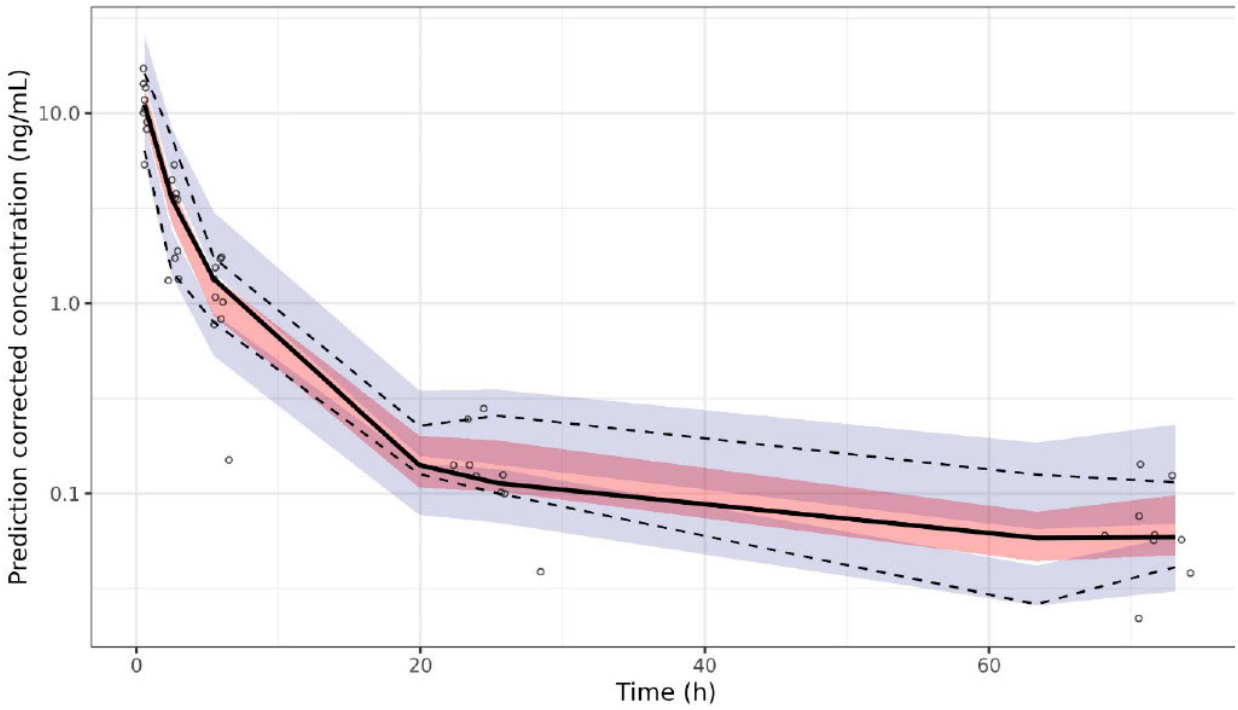
Black dots: the concentrations, Black line: the identity line, Blue line: the regression line with the 95% confidence interval in grey

Figure 5: Residual diagnostic from the final PopPK model



Black dots: observed concentrations, Blue solid lines: correspond to the splines, Black dotted lines: -2 and 2 of individual weighted residuals and numerical prediction distribution error.

Figure 6: Prediction-corrected Visual Predictive Check for the plasma concentration – Final PopPK Model



Black dots: observed concentrations, Dashed lines: the 5th and 95th percentiles of the observed concentrations, Solid black line: the 50th percentile of the observations, Blue-shaded areas: model-predicted percentiles and a 90% confidence interval for the 5th and 95th percentile, Red-shaded areas: a 90% confidence interval for the 50th percentile.

Table 12: Pharmacokinetic metrics predicted adult vs. predicted adolescent and observed adult vs. observed adolescent

Scenario		N	AUClast (ng.h/mL)[a]	Cmax (ng/mL)[a]	Tmax (h)[b]
Observed	Adult GEP-NET	20	30.08 (50.38)	8.98 (73.28)	0.47 (0.25-1.17)
	Adolescent GEP-NET and PPGL	9	41.14 (24.46)	11.56 (33.00)	0.57 (0.5-0.75)
	Pooled Adult GEP-NET and adolescent GEP-NET and PPGL	29	33.15 (45.99)	9.71 (63.11)	0.5 (0.25-1.17)
Predicted	Adult GEP-NET	20	31.01 (40.95)	6.8 (49.04)	0.5 (0.3-0.8)
	Adolescent GEP-NET and PPGL	9	32 (10.04)	10.35 (4.49)	0.5 (0.5-0.7)
	Pooled Adult GEP-NET and adolescent GEP-NET and PPGL	29	31.31 (33.82)	7.75 (45.19)	0.5 (0.3-0.8)

[a]Geometric mean (geometric CV%)

Geo-mean = exp(mean(log(x)); Geo-CV% = sqrt(exp(sd^2)-1)x100%, where sd is the sd of log(x)

[b]Median (Min-Max)

The FDA's Assessment:

FDA verified the Applicant's analysis and agreed with the Applicant's position. The population PK model described the observed data reasonably well and was considered adequate to predict individual PK estimates, although there were some deviations between observed and predicted parameters at lower and higher drug concentrations.

No significant covariates effects were identified in the final model. However, the covariate analysis is limited by the small sample size included in the popPK analysis.

Based on the popPK modeling, model-predicted [177Lu] Lu-DOTA-TATE exposure (i.e., AUC, Cmax) was similar between adults and adolescents, while the observed PK exposure in adolescents was slightly higher compared to those observed in adults.

13.4.4. Kidney/Bone Marrow dosimetry Analyses

13.4.5. Executive Summary

The kidney and bone marrow (BM) dosimetry analyses were conducted to support the proposed recommended dosage for pediatric patients based on the dose-dosimetry dataset (pooled adult and adolescent data), which were included in this NDA. These activities included the following objectives:

- Confirm comparable dose-dosimetry relationship for kidney and BM between adults and adolescents;
- Provide support for the proposed flat dosing in adolescents

Method: The dose-dosimetry analyses were based on the pooled adult (NETTER-1 and ERASMUS) and adolescent data (NETTER-P). The covariate effect (e.g., adult or adolescent populations) on CLcrClcr and other baseline features with kidney and BM dosimetry were explored. Covariate selection was performed using data exploration and visual inspection. Furthermore, probabilities of both observed and predicted adult and adolescent populations exceeding kidney and BM EBRT thresholds were calculated using 29 Gy for kidneys and 2 Gy for BM after 4 cycles of 7.4 GBq treatment with [177Lu] Lu-DOTA-TATE. The predicted probabilities were calculated by simulating a group of 500 patients with replacement from the adult population (N = 20) using the adult model on kidney and bone marrow dosimetry, where the process was repeated 500 times.

Results: 47 patients from two adult studies (NETTER-1 and ERASMUS) and 8 adolescent patients in NETTER-P were pooled for dose-dosimetry analyses. Dose and CLcr were considered as predictors for both kidney and BM dosimetry models. For kidney dosimetry, the final model

was a model with different relationship of CLcr with dosimetry depending on adult or adolescent populations. However, this result should be interpreted with caution due to small sample size of adolescent population (N = 8). For BM dosimetry, no improvement in parameter estimates was observed when additional covariates (e.g., body weight) were added.
The probability exceeding the kidney and BM EBRT thresholds was calculated based on the sample with replacement from the patient population and all the sampled information including study (NETTER-1 or NETTER-P), dose and CLcr. The model predicted probability (%) > 29 Gy of kidney dosimetry for adults and adolescents were 10.2% and 21.0%. The model predicted probability (%) >2 Gy of bone marrow dosimetry for adults and adolescents were 12.4% and 2.6%.

Conclusions: FDA agreed with the Applicant's position that the kidney dosimetry model predicted the median probability exceeding the EBRT thresholds reasonably well. However, the developed model couldn't capture the higher bounds for both populations. Also, the adolescent population was estimated to have higher probability exceeding the kidney EBRT thresholds compared with adult population, which was consistent with the observed data.
Exposure-response relationship for kidney and BM dosimetry were not conducted due to limited PK data collected in adult and adolescent patients.

13.4.6. Kidney/Bone Marrow dosimetry Analyses Assessment Summary

The dose-dosimetry analyses were based on the pooled adult (NETTER-1 and ERASMUS) and adolescent data (NETTER-P). Dose and CLcr were considered as predictors for both dosimetry models. For kidney dosimetry, the final model was a model with different relationship of CLcr with dosimetry depending on adult or adolescent populations. However, this result should be interpreted with caution due to small sample size of adolescent population (N = 8). For BM dosimetry, no improvement in parameter estimates was observed when additional covariates (e.g., body weight) were added.

General Information	
Goal of kidney and bone marrow dosimetry Analyses	Kidney and bone marrow dosimetry models were developed to evaluate the dose-dosimetry between two populations, which included the following objectives: • Confirm comparable dose-dosimetry relationship for kidney and BM between adults and adolescents; • Confirm the applicability of the same proposed recommended dosage for adults and adolescents
Studies Included	NETTER-P, NETTER-1, ERASMUS

Dose(s) Included		7.4 GBq (multiple dose)
EBRT thresholds		Kidney dosimetry ≤29 Gy; BM dosimetry ≤2 Gy
Population characteristics	Pediatrics	Age median (range): 15 yrs (14-16) Weight median (range): 54.15 kg (40,71) Male: 3 (38%); Female: 5 (62%) GEP-NET: 4 (50%); PPGL: 4 (50%)
	Adults	Age median (range): 56 yrs (29, 83) Weight median (range): 75 kg (48,145) Male: 24 (51%); Female: 23 (49%) GEP-NET: 47 (100%)
Exposure Metrics Explored (range)		Dose (exposure-metrics): 1.8 - 7.9 GBq, CLcr: 47 – 190 mL/min
Covariates Evaluated		The following pre-specified covariate-parameter relationships were examined for kidney and BM dosimetry inclusion: • Weight, body mass index, body surface area, height, CLcr, and dose

Final Model	**Summary**	**Acceptability [FDA's comments]**
Model Structure	The essence of the model chosen was to describe the effect of [177Lu] Lu-DOTA-TATE on kidney and BM dosimetry with a linear relationship of the log-transformed administered [177Lu] Lu-DOTA-TATE to specific standardized covariates. Dose (exposure-metric) and CLcr were used as predictors for kidney and BM dosimetry model, based on the pooled adults and adolescent data. The following equations illustrated the structure of final models: $Kidney\ Dosimetry\ =\ \mathrm{Theta}(1) \times$ [illegible] $Bone\ marrow\ = Theta(4) \times \left[\left[\frac{Dos}{}\right.\right.$	Yes, dose and CLcr were considered as the most relevant predictors for kidney and BM dosimetry models. Dose was used as a surrogate for exposure metric.

	Where, $C = C_{pop}$ + beta_C_STUDY_NETTER_P[STUDY = NETTER-P], Theta(1) refers to A, Theta(2) to B, Theta(3) to C, Theta(4) to D, Theta(5) to E and Theta(6) to F, 7.4 (GBq) was median dose and 99 (mL/min) was the median of CLcr used in the NETTER-1 modeling and simulation report.	
Model Parameter Estimates	Table 13	Yes
Model Evaluation	Final kidney/BM dosimetry models were determined based on maximized likelihood (lowest stable OFV), successful numerical convergence, parameter precision and acceptable VPC.	Yes
Covariates and Clinical Relevance	Study (adult vs. adolescent) was used as a categorical covariate for age in the pooled dose/exposure-dosimetry modeling, which should be interpreted with caution due to small sample size of adolescent population (N = 8).	Yes, the potential covariate effects (e.g., body weight and age) couldn't be identified due to the limited data in this submission.
Visualization of kidney/BM dosimetry analyses	VPC plots from final model are in figures below.	Yes, overall, the model predictions fell within the 90% interval with deviations at higher end for both populations.
Overall Clinical Relevance for kidney/BM dosimetry analyses	• Comparable kidney and BM dosimetry and exposure-response relationship between adults and adolescents were confirmed, with similar probabilities of kidney and BM dosimetry remaining ≤29 Gy and ≤2 Gy EBRT thresholds, respectively;	Yes, the kidney dosimetry model predicted the median probability exceeding the EBRT thresholds reasonably well but couldn't capture the higher bounds for both populations.

	• Based on modeling and simulation results presented 7.4 GBq dose of [177Lu] Lu-DOTA-TATE administered on 4 cycles for adults was also confirmed to be appropriate in the adolescent population.	The adolescent population was estimated to have higher probability exceeding the kidney EBRT thresholds compared with adult population, which was consistent with the observed data.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmaco-dynamics	Lutetium Lu 177 dotatate exposure-response relationships and the time course of pharmacodynamics response are unknown. <u>Cardiac Electrophysiology</u> The ability of LUTATHERA to prolong the QTc interval at the recommended 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.	Acceptable, the exposure-response relationship was not conducted in this submission.

Table 13: Population PD parameter estimates from the Final dosimetry models (N=55)

Parameter	Dosimetry model parameters (%RSE)
A_pop - Kidney baseline	4.35 ± 0.326 (7.49)
B_pop - Dose effect on kidney	0.653 ± 0.146 (22.3)
C_pop - CRCL effect on kidney	-0.555 ± 0.197 (35.5)
beta_C_STUDY_NETTER_P- CrCl effect on kidney dosimetry based on adult or adolescent populations	1.45 ± 0.615 (42.4)
D_pop - Bone marrow baseline	0.243 ± 0.0224 (9.19)
E_pop - Dose effect on BM	0.531 ± 0.198 (37.3)
F_pop - CRCL effect on BM	-1.17 ± 0.237 (20.2)
Error (proportional) b_1	0.485 ± 0.0561 (11.6)
Error (proportional) b_2	0.632 ± 0.0808 (12.8)

A=A_pop, B = B_pop, C= $Cpop$ + beta_C_STUDY_NETTER_P[if STUDY = NETTER — P], = D_pop, E =E_pop, F = F_pop

The final dosimetry models equations with the parameter estimates are detailed below:

$$Kidney\ Dosimetry = 4.35 \times \left[\left[\frac{Dose\ (GBq)}{7.4}\right]^{0.653} \times \left[\frac{CRCL}{99}\right]^{(-0.555[+1.45\ if\ STUDY = NETTER-P])}\right.$$

$$Bone\ marrow = 0.243 \times \left[\left[\frac{Dose\ (GBq)}{7.4}\right]^{0.531} \times \left[\frac{CRCL}{99}\right]^{-1.17}\right]$$

Figure 7: VPC of kidney and bone marrow dosimetry as functions of dose and CrCl from final dosimetry models

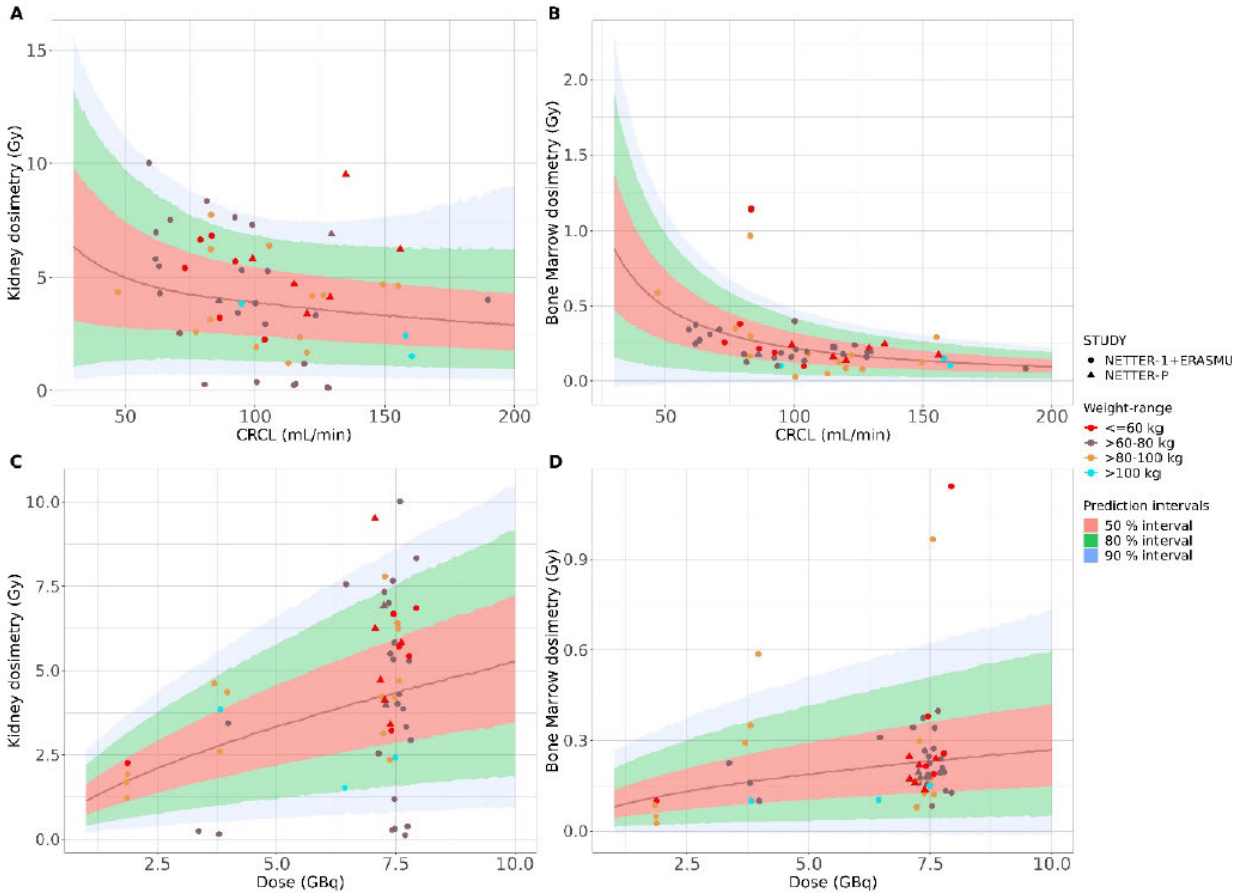


Figure 8: Correlation between kidney dosimetry and weight (N=55)

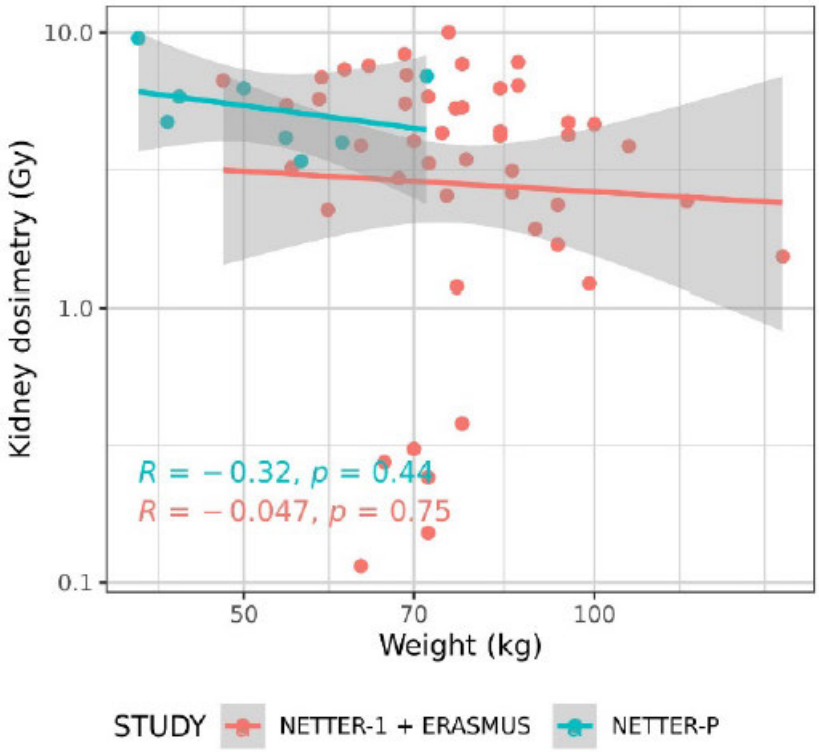


Table 14: Summary of predicted adult and adolescent dosimetry in kidney and bone marrow based on dose-dosimetry model for 4 cycles of 7.4 GBq ±10% dose

	ERASMUS (N=17)	NETTER-1 (N=17)	NETTER-P (N=8)	Overall (N=42)
Kid_obs (Gy)				
Mean (SD)	17.3 (11.7)	19.2 (8.24)	22.4 (8.00)	19.0 (9.72)
CV%	67.8%	43.0%	35.7%	51.1%
Median [Min, Max]	17.2 [0.460, 40.1]	18.8 [4.75, 33.3]	21.1 [13.6, 38.0]	18.8 [0.460, 40.1]
Kid_pred (Gy)				
Mean (SD)	18.3 (2.84)	18.2 (2.86)	20.6 (3.10)	18.7 (2.97)
CV%	15.5%	15.7%	15.1%	15.9%
Median [Min, Max]	17.9 [12.3, 23.6]	19.0 [13.5, 22.5]	21.2 [15.2, 25.4]	18.6 [12.3, 25.4]
BM_obs (Gy)				
Mean (SD)	1.02 (0.794)	1.09 (0.968)	0.773 (0.155)	0.999 (0.793)
CV%	78.0%	89.0%	20.1%	79.3%
Median [Min, Max]	0.768 [0.332, 3.87]	0.780 [0.316, 4.57]	0.743 [0.548, 0.987]	0.773 [0.316, 4.57]
BM_pred (Gy)				
Mean (SD)	1.09 (0.357)	1.09 (0.353)	0.792 (0.188)	1.03 (0.344)
CV%	32.7%	32.5%	23.8%	33.3%
Median [Min, Max]	1.03 [0.458, 1.81]	1.19 [0.566, 1.69]	0.742 [0.557, 1.14]	0.980 [0.458, 1.81]

Table 15: Predicted probabilities of dosimetry in kidney and bone marrow exceeding the predefined threshold based on dose-dosimetry model

Predicted	Model	Kidney (Probability (%) >29 Gy)	Bone Marrow (Probability (%) >2 Gy)
Adults (GEP-NET)	Adult Dose-dosimetry model	10.2 (5.2, 16.0)	12.4 (7.6, 17.8)
Adolescent (GEP-NET and PPGL)	Pooled Dose-dosimetry model	21.0 (6.3, 40.3)	2.6 (0.0, 7.1)
Pooled adult GEP-NET and adolescents GEP-NET and PPGL	Pooled Dose-dosimetry model	11.8 (6.2, 17.8)	10.0 (5.2, 15.2)

The FDA's Assessment:

FDA agreed with the Applicant's position that the kidney dosimetry model predicted the median probability exceeding the EBRT thresholds reasonably well. However, the developed model couldn't capture the higher bounds for both populations. Also, the adolescent population was estimated to have higher probability exceeding the kidney EBRT thresholds compared with adult population, which was consistent with the observed data. Exposure-response relationship for kidney and BM dosimetry were not conducted due to limited PK data collected in adult and adolescent patients.

13.5. Additional Clinical Outcome Assessment Analyses

N/A

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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