21 October 2025
EMA/CHMP/139486/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lutathera

International non-proprietary name: Lutetium (177Lu) oxodotreotide

Procedure No. EMEA/H/C/004123/II/0058

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential

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List of abbreviations

177Lu	Lutetium-177
AA	Amino acid
AE	Adverse event
AESI	Adverse event of special interest
AL	Acute leukaemia
AUC	Area under the curve
AUCinf	Area under the concentration-time curve from time zero extrapolated to infinity
AUClast	Area under the concentration-time curve from dosing (time 0) to the time of the last measured concentration
BM	Bone marrow
BSA	Body surface area
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cmax	Maximum blood concentrations
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DAS	Dosimetry analysis set
DCO	Data cut-off
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTA-TATE	DOTA-(Tyr3)-octreotate
DSMB	Data and Safety Monitoring Board
EBRT	External Beam Radiation therapy
ECG	Electrocardiogram
eCRS	Electronic Case Retrieval Strategy
EMA	European Medicines Agency
ENETS	European Neuroendocrine Tumor Society
ESMO	European Society for Medical Oncology
ES-SCLC	Extensive Stage- Small cell lung cancer
FAS	Full Analysis Set
FDA	Food and Drug Administration
GEP-NET	Gastroenteropancreatic neuroendocrine tumour
IBD	International birth date
IRC	Independent Radiology Committee
IP	Investigational product
LAR	Long-Acting Release (Octreotide LAR)
MDL	Myelodysplastic leukaemia
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
n/a	Not applicable
NANETS	North American Neuroendocrine Tumor Society
NCA	Non-compartmental analysis
NE	Not evaluable
NELM	NETs with liver metastasis
NET-NCCN	National Comprehensive Cancer network for Neuroendocrine Tumors
NR	Not reached
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PIP	Paediatric investigation plan
popPK	Population Pharmacokinetics
PPGL	Pheochromocytomas and paragangliomas
PK	Pharmacokinetics
PPSR	Proposed Paediatric Study Request
PRRT	Peptide receptor radionuclide therapy
RECIST	Response Evaluation Criteria in Solid Tumors
RLT	Radioligand therapy

ROI	Regions of Interest
SAE	Serious adverse event
SEER	Surveillance, Epidemiology, and End Results
SOC	System organ class
SSTR	Somatostatin receptor
TAC	Time activity curve
Tmax	Time to reach maximal drug concentration
UPCR	Urine protein creatinine ratio
VPC	Visual predictive check

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Advanced Accelerator Applications submitted to the European Medicines Agency on 27 November 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of unresectable or metastatic, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adolescents aged 12 years and older for LUTATHERA based on primary analysis results from study CAAA601A32201 (also referred to as NETTER-P) as well as results from modelling and simulation analysis of PK and dosimetry data of Lutathera in adolescents. NETTER-P study is a Phase II, multicenter open-label study which evaluated the safety and dosimetry of Lutathera in adolescent patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) and pheochromocytoma and paragangliomas (PPGLs). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 11 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

During the procedure, the applicant decided to convert the current application from a new indication (type C.I.6) to a SmPC label update (type C.I.4).

Information relating to orphan designation

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0461/2023 on the agreement of a paediatric investigation plan (PIP) and the granting of a product-specific waiver for the paediatric population from birth to less than 12 years of age

At the time of submission of the application, the PIP P/0461/2023 was completed.

The PDCO issued an opinion on compliance for the PIP P/0461/2023 on 18 October 2024.

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Janet Koenig

Timetable	Actual dates
Submission date	27 November 2024
Start of procedure:	28 December 2024
CHMP Rapporteur Assessment Report	26 February 2025
PRAC Rapporteur Assessment Report	3 March 2025
PRAC Outcome	13 March 2025
CHMP members comments	13 March 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 March 2025
Request for supplementary information (RSI)	27 March 2025
PRAC Rapporteur Assessment Report	30 May 2025
PRAC members comments	04 June 2025
Updated PRAC Rapporteur Assessment Report	04 June 2025
CHMP Rapporteur Assessment Report	05 June 2025
PRAC Outcome	05 June 2025
CHMP members comments	19 June 2025
Updated CHMP Rapporteur Assessment Report	13 June 2025
Request for supplementary information (RSI)	19 June 2025
CHMP Rapporteur Assessment Report	21 August 2025
PRAC Rapporteur Assessment Report	26 August 2025
PRAC Outcome	04 September 2025
CHMP members comments	08 September 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	11 September 2025

Timetable	Actual dates
Opinion	18 September 2025
Revised Opinion	21 October 2025

An opinion was adopted by the CHMP on 18 September 2025.

A revised opinion was adopted by the CHMP on 21 October in order to update section 5.1 of the SmPC to reflect that long-term safety data for Lutathera in adolescent patients are not currently available.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Neuroendocrine tumours (NETs) are a relatively rare, clinically diverse group of epithelial malignancies that originate most commonly from the gastrointestinal tract and the pancreas (GEP-NETs). The natural history of GEP-NETs is heterogenous and appears to be affected by the primary site of disease, degree of differentiation, expression of somatostatin receptors (SSTRs), and presence of metastases at diagnosis (Díez et al., 2013).

GEP-NETs usually have high levels of SSTR type 2 (SSTR2) expression, typically in >80% of the patients (Krenning et al., 1993; Reubi et al 2000). Peptide receptor radionuclide therapy (PRRT) has been considered most appropriate in patients with well-differentiated tumours as SSTR expression appears to decrease as tumours become less differentiated (Kayani et al., 2008).

State the claimed the therapeutic indication

The initially claimed therapeutic indication for this application was: Lutathera is indicated for the treatment of unresectable or metastatic, somatostatin receptor-positive GEP-NETs in adolescents aged 12 years and older.

During the procedure, the applicant decided to convert the current application from a new indication (type C.I.6) to a SmPC label update (type C.I.4) and to continue under the ongoing procedure with the paediatric data available from the NETTER-P study proposed for inclusion in sections 4.8, 5.1, 5.2 and 11 of the Lutathera SmPC.

Epidemiology and risk factors, screening tools/prevention

Due to its low incidence, GEP-NETs are recognised collectively as rare conditions and as such an orphan designation for the treatment of GEP-NETs with Lutathera was granted in 2008 in the EU. Based on national and regional registries in Europe, the incidence of GEP-NETs has increased over the last two decades from 2.5/100,000 population (van der Zwan et al 2013) to 3.35 - 6.22/100,000 population (Grundmann et al 2023, Thiis- Evensen and Cetinkaya 2023, Alwan et al 2020, Genus et al 2019,

Gudmundsdottir et al 2019). The estimated incidence rate of GEP-NETs in the US increased from 1.05 (95% CI: 0.9, 1.21) per 100,000 persons in 1975 to 5.45 (95% CI: 5.31, 5.61) per 100,000 persons in 2015 (Xu et al 2021). Overall, the estimated prevalence of GEP-NETs in the recent studies in the EU, Norway, and USA ranged from 31 per 100,000 individuals to 63 per 100,000 individuals, depending on region and duration of prevalence period (Thiis-Evensen and Cetinkaya 2023, Dasari et al 2017).

GEP-NETs occur with an approximate median onset of >50 years of age and are very rare in the paediatric age group, accounting for less than 1% of paediatric malignancies. In the EU, the estimated annual incidence from published studies is <1 per 100,000 person-years (Pastore et al 2009, Diets et al 2017). In the US, the age-adjusted incidence for all GEP-NETs in the paediatric population estimated from SEER (version 8.3.6 released on May 2020) using 18 cancer registries was 0.08 per 100,000 population. In the same year, the incidence rate (per 100,000) for adolescents aged 12 to <18 years was 0.27 and 0.03 in children aged <12 years. Similar to adults, there has been an overall rise in NET incidence in paediatric patients in the last few decades, likely driven by improved diagnostics and increased disease detection rates (Kartal 2022).

GEP-NET incidence is extremely rare in children below 12 years of age and are nearly all represented by appendiceal NETs diagnosed at Stage I, which can be surgically removed and are not in the scope for Lutathera treatment. However, GEP-NETs diagnosed in adolescents 12 to <18 years of age range from Stage I to Stage IV, including metastatic disease, and are therefore in scope of Lutathera treatment. Hence the Paediatric committee (PDCO) granted a waiver in the age group below 12 years (EMEA-002950-PIP01-20-M01).

Biologic features, aetiology and pathogenesis

Carcinoid tumours represent the largest group of GEP-NETs (about two thirds). A long-standing classification system divides carcinoids into foregut, midgut and hindgut tumours, based on the embryonic origin of the tumours. Foregut primaries are located in the lung, thymus, stomach, duodenum, and pancreas; the midgut with primary tumours in the ileum, caecum and proximal colon; and the hindgut with the primaries in the distal colon and rectum. Note that some of these locations (e.g., lung and thymus) are outside the definition of GEP-NET (but not carcinoid), so the classification systems contribute to some confusion (Rindi et al., 2006).

A more recent WHO classification system has been developed which is considered more clinically relevant. The current World Health Organization (WHO) classification specifies four subtypes (irrespective of site of origin) under two main categories (well differentiated and poorly differentiated) and is therefore relevant for all neuroendocrine tumour types:

Neuroendocrine neoplasm (well differentiated)

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

Neuroendocrine carcinoma (poorly differentiated)

- grade 1 (20% Ki67 index)
- grade 3, large neuroendocrine carcinoma (>20% Ki67 index)

GEP-NETs in paediatric patients 12 to <18 years of age present the same course of disease progression, morbidity, diagnostics and outcomes as in adults. Due to the common aetiology, prognosis of GEP-NET and the presence of the SSTR target, Lutathera was presumed to be effective and safe in paediatric patients aged 12 years and older, similar to what is observed in adult patients.

In line with the PIP for Lutathera, pheochromocytoma and paraganglioma (PPGL) patients were also included in the pivotal trial of this application (NETTER-P) as an exploratory cohort since. PPGL are other kind of rare neuroendocrine tumours arising from the chromaffin cells of the adrenal medulla or sympathetic/parasympathetic ganglia. The pathophysiology of the two diseases (GEP-NET and PPGL) is not substantially different in adolescents compared to adult patients. Increased SSTR expression in PPGL, particularly that of SSTR2 (Kong et al 2019, Han et al 2019), has been demonstrated by uptake on somatostatin receptor scintigraphy, thus providing the rationale for the investigation of the potential use of Lutathera in both these indications.

With this application, the MAH did not apply for an indication in PPGL. These data are presented as supportive only.

NETTER-P study aimed to enrol at least 8 adolescents with a minimum of 3 in the GEP-NET cohort.

Clinical presentation, diagnosis and stage/prognosis

The most common sites of malignant NETs in children and young adults are lung, breast, and appendix, with an incidence of 0.6, 0.5, and 0.4 per million population respectively. Approximately 10% to 20% of children and young adolescents have metastatic disease at presentation (Farooqui and Chauhan 2019). Similar to adults, paediatric patients with pancreatic NETs often present with more extensive disease that confers a worse prognosis.

Management

Management of paediatric NETs depends on tumour location, grade, growth rate, extent of disease, and symptoms. Surgical resection for local or loco-regional disease is the standard of care and is associated with long-term survival in most patients. For the subset of patients with unresectable, metastatic disease, the approach to diagnosis, staging, and treatment is similar to that of adult NETs. No systemic pharmacological therapies are currently approved for paediatric patients with GEP-NET in EU. Peptide receptor radionuclide therapy, targeted agents, or chemotherapy are the most frequently used off-label treatments in the paediatric population. Thus, GEP-NETs in paediatric patients 12 to < 18 years of age represent an area of unmet medical need.

2.1.2. About the product

Lutathera, also referred to as [177Lu]Lu-DOTA-TATE (INN: lutetium (177Lu) oxodotreotide, USAN: lutetium Lu 177 dotatate, chemical name: DOTA-Tyr3-Octreotate), is a radiopharmaceutical consisting of a ligand (an oligopeptide, coupled to the metal chelating moiety 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)), and radiolabeled with lutetium-177 [177Lu]. The ligand binds to somatostatin receptors (SSTRs) with the highest affinity for somatostatin subtype 2 receptors (SSTR2s), thus making it a treatment option for patients with tumors that express SSTRs. These receptors are an attractive target for radioligand therapy, as the SSTR density is much higher on tumors than on non-tumor tissues.

The biological basis for radioligand therapy with Lutathera is the receptor-mediated internalization and intracellular retention of this radiolabeled SSA. The specific binding of [177Lu]Lu-DOTA-TATE to malignant cells enables the direct delivery of tumoricidal radiation doses to target tissue expressing SSTRs. Lutetium-177 is a β-emitting radionuclide that causes the death of targeted tumor cells, with a limited effect on neighboring normal cells.

Lutathera is supplied as a sterile, ready-to-use radiopharmaceutical solution for infusion with a fixed volumetric activity of 370 MBq/mL at the date and time of calibration. The volume of the solution in the vial ranges between 20.5 and 25.0 mL in order to provide the required amount of radioactivity at the date and time of infusion.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development program of Lutathera was initially focused on the GEP-NET indication. The NETTER-1 phase III study compared treatment with Lutathera (4 cycles of 7.4 GBq, every 8 weeks) plus octreotide LAR 30 mg to treatment with high dose (60 mg) octreotide LAR in patients with SSTR-positive progressive midgut carcinoid tumours. The results from NETTER-1 study combined with data from ERASMUS phase I/II trial, which was an open- label trial based on data from 1,214 patients with somatostatin receptor-positive tumours who received [177Lu]Lu-DOTA-TATE, have led to approvals of Lutathera for the treatment of SSTR-positive GEP-NET in adults.

The NETTER-2 phase III study was a randomised, open-label, comparator-controlled trial conducted in patients with somatostatin receptor-positive, newly diagnosed, metastasized or locally advanced, inoperable, well-differentiated Grade 2 (G2) and Grade 3 (G3) GEP-NETs. It aimed to complement the NETTER-1 study by providing clinical evidence in an earlier line of treatment and in higher grade tumours. Clinical trials of Lutathera in adolescent patients with GEP-NET are limited. The NETTER-2 trial conducted by the MAH allowed the participation of patients ≥15 years old, but no paediatric patient was enrolled. There was only 1 paediatric patient enrolled in ERASMUS MC trial due to the rarity of disease in the target adolescent population, but this 16-year-old male had a non-GEP-NET. The NETTER-2 results were submitted to EMA as part of the Lutathera II/52 procedure, which was subsequently withdrawn by the MAH (see WPAR Lutathera II/52).

Given the lack of approved therapeutic options for GEP-NETs in the paediatric population, there is a high unmet medical need.

Therefore, NETTER-P trial was conducted to evaluate the safety and dosimetry of Lutathera in adolescent patients with GEP-NETs and PPGLs as a pooled cohort), in line with the approved PIP. Importantly, this study provides the data for the modelling and simulation analysis that were carried out to support the application.

The results of the primary analysis conducted after all participants had completed the first cycle of Lutathera or later, in case dosimetry assessment was not done after the first dose (DCO: 12 Mar 2024), are included in this submission.

The primary analysis combines patients with GEP-NET and PPGL, based on the consideration that there are no expected differences from dosimetry or critical organ toxicity across these two indications.

The purpose of this submission was to include the results of studies as described in the agreed PIP (EMEA-002950-PIP01-20-M01) and to extend the indication for Lutathera for the treatment of unresectable or metastatic SSTR-positive GEP-NETs in adolescents aged 12 years and older. The data provided from the PPGL cohort were intended exclusively to support the GEP-NET indication. A PPGL indication was not sought as part of this application.

During the procedure, the applicant decided to convert the current application from a new indication (type C.I.6) to a SmPC label update (type C.I.4) and to continue under the ongoing procedure with the paediatric data available from the NETTER-P study proposed for inclusion in sections 4.8, 5.1, 5.2 and 11 of the Lutathera SmPC. Section 4.1 remained unchanged.

This application is based on:

- A modelling and simulation analysis performed to justify the appropriateness of the adult dose for use in the adolescent population based on extrapolation of adult dosimetry data from kidney and bone marrow.
- The full extrapolation approach for clinical efficacy from adults to adolescents that was agreed with EMA based on i) similar disease characteristics and potential response to Lutathera treatment; ii) same mechanism of action; iii) similar exposure/response relationship; and iv) that the drug amount (i.e. dose, concentration, exposure) is measurable and predictive of clinical response.
- Primary analysis results from NETTER-P study, a Phase II, multicenter open-label study of Lutathera in adolescent patients with somatostatin receptor positive GEP- NETs or PPGLs which evaluated the safety and dosimetry of Lutathera in the adolescent population.
- The results from a modelling and simulation analysis of PK and dosimetry data of Lutathera in adolescents based on both PopPK model and empirical kidney and bone marrow dosimetry models as well as NETTER-P data.
- These data are complemented with safety and efficacy data from published literature and spontaneous reports on the use of lutetium Lu 177 dotatate and yttrium Y 90 dotatoc in paediatric patients with GEP-NETs, and other interventions in the paediatric population.

Comparative assessment of dosimetry in adolescent and adults based on both predicted and NETTER-P data aimed to confirm similar dosimetry estimates as well as similar probability of going beyond External Beam Radiation Therapy (EBRT) thresholds for adolescents and adults. Additionally, comparative assessment of PK metrics using the population PK model predictions and NETTER-P data aimed to reveal that the exposure results were comparable between adolescent and adult populations. The results are discussed below.

2.2. Non-clinical aspects

2.2.1. Introduction

No new non-clinical data have been submitted in this application.

A discussion on "Ecotoxicity/environmental risk assessment" has been submitted in this application.

2.2.2. Ecotoxicity/environmental risk assessment

The changes in indication and patient population in this application do not lead to an increase in environmental exposure of Lutathera. Therefore, an updated ERA is not required. Lutathera is not expected to pose a risk to the environment when used according to the product information.

2.2.3. Discussion on non-clinical aspects

No new non-clinical data but a discussion on "Ecotoxicity/environmental risk assessment" have been submitted in this application, which is considered acceptable.

Lutathera is not expected to pose a risk to the environment.

2.2.4. Conclusion on the non-clinical aspects

Approval may be considered acceptable from a non-clinical point of view.

Considering the above data, lutetium (177Lu) oxodotreotide is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- Tabular overview of clinical studies

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status & Reports of Study Results
Protocol: CAAA601A32201 **Countries**: France, Poland, Spain, United Kingdom, United States **Start**: 31-Aug-2022 **Data Cut Off:** 12-Mar-2024 **End**: Ongoing	**Design, purpose & population**: 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 paragangliomas	**Total**: 12 screened, 11 enrolled as of data cut-off 12-Mar-2024 **Age**: 13-17 (15) years **Groups**: 2 GEP-NET cohort: 4 PPGL cohort: 7	**Form(s)**: Lutathera radiopharmaceutical solution (7.4 GBq / 200 mCi of Lutathera per 30 ml vial), infusion **Duration**: Treatment period 24 weeks Follow-up period 5 years **Doses**: Lutathera (7.4 GBq / 200 mCi), 4 administrations every 8 ±1 weeks	**Study Status**: ongoing **Report no**. [NETTER-P Primary CSR-2024] full, final **Report date**: 25-Oct-2024 **Other reports**: **Report no**. NETTER-P Interim CSR-2023 full, final **Report date**: 15-Sep-2023 **Other reports**: **Report no**. [NETTER-P Final Radiation Dosimetry Report] **Report date**: 23-Aug-2024 **Report no**. [NETTER-P Dosimetry report-2023] **Report date**: 23-Aug-2023

CAAA601A32201 = NETTER-P

2.3.2. Pharmacokinetics

Demographics and other baseline characteristics

The median age of participants was 15.0 (range: 13 to 17) years. Of the 11 treated participants in the full analysis set (FAS), 5 were male, and 6 were female, with 5 of them being White. The mean (SD) baseline BMI was 20.4 (3.1) kg/m^2, and the mean (SD) baseline creatinine clearance was 122.1 (24.0) mL/min.

Diagnosis and extent of cancer in participants with GEP-NET

Of the 4 participants with GEP-NET at baseline, two had pancreas as the primary site of cancer.

One participant had rectum and another one stomach as the primary site of cancer. All tumours were well-differentiated (Grade 1 or 2). All 4 participants received surgery.

- One participant had Grade 1 (<3%) GEP-NET in the pancreas with documented relapse/progression and metastases to bone, liver, pancreas and thyroid gland.

- One participant had Grade 1 (<3%) GEP-NET in the stomach with documented relapse/progression and metastases to regional lymph nodes and peritoneum.
- One participant had Grade 2 (3% to ≤20%) GEP-NET in the rectum with documented relapse/progression and metastases to bone, regional lymph nodes, and pelvis.
- One participant had Grade 2 (3% to ≤20%) GEP-NET in the pancreas with documented relapse/progression and metastases to abdominal region, liver, lungs, regional lymph nodes, distant lymph nodes, and mediastinum.

Diagnosis and extent of cancer in participants with PPGL

Of the 7 participants with PPGL at baseline, 5 participants were diagnosed with extra-adrenal paraganglioma (most of them with the abdominal cavity as the primary origin) and 2 participants with adrenal pheochromocytoma. Five participants underwent surgery, and one participant underwent surgery and radiotherapy.

- One participant had a Stage IV extra-adrenal paraganglioma (abdominal cavity) with documented relapse/progression and metastases to bone and liver.
- One participant had a Stage IV extra-adrenal paraganglioma (abdominal cavity) with documented relapse/progression and metastases to bone and distant lymph nodes.
- One participant had a Stage IV extra-adrenal paraganglioma (abdominal cavity) with documented relapse/progression and metastases to regional lymph nodes, pancreas and mesentery.
- One participant had a Stage IV extra-adrenal paraganglioma (other) with documented relapse/progression and metastases to liver, regional lymph nodes, pelvis and the peritoneum.
- One participant had a Stage IV extra-adrenal paraganglioma (abdominal cavity) with metastases to regional lymph nodes and right epididymis.
- One participant had a Stage IV adrenal pheochromocytoma with documented relapse/progression and metastases to bone, liver, lungs, and peritoneum.
- One participant had a Stage IV adrenal pheochromocytoma with documented relapse/progression and metastases to bone

Dose modifications

Of the 11 participants enrolled in the study, 6 participants (54.5%; 1 with GEP-NET, 5 with PPGL) had at least one Lutathera dose delay (i.e. visit out of scheduled window, captured in the CRF as dose interruption), or dose reduced:

• Three participants (1 GEP-NET, 2 PPGL) had at least one Lutathera dose delay (e.g. technical / administrative issues on sites).

• Three participants from the PPGL cohort (none in the GEP-NET cohort) had at least one dose reduction/change (e.g. related to toxicity, adverse events or target organ exceeding thresholds).

Absorption and dosimetry

Assessment of PK of Lutathera in adolescent participants in NETTER-P study (observed and predicted values)

Figure 1. Arithmetic mean (SD) blood concentration-time (ng/mL) profiles for Lutathera (PKAS) in NETTER-P study

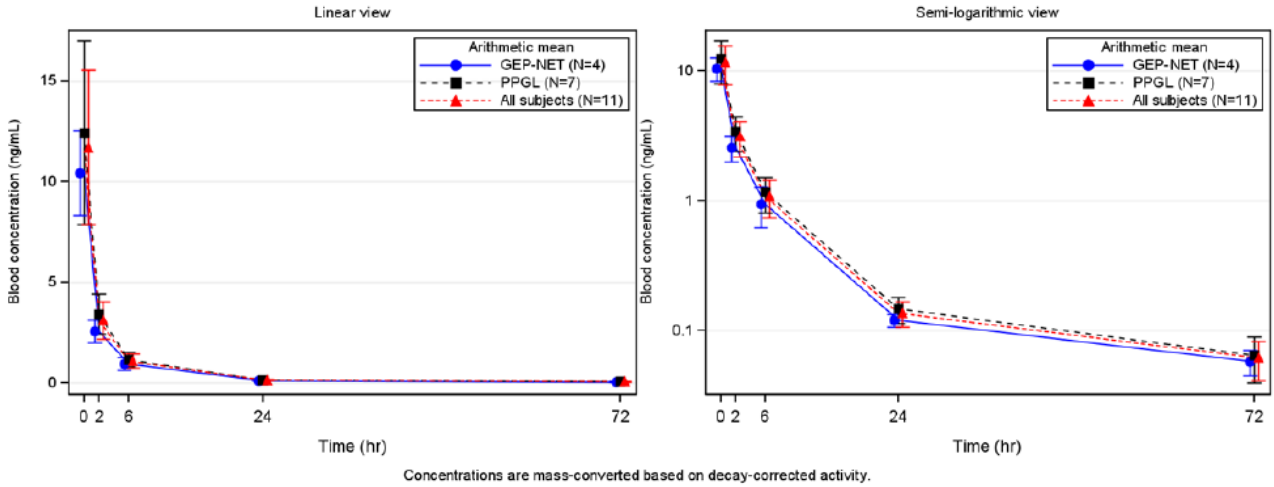


Table 1. Summary of measured blood concentrations (ng/mL) of Lutathera (PKAS) in NETTER-P study

Scheduled sampling time point	Statistics	GEP-NET (N=4)	PPGL (N=7)	All subjects (N=11)
0 Hours Dose (at the end of infusion)	n	4	7	11
	m	4	7	11
	Mean (SD)	10.4 (2.11)	12.4 (4.56)	**11.7 (3.85)**
	CV%	20.2	36.6	32.9
	Geo-mean	10.3	11.7	11.2
	Geo-CV%	21.2	39.3	33.0
	Median	10.5	12.6	10.5
	Min-Max	7.79-13.0	7.27-18.9	7.27-18.9
2 Hours Post Dose	n	4	7	11
	m	4	7	11
	Mean (SD)	2.58 (0.570)	3.42 (1.00)	3.12 (0.940)
	CV%	22.1	29.3	30.2
	Geo-mean	2.53	3.31	3.00
	Geo-CV%	22.3	27.6	28.3
	Median	2.50	3.13	2.85
	Min-Max	2.06-3.25	2.51-5.35	2.06-5.35
6 Hours Post Dose	n	4	7	11
	m	4	7	11
	Mean (SD)	0.947 (0.323)	1.17 (0.358)	1.09 (0.347)
	CV%	34.1	30.7	31.9
	Geo-mean	0.909	1.12	1.04
	Geo-CV%	33.0	31.7	32.4
	Median	0.868	1.08	0.977
	Min-Max	0.647-1.41	0.696-1.76	0.647-1.76

24 Hours Post Dose		4	7	11
	m	4	7	11
	Mean (SD)	0.121 (0.0137)	0.147 (0.0338)	**0.137 (0.0304)**
	CV%	11.4	23.0	22.1
	Geo-mean	0.120	0.144	0.135
	Geo-CV%	11.3	24.1	21.7
	Median	0.119	0.145	0.133
	Min-Max	0.106-0.138	0.0998-0.196	0.0998-0.196
72 Hours Post Dose	n	4	7	11
	m	4	7	11
	Mean (SD)	0.0576 (0.0129)	0.0647 (0.0251)	**0.0621 (0.0210)**
	CV%	22.4	38.9	33.8
	Geo-mean	0.0563	0.0601	0.0587
	Geo-CV%	25.6	45.8	37.9
	Median	0.0618	0.0600	0.0600
		0.0389-0.0678	0.0261-0.107	

Comparative assessment of PK of Lutathera in adolescent and adult participants (observed and predicted values)

The Lutathera concentration-time profiles following the first dose administration were described for both adult and adolescent populations using population PK models. Observed data in adult GEP-NET patients are derived from NETTER-1 study.

Table 2. Comparative assessment of Lutathera PK in adolescent and adult participants (observed and predicted)

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	11	41 (24.15)	11.17 (33.04)	0.58 (0.5-0.77)
	Pooled Adult GEP-NET and adolescent GEP-NET and PPGL	31	33.57 (45.07)	9.7 (61.18)	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	11	32.34 (10.43)	10.31 (5.22)	0.5 (0.5-0.7)
	Pooled Adult GEP-NET and adolescent GEP-NET and PPGL	31	31.48 (32.81)	7.89 (44.19)	0.5 (0.3-0.8)

a Geometric mean (geometric CV%)

b Median (Min-Max)

Assessment dosimetry results

As per protocol, dosimetry assessments were performed during the first week after the first Lutathera dose, and as soon as feasible if dosimetry could not be performed after the first dose. In the NETTER-P study, dosimetry assessments were performed at the first cycle in 10 participants. One participant with PPGL had dosimetry assessed at Cycle 2 due to technical issues in imaging equipment.

Target organ dosimetry results

The mean dosage-normalised absorbed radiation doses (Mean +SD) of Lutathera in the organs at risk, i.e., kidney and bone marrow (estimated using blood data), were 0.78 (±0.28) Gy/GBq and 0.026 (±0.005) Gy/GBq, respectively, in the 10 participants of the Dosimetry Analysis Set (DAS, see table below).

Table 3. Summary of adolescent dosimetry parameters of Lutathera for target organs (DAS)

Organ	Parameter	Statistics	GEP-NET (N=4)	PPGL (N=6)	All participants (N=10)
	Effective Dose (mSv/MBq)	N	4	6	10
		Mean (SD)	0.082 (0.017)	0.097 (0.015)	0.091 (0.017)
		CV%	20.5	15.7	18.5
		Min-Max	0.060-0.10	0.081-0.12	0.060-0.12
Kidney	Absorbed Dose (Gy/GBq)	N	4	6	10
		Mean (SD)	0.71 (0.25)	0.82 (0.32)	**0.78 (0.28)**
		CV%	34.5	38.3	36.0
		Min-Max	0.46-0.96	0.55-1.3	0.46-1.3
	Theoretical cumulative absorbed dose (Gy)	Mean (SD)	21 (7.3)	24 (9.3)	23 (8.3)
		CV%	34.5	38.3	36.0
		Min-Max	14-28	16-40	14-40
Pituitary	Absorbed Dose (Gy/GBq)	N	3	6	9
		Mean (SD)	1.2 (0.43)	1.0 (0.45)	1.1 (0.43)
		CV%	34.3	42.7	38.2
		Min-Max	0.93-1.7	0.61-1.9	0.61-1.9
	Theoretical cumulative absorbed dose (Gy)	Mean (SD)	37 (13)	31 (13)	33 (13)
		CV%	34.3	42.7	38.2
		Min-Max	28-51	18-56	18-56
Red Marrow (Blood)	Absorbed Dose (Gy/GBq)	N	4	6	10
		Mean (SD)	0.024 (0.0035)	0.028 (0.0052)	**0.026 (0.0050)**
		CV%	15.0	18.6	19.1
		Min-Max	0.019-0.027	0.022-0.035	0.019-0.035
	Theoretical cumulative absorbed dose (Gy)	Mean (SD)	0.70 (0.10)	0.83 (0.16)	0.78 (0.15)
		CV%	15.0	18.6	19.1
		Min-Max	0.55-0.79	0.64-1.0	0.55-1.0
Red Marrow (Image)	Absorbed Dose (Gy/GBq)	N	4	6	10
		Mean (SD)	0.043 (0.018)	0.067 (0.028)	0.057 (0.027)
		CV%	43.1	42.5	46.9
		Min-Max	0.025-0.066	0.024-0.093	0.024-0.093
	Theoretical cumulative absorbed dose (Gy)	Mean (SD)	1.3 (0.54)	2.0 (0.84)	1.7 (0.79)
		CV%	43.1	42.5	46.9
		Min-Max	0.74-1.9	0.70-2.8	0.70-2.8
Spleen	Absorbed Dose (Gy/GBq)	N	4	6	10
		Mean (SD)	0.63 (0.39)	0.82 (0.17)	0.74 (0.27)
		CV%	61.7	20.7	37.0
		Min-Max	0.28-1.1	0.64-1.1	0.28-1.1
	Theoretical cumulative absorbed dose (Gy)	Mean (SD)	19 (12)	24 (5.0)	22 (8.1)
		CV%	61.7	20.7	37.0
		Min-Max	8.3-34	19-31	8.3-34
Urinary Bladder Wall	Absorbed Dose (Gy/GBq)	N	4	6	10
		Mean (SD)	0.50 (0.034)	0.59 (0.096)	0.55 (0.089)
		CV%	6.9	16.2	16.1
		Min-Max	0.47-0.54	0.47-0.68	0.47-0.68
	Theoretical cumulative absorbed dose (Gy)	Mean (SD)	15 (1.0)	17 (2.8)	16 (2.6)
		CV%	6.9	16.2	16.1
		Min-Max	14-16	14-20	14-20
Total Body	Absorbed Dose (Gy/GBq)	N	4	6	10
		Mean (SD)	0.040 (0.013)	0.041 (0.0073)	0.040 (0.0095)
		CV%	34.2	17.8	23.6
		Min-Max	0.022-0.055	0.033-0.052	0.022-0.055
	Theoretical cumulative absorbed dose (Gy)	Mean (SD)	1.2 (0.40)	1.2 (0.21)	1.2 (0.28)
		CV%	34.2	17.8	23.6
		Min-Max	0.66-1.6	0.97-1.5	0.66-1.6

n= number of participants with evaluable dosimetry parameters.
Gy/GBq: absorbed dose per unit administered activity
Theoretical cumulative absorbed dose (Gy) is defined as Absorbed dose per unit activity (Gy/GBq)*4*7.4
Zero values are excluded from summary statistics
One participant was excluded from the DAS due to the following reason: several imaging issues, hybrid methodology not utilized (only planar).
Dosimetry for one participant was obtained at Cycle 2

One participant (PPGL cohort) was excluded from the DAS due to several imaging issues. This participant had kidney and image-based bone marrow estimates for theoretical cumulative absorbed radiation dose of Lutathera that exceeded the reference limits (kidney: 45 Gy vs. 29 Gy; bone marrow: 3.6 Gy vs. 2 Gy).

In addition, individual bone marrow theoretical cumulative absorbed radiation doses estimated using imaging data and exceeding the limit of 2 Gy were reported in 4 other participants from the PPGL cohort (2.2, 2.4, 2.7 and 2.8 Gy) and are included in the DAS. Individual bone marrow theoretical cumulative absorbed radiation doses estimated using blood data were <2 Gy for all participants.

Comparative assessment of dosimetry in adolescent and adults (observed and predicted)

The table below mean organ dosimetry estimates derived for the 10 adolescent participants in NETTER-P were compared to the mean dosimetry data from adults (n=20) from NETTER-1 (mean (± SD):

Table 4. Estimated organ radiation absorbed dose for Lutathera in adolescents (NETTER-P) and adults (NETTER-1)

	Absorbed dose per unit activity (Gy/GBq)		Calculated absorbed dose for 4 x 7.4 GBq (29.6 GBq cumulative activity) (Gy)	
Organ	Adolescents (N=10) Mean ± SD	Adults (N=20) Mean ± SD	Adolescents (N=10) Mean ± SD	Adults (N=20) Mean ± SD
Adrenals	0.045 ± 0.011	0.037 ± 0.016	1.3 ± 0.32	1.1 ± 0.5
Brain	0.020 ± 0.0055	0.027 ± 0.016	0.61 ± 0.16	0.8 ± 0.5
Breasts*	0.018 ± 0.0053 (n=5)	0.027 ± 0.015 (n=9)	0.52 ± 0.16 (n=5)	0.8 ± 0.4 (n=9)
Esophagus	0.023 ± 0.0058	NA	0.69 ± 0.17	NA
Eyes	0.020 ± 0.0055	NA	0.61 ± 0.16	NA
Gallbladder wall	0.030 ± 0.0098	0.042 ± 0.019	0.89 ± 0.29	1.2 ± 0.6
Heart wall	0.023 ± 0.0058	0.032 ± 0.015	0.68 ± 0.17	0.9 ± 0.4
Kidneys	0.78 ± 0.28	0.654 ± 0.295	23 ± 8.3	19.4 ± 8.7
Left colon	0.27 ± 0.074	NA	8.1 ± 2.2	NA
Liver	0.21 ± 0.20	0.299 ± 0.226 [a]	6.2 ± 6.1	8.9 ± 6.7 [a]
Lower large intestinal wall	NA	0.029 ± 0.016	NA	0.9 ± 0.5
Lungs	0.023 ± 0.0057	0.031 ± 0.015	0.67 ± 0.17	0.9 ± 0.4
Muscle	NA	0.029 ± 0.015	NA	0.8 ± 0.4
Osteogenic cells	0.045 ± 0.017	0.151 ± 0.268	1.3 ± 0.51	4.5 ± 7.9

Organ	Absorbed dose per unit activity (Gy/GBq)		Calculated absorbed dose for 4 x 7.4 GBq (29.6 GBq cumulative activity) (Gy)	
	Adolescents (N=10) Mean ± SD	Adults (N=20) Mean ± SD	Adolescents (N=10) Mean ± SD	Adults (N=20) Mean ± SD
Ovaries	0.026 ± 0.0069 (n=6)	0.031 ± 0.013 (n=9)	0.76 ± 0.20 (n=6)	0.9 ± 0.4 (n=9)
Pancreas	0.027 ± 0.0062	0.038 ± 0.016	0.79 ± 0.18	1.1 ± 0.5
Pituitary**	1.1 ± 0.43 (n=9)	NA	33 ± 13 (n=9)	NA
Prostate***	0.025 ± 0.0056 (n=4)	NA	0.73 ± 0.17 (n=4)	NA
Rectum	0.28 ± 0.076	NA	8.2 ± 2.2	NA
Red marrow (blood)****	0.026 ± 0.0050	0.035 ± 0.029	0.78 ± 0.15	1.0 ± 0.8
Red marrow (image)****	0.057 ± 0.027	NA	1.7 ± 0.79	NA
Right colon	0.16 ± 0.041	NA	4.6 ± 1.2	NA
Salivary glands	0.033 ± 0.017	NA	0.96 ± 0.51	NA
Skin	NA	0.027 ± 0.015	NA	0.8 ± 0.4
Small intestine	0.045 ± 0.011	0.031 ± 0.015	1.3 ± 0.33	0.9 ± 0.5
Spleen	0.74 ± 0.27	0.846 ± 0.804	22 ± 8.1	25.1 ± 23.8
Stomach wall	0.026 ± 0.0060	0.032 ± 0.015	0.77 ± 0.18	0.9 ± 0.5
Testes***	0.020 ± 0.0048 (n=4)	0.026 ± 0.018 (n=11)	0.60 ± 0.14 (n=4)	0.8 ± 0.5 (n=11)
Thymus	0.022 ± 0.0055	0.028 ± 0.015	0.64 ± 0.16	0.8 ± 0.5
Thyroid	0.027 ± 0.017	0.027 ± 0.016	0.79 ± 0.0095	0.8 ± 0.5
Total body	0.040 ± 0.0095	0.052 ± 0.027	1.2 ± 0.28	1.6 ± 0.8
Upper large intestinal wall	NA	0.032 ± 0.015	NA	0.9 ± 0.4
Urinary bladder wall	0.55 ± 0.089	0.437 ± 0.176	16 ± 2.6	12.8 ± 5.3
Uterus*	0.030 ± 0.0079	0.032 ± 0.013 (n=9)	0.90 ± 0.23	1.0 ± 0.4 (n=9)

a n=18 adults (two participants excluded because the liver absorbed dose was biased by the uptake of the liver metastases)
* Female participants only (NETTER-P n=6; NETTER-1 n=9)
** Pituitary dosimetry estimates were only performed when pituitary uptake was clearly observed on the planar images. Due to the small size of the pituitary gland, availability for quantification only from planar images and interference from activity in the nasal mucosa, estimates can be associated with a large uncertainty (NETTER-1 Dosimetry Report) and [NETTER-P Final Radiation Dosimetry Report].
*** Male participants only (NETTER-P n=4; NETTER-1 n=11)
****Red marrow dosimetry estimates were determined either using blood radioactivity or by imaging and scaling of a representative region of the lumbar spine (NETTER-P) or blood-only (NETTER-1)

In order to confirm similar dosimetry for organs at risk, specifically kidneys and bone marrow, the dosimetry values and the potential probability of exceeding 29 Gy for kidneys and 2 Gy for bone marrow thresholds after 4 cycles of 7.4 GBq treatment with Lutathera were compared between adult (NETTER-1 study) and adolescent populations based on both predicted and observed data (table below).

Both kidney and bone marrow (blood-based) dosimetry values, observed and predicted, were re-estimated in the pooled analysis of adolescent data from this study and adult data from the NETTER-1 and ERASMUS study.

Table 5. Comparative assessment of Lutathera dosimetry in kidney and bone marrow (probability of exceeding indicated thresholds) of adolescent and adult participants (DAS) (observed and predicted)

Scenario		N	Kidney (Probability (%) >29 Gy)[a]	Bone Marrow (Probability (%) >2 Gy)[a]
Observed	**Adults** (GEP-NET)	47	12.8	6.4
	Adolescents (GEP-NET and PPGL)	10	20.0	0.0
	Pooled adult GEP-NET and adolescents GEP-NET and PPGL	57	14.0	5.3
Predicted[a]	**Adults** (GEP-NET)		10.0 (7.8, 12.2)	11.0 (8.8, 13.4)
	Adolescent (GEP-NET and PPGL)		20.9 (7.7, 36.7)	2.4 (0.0, 6.8)
	Pooled adult GEP-NET and adolescents GEP- NET and PPGL		11.8 (6.4, 17.6)	9.2 (4.8, 13.6)

a Predicted probability median (5th, 95th percentile)

Both kidney and bone marrow (blood-based) dosimetry values, observed and predicted, were re-estimated in the pooled analysis of adolescent data from this study and adult data from the NETTER-1 and ERASMUS study

Tumour dosimetry in adolescents and adults

Table 6. Summary of dosimetry parameters of Lutathera for tumour (DAS)

Organ/Tumor	Parameter	Statistics	GEP-NET (N=4)	PPGL (N=6)	All participants (N=10)
Tumor	Absorbed Dose	n*	8	10	18
	(Gy/GBq)	Mean (SD)	**2.6 (1.2)**	**1.5 (1.1)**	2.0 (1.2)
		CV%	46.1	76.4	63.6
		Min-Max	1.4-5.1	0.17-3.3	0.17-5.1
	Theoretical cumulative	n*	8	10	18
	absorbed dose (Gy)	Mean (SD)	**76 (35)**	**44 (34)**	58 (37)
		CV%	46.1	76.4	63.6
		Min-Max	41-150	4.9-98	4.9-150

n= number of participants with corresponding evaluable dosimetry parameters.
Gy/GBq: absorbed dose per unit administered activity
Theoretical cumulative absorbed dose (Gy) is defined as Absorbed dose per unit activity (Gy/GBq)*4*7.4
* Summary statistics are based on individual lesions.
Zero values are excluded from summary statistics
One participant was excluded from the DAS due to the following reason: several imaging issues, hybrid methodology not utilized (only planar).
Dosimetry for one participant was obtained at Cycle 2

Table 7. Estimated tumour radiation absorbed dose for Lutathera in GEP-NET in adolescents (NETTER-P) and adults (NETTER-1) (DAS)

	Absorbed dose per unit activity (Gy/GBq)		Calculated absorbed dose for 4 x 7.4 GBq (29.6 GBq cumulative activity) (Gy)	
	Adolescents (N=4*) Mean ± SD	**Adults (N=20**) Mean ± SD**	**Adolescents (N=4*) Mean ± SD**	**Adults (N=20**) Mean ± SD**
Tumor	2.6 ± 1.2 (n=8)	8.1 ± 10.8 (n=65)	76 ± 35 (n=8)	240 ± 320 (n=65)

Values rounded to 2-significant digits
n=number of lesions

* Absorbed doses to the lesions could be evaluated for 3 GEP-NET participants in NETTER-P
** Absorbed doses to the lesions could be evaluated for 17 participants in NETTER-1

No new data on distribution, elimination, dose proportionality and special populations were submitted as part of this application.

2.3.3. Pharmacodynamics

No new data were submitted to support this application.

2.3.4. PK/PD modelling

In order to expedite the development of [177Lu]Lu-DOTA-TATE in the adolescent GEP-NET patient population, an adolescent dose justification was based on confirming similar exposure and dosimetry relationship between adults and adolescents using the same dose. The current approved adult dosage is 7.4 GBq every 8 weeks repeated 4 times, a total cumulative dose of 29.6 GBq. The popPK model from the interim analysis was updated with the primary analysis data. Kidney and bone marrow (BM) dosimetry

relationships with dose and CrClBL were investigated and comparability was assessed between adults and adolescents using the same empirical models from interim analysis final model.

Population PK modelling

A descriptive summary of demographic variables and baseline characteristics is given in Table 8. In comparison to the previous analyses, kidney mass is also included in the demographic characteristics of this analysis.

Table 8. Summary of demographic variables and baseline characteristics

	Continuous variables					
	Min	**1st quartile**	**Median**	**Mean**	**3rd quartile**	**Max**
Age (years)	13.0	14.0	15.0	15.1	16.0	17.0
Weight (kg)	39.5	46.55	55.0	54.04	60.0	71.0
Height (cm)	155.0	157.0	161.8	162.7	166.5	174.0
BSA (m^2)	1.30	1.45	1.58	1.56	1.62	1.85
$CrCl_{BL}$[a] (mL/min)	86.0	107.0	122.1	125.5	132.2	160.0
Kidney mass (g)	169.3	231.2	273.7	265.5	302.9	346.7
Categorical variables – number of patients (%)						
Sex:						
Female	6 (54.5%)					
Male	5 (45.5%)					
Indication:						
GEP-NET	4 (36.4%)					
PPGL	7 (63.6%)					

$CrCl_{BL}$: baseline creatinine clearance; BSA: body surface area

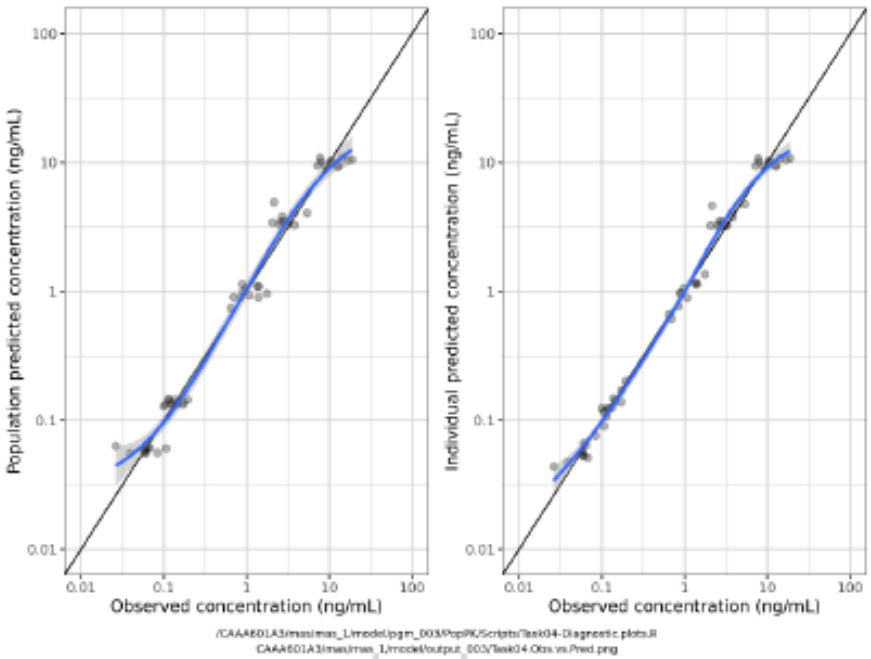
[a] $CrCl_{BL}(mL/min) = \frac{(140 - AGE) \cdot WEIGHT\ (kg)}{Serum\ creatinine(mg/dL) \cdot 72}(\cdot 0.85\ if\ female)$; serum creatinine, available in µmol/L was converted to mg/dL: 1 mg/dL = 88.4 µmol/L.

The final structural model was the same as the interim analysis, with the inclusion of two more patients in the current dataset. The covariate search using stepwise covariate model-selection (SCM) approach suggested kidney mass and body surface area (BSA) effects on clearance. Therefore, a popPK model including both kidney mass and BSA as covariates was assessed.

The parameter estimates of the final adolescent model with no covariates are presented in

Table 9. The observed [177Lu]Lu-DOTA-TATE concentrations vs. popPK model-predicted concentrations (both population and individual) were plotted in Figure 2.

Figure 2. Observed concentrations vs. population or individual prediction on log scale from the final PopPK model



Black dots are the concentrations. The black line is the identity line, blue line is the regression line with the 95% confidence interval in grey.

Table 9. Population PK parameter estimates from the final model

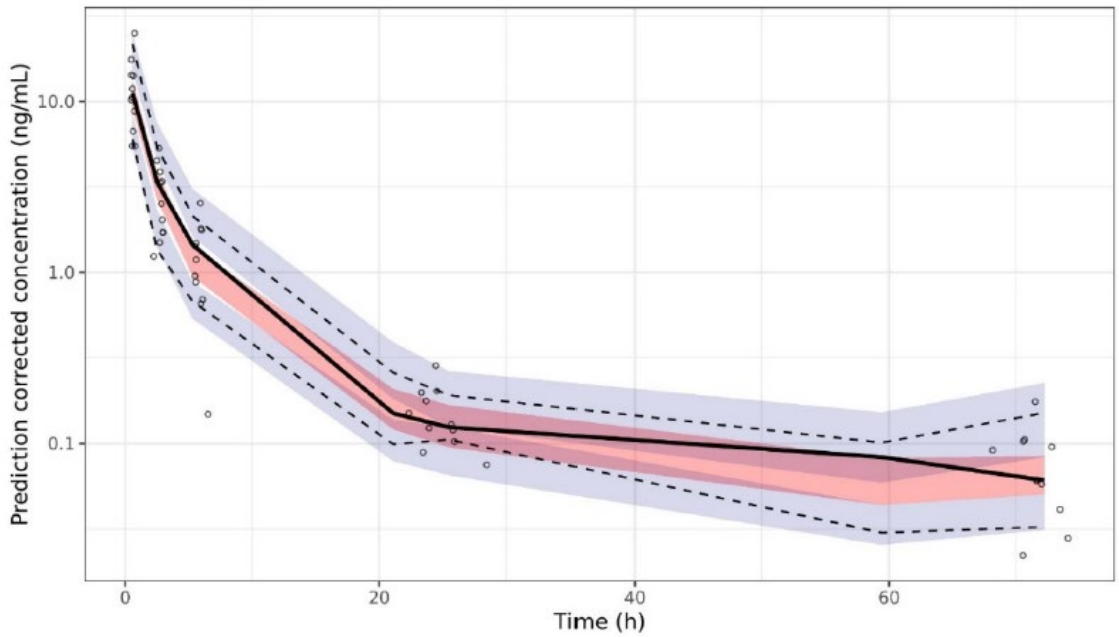
Parameter	Parameter estimate	RSE (%)
Cl (L/h)	5.92	5.43
V1 (L)	17.86	7.22
Q2 (L/h)	2.63	8.89
V2 (L)	99.42	15.04
ω_{Cl}	0.14	30.72
Constant residual error	0.25	10.62

%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 3. pcVPC for plasma concentration



The observed concentrations vs. time from 11 NETTER-P patients were plotted in the pcVPC (Figure 3). PopPK parameters for [177Lu]Lu-DOTA-TATE derived from the model are summarised in Table 10.

Table 10. Summary of [177Lu]Lu-DOTA-TATE PK parameters in blood from population PK model (Pharmacokinetic analysis set)

Parameter	Statistics	GEP-NET (N=4)	PPGL (N=7)	All subjects (N=11)
AUC Infinity (ng.h/mL)	n	4	7	11
	Mean (SD)	34.89 (1.89)	36.39 (5.55)	35.84 (4.49)
	CV%	5.42	15.25	12.53
	Geo-mean	34.85	36.05	35.61
	Geo-CV%	5.37	14.59	11.79
	Median	34.69	35.01	34.78
	Min-Max	32.81-37.39	30.71-46.83	30.71-46.83
AUC to Last Nonzero Concentration (ng.h/mL)	n	4	7	11
	Mean (SD)	31.81 (1.61)	32.9 (4.43)	32.5 (3.58)
	CV%	5.06	13.47	11.02
	Geo-mean	31.78	32.66	32.34
	Geo-CV%	5.03	12.88	10.43
	Median	31.67	31.88	31.88
	Min-Max	30.01-33.89	28.48-41.3	28.48-41.3
Clearance (L/h)	n	4	7	11
	Mean (SD)	6.13 (0.32)	5.89 (0.85)	5.98 (0.69)

	CV%	5.22	14.43	11.54
	Geo-mean	6.12	5.84	5.94
	Geo-CV%	5.25	14.59	11.88
	Median	6.09	6.05	6.05
	Min-Max	5.81-6.5	4.74-7.22	4.74-7.22
Cmax (ng/mL)	n	4	7	11
	Mean (SD)	10.46 (0.68)	10.25 (0.48)	10.33 (0.54)
	CV%	6.5	4.68	5.23
	Geo-mean	10.44	10.24	10.31
	Geo-CV%	6.59	4.7	5.22
	Median	10.5	10.5	10.5
	Min-Max	9.65-11.18	9.62-10.75	9.62-11.18
Tmax (h)	n	4	7	11
	Median	0.5	0.5	0.5
	Min-Max	0.5-0.7	0.5-0.7	0.5-0.7

n=number of subjects with corresponding evaluable PK parameters.
PK parameters estimates were obtained from population PK model.

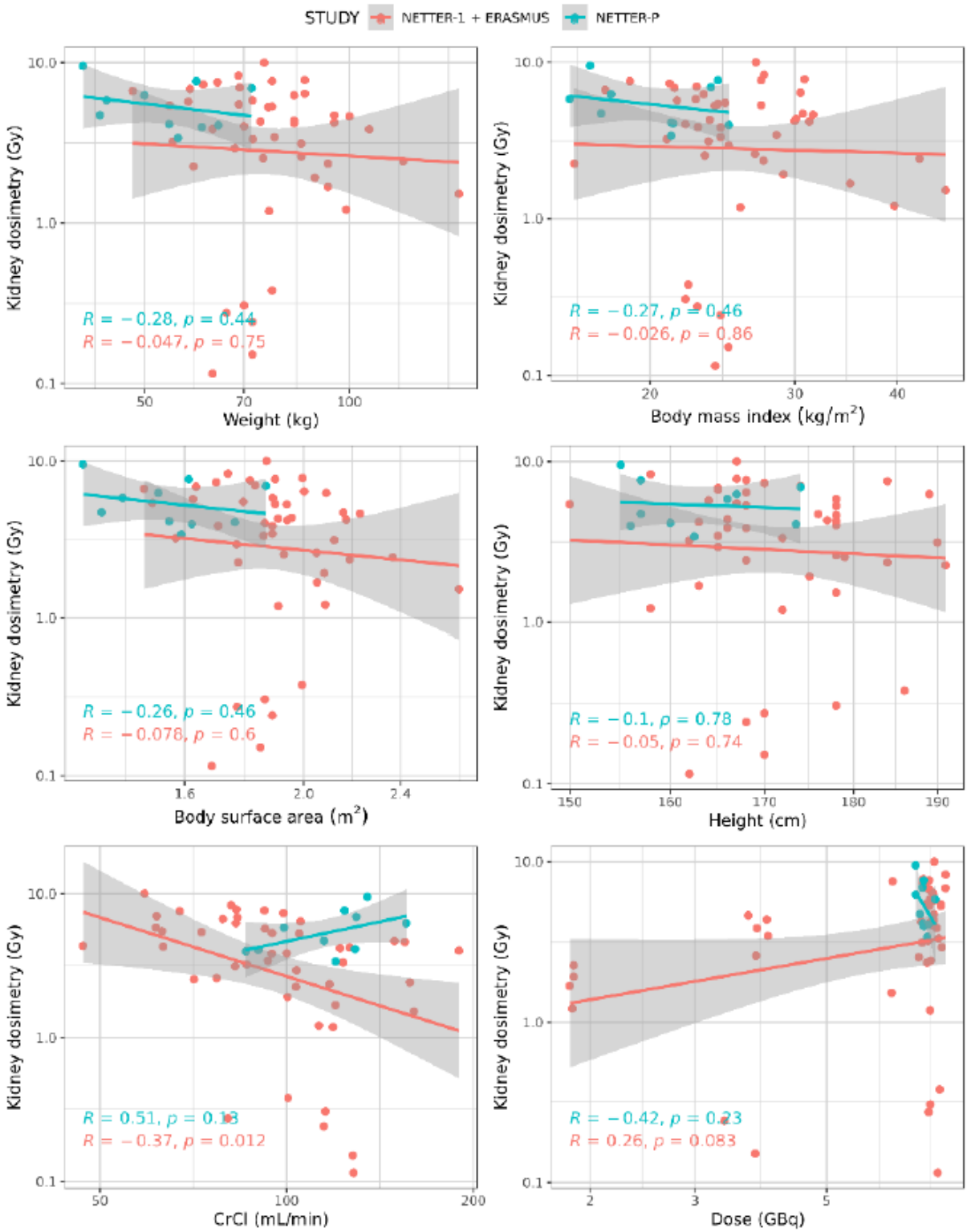
The observed (calculated using non-compartmental analysis, NCA) and popPK predicted PK metrics, AUClast, Cmax, Tmax, were compared between the 20 adults from the NETTER-1 study and the 11 adolescents from the NETTER-P study, and are summarised in Table 2 in the PK section of this report above.

Dosimetry modelling

Exposure-dosimetry analyses were based on the pooled adult and adolescent data. Adult dosimetry data are available from both NETTER-1 and ERASMUS studies. The correlation of demographics and other baseline features with kidney and BM dosimetry was explored. As no new exposure-dosimetry data was available for adults, only the adolescent data were updated based on the primary DCO. The final structural model for the pooled data from the interim analysis was tested for the updated data. The statistical model for kidney dosimetry was updated with different CrCl effects on dosimetry depending on adult or adolescent populations, as this model reduced the -2xLL as compared to the model without this effect. The BM dosimetry model remained the same as before, and none of the covariates showed any significant effect. Furthermore, probabilities of both observed and predicted dosimetry of adult and adolescent populations exceeding kidney and BM theoretical thresholds were calculated. The model predicted kidney probability was in the range of the observed for all tested scenarios, while the predicted BM probability for adults was higher than the observed. All predicted probabilities, but the adolescents' scenario did not go above the 20% chance to exceed the EBRT thresholds of 29 Gy for kidneys and 2 Gy for BM after 4 cycles of 7.4 GBq treatment with [177Lu]Lu- DOTA-TATE as demonstrated in the NETTER-1 report used for adolescent sample size calculation.

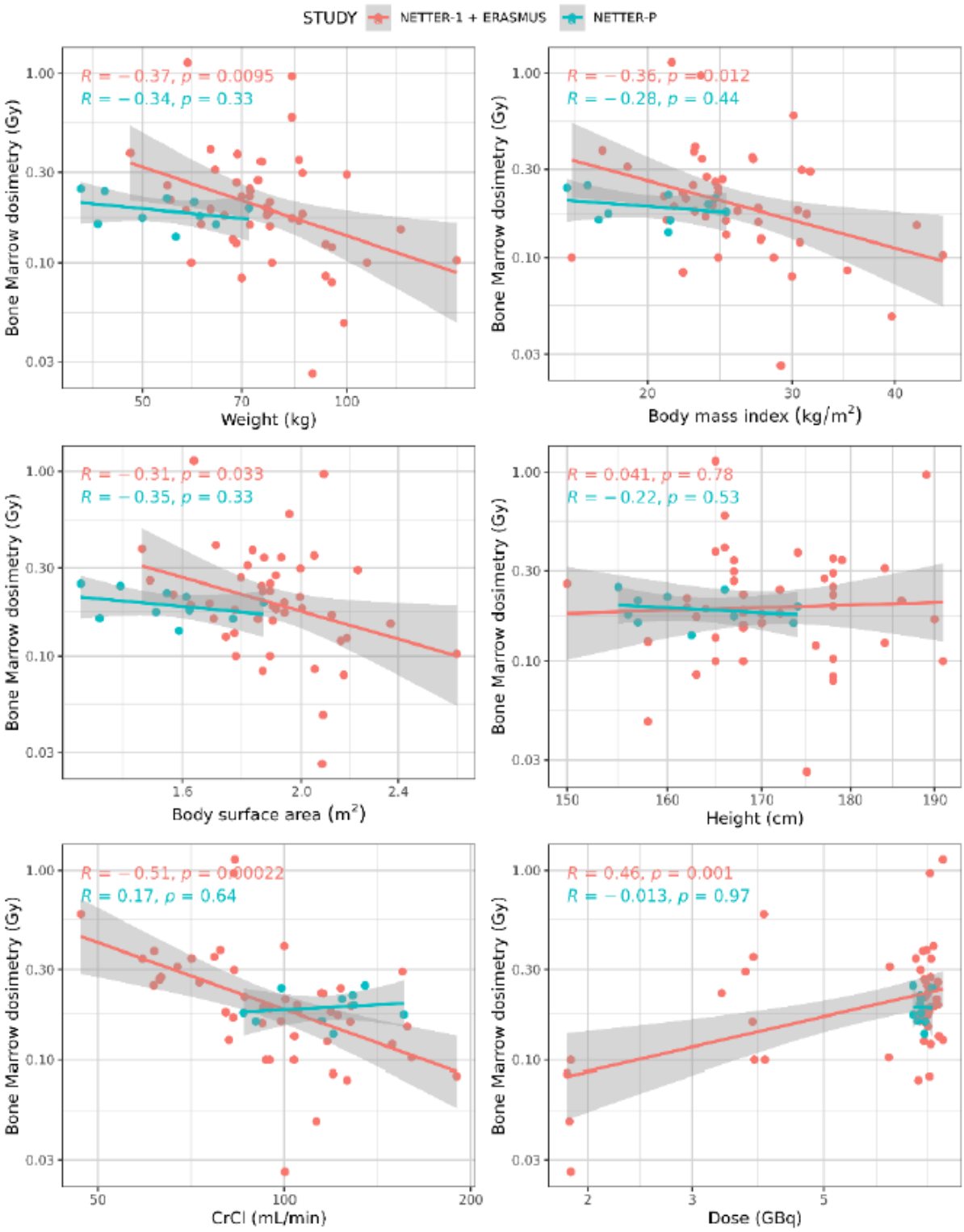
Dose and CrCl are considered as covariates for model building as explained in the first modelling report (of May 2023). Covariates for kidney and BM dosimetry were tested based on adult and adolescent studies. The correlation and the p-values, along with the clinical relevance, were considered for covariate selection. Relationships between covariates and kidney dosimetry are illustrated in Figure 4. There was no significant correlation between additional covariates and kidney dosimetry based on studies (NETTER-1+ERASMUS and NETTER-P).

Figure 4. Correlation between kidney dosimetry and covariates (N = 57)



Relationships between covariates and BM dosimetry are illustrated in Figure 5.

Figure 5. Correlation between bone marrow dosimetry and covariates (N = 57)



The same model with dose (exposure-metric) and CrCl as covariates for kidney and BM dosimetry model, based on the previously developed model for pooled adults and adolescent was tested in this primary analysis. Different kidney and BM dosimetry models were tested by adding the covariate effect (for significant covariates) to the original model structure.

Study effect, which can be assumed as adult vs. adolescent was used instead of using age as a categorical covariate. For kidney dosimetry, the final model was a model with different relationship of CrCl with dosimetry depending on adult or adolescent populations. Although adding study as a covariate for kidney dosimetry model improved the parameter estimates and decreased the -2xLL by 8.19 this result should be interpreted with caution due to the low sample size of the adolescent population (N = 10). Additionally, the predicted median values for kidney dosimetry based on the final model for adults and adolescents for cycle 1 are 4.37 and 5.39 respectively, which are below the threshold of 29 Gy for 4 cycles.

For BM dosimetry, no improvement in parameter estimates was observed when additional covariates were added. Referring to equation 4 and equation 5, Theta(1) refers to Apop, Theta(2) to Bpop, Theta(3) to Cpop, Theta(4) to Dpop, Theta(5) to Epop and Theta(6) to Fpop, the structure of final models are illustrated below.

$$Kidney\ Dosimetry = Apop \times \left[\left[\frac{Dose\ (GBq)}{7.4}\right]^{Bpop} \times \left[\frac{CRCL}{99}\right]^{Cpop}\right] : \text{Equation 6}$$

$$\text{where, } C = C_{pop} + \text{beta\_C\_STUDY\_NETTER\_P}[\text{STUDY} = \text{NETTER} - \text{P}]$$

$$Bone\ marrow = Dpop \times \left[\left[\frac{Dose\ (GBq)}{7.4}\right]^{Epop} \times \left[\frac{CRCL}{99}\right]^{Fpop}\right] : \text{Equation 7}$$

Final parameter estimates for the model are shown in Table 11.

Table 11. Population PD parameter estimates from the Final dosimetry models (N = 57)

Parameter	Dosimetry model parameters (%RSE)
Apop – Kidney dosimetry baseline	4.37 ± 0.32 (7.22)
Bpop - Dose effect on kidney	0.65 ± 0.14 (22.0)
Cpop - CRCL effect on kidney	-0.55 ± 0.19 (35.1)
beta_C_STUDY_NETTER_P- CrCl effect on kidney dosimetry based on adult or adolescent populations	1.58 ± 0.59 (37.5)
Dpop - Bone marrow dosimetry baseline	0.24 ± 0.022 (8.90)
Epop - Dose effect on BM	0.52 ± 0.2 (37.8)
Fpop - CRCL effect on BM	-1.18 ± 0.23 (19.7)
Error (proportional) b_1	0.48 ± 0.054 (11.3)
Error (proportional) b_2	0.63 ± 0.078 (12.5)

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

$$Kidney\ Dosimetry = 4.37 \times \left[\left[\frac{Dose\ (GBq)}{7.4}\right]^{0.65} \times \left[\frac{CRCL}{99}\right]^{(-0.55[+1.58\ if\ STUDY = NETTER-P])}\right]$$

$$Bone\ marrow = 0.24 \times \left[\left[\frac{Dose\ (GBq)}{7.4}\right]^{0.52} \times \left[\frac{CRCL}{99}\right]^{-1.18}\right]$$

Figure 6. Kidney and bone marrow dosimetry with CrCl (N=57)

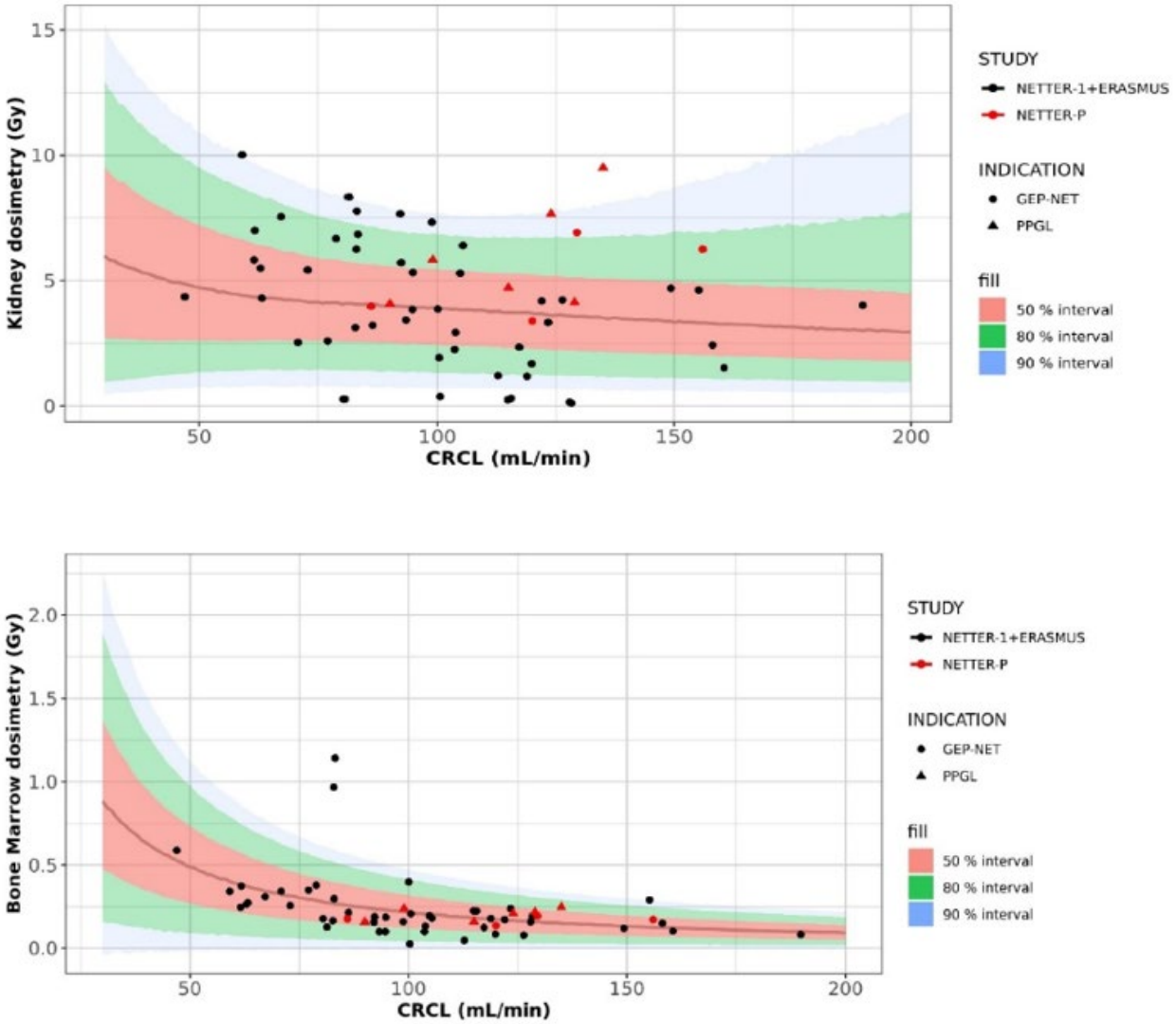
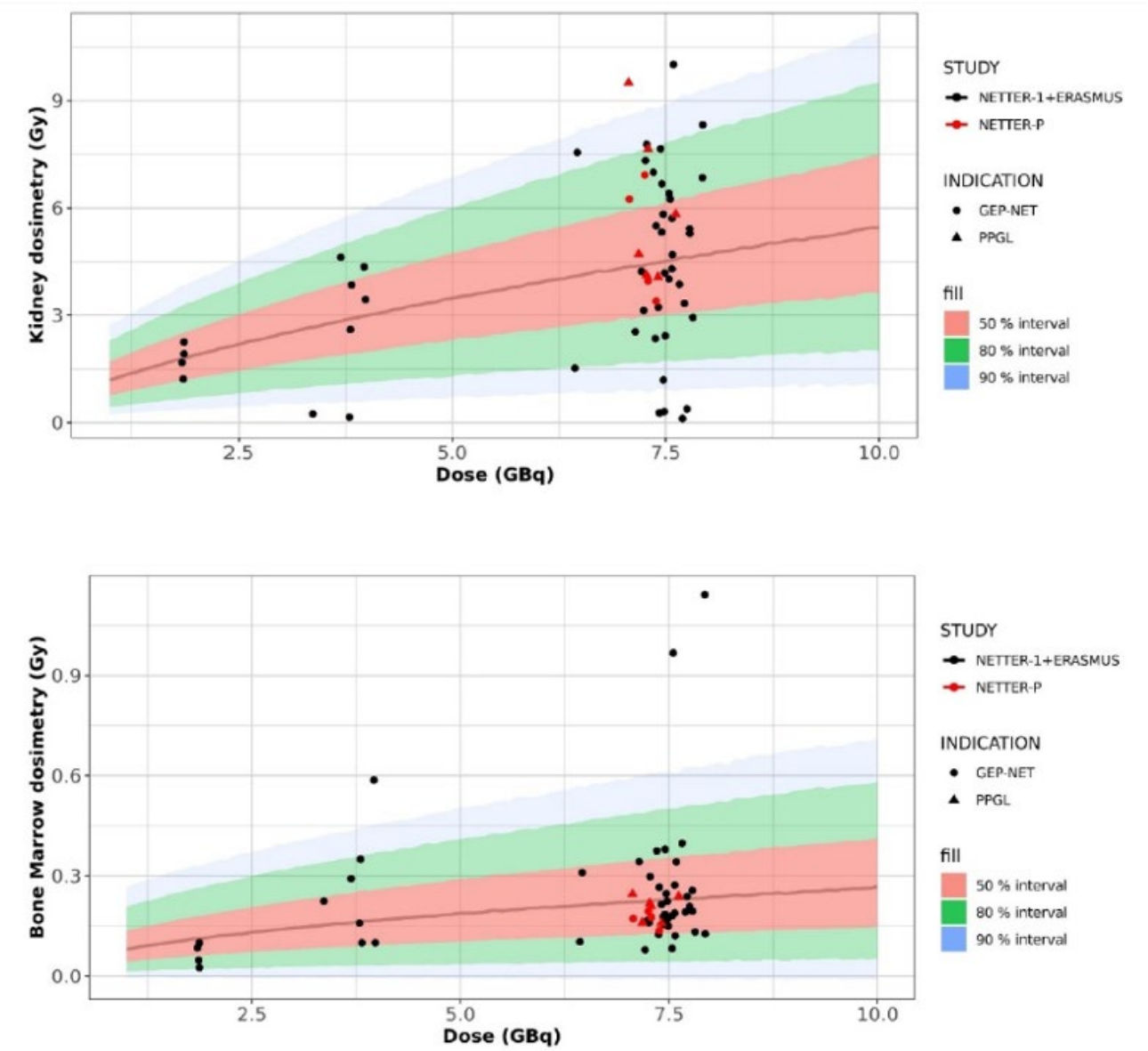
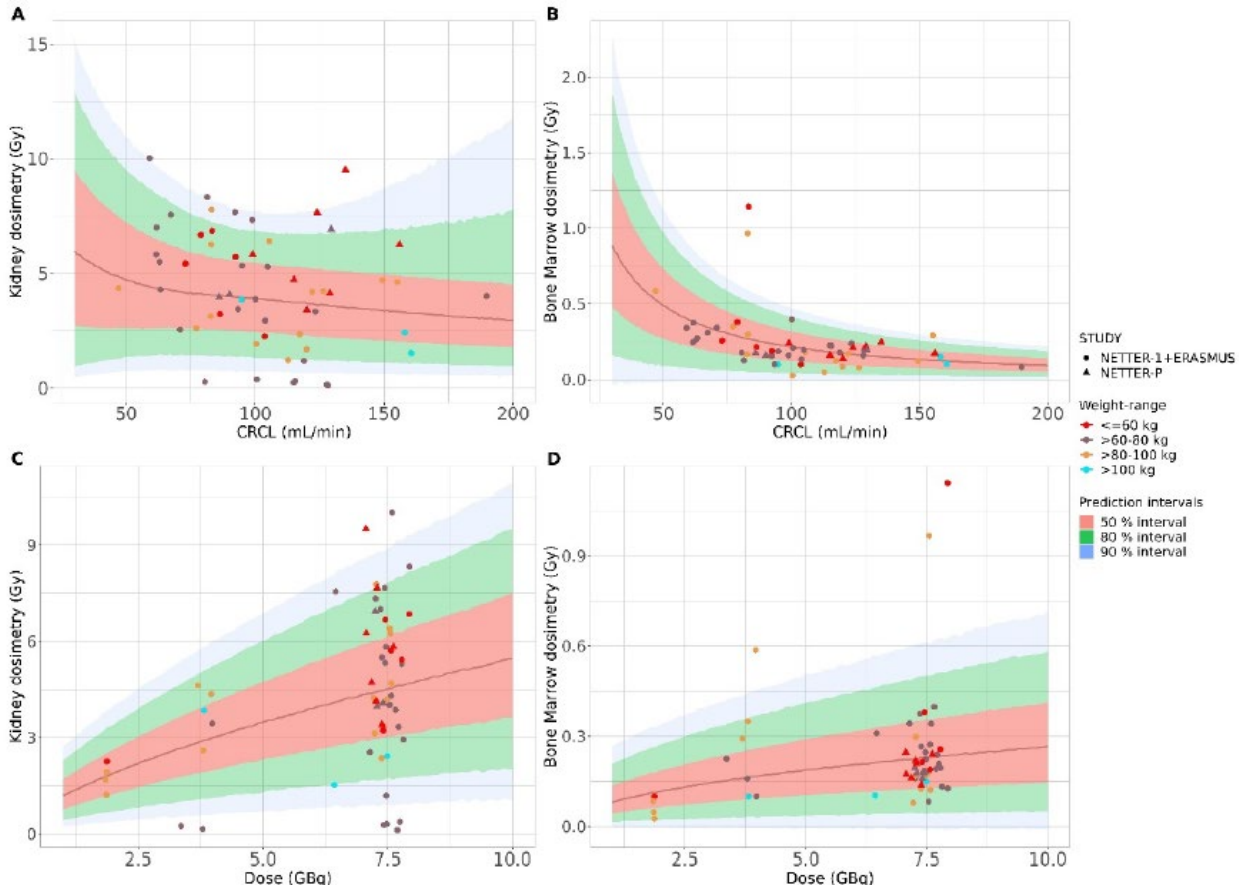


Figure 7. Kidney and bone marrow dosimetry with dose (N=57)



The impact of weight on the model derived for kidney and BM dosimetry was also assessed for adults and adolescents by grouping patients into 4 categories: ≤60 kg, >60-80 kg, >80-100 kg, or >100 kg. The kidney and BM dosimetry vs. CrCl and dose by weight categories were plotted (Figure 8).

Figure 8. Impact of body weight on kidney and bone marrow dosimetry



Furthermore, the probabilities for different scenarios for observed and predicted values of kidney and BM dosimetry to exceed the given EBRT threshold were calculated. Predicted probabilities were calculated by simulating a trial of 500 patients with replacement from the adult population (N = 47) using the adult model on kidney and BM dosimetry. This process was repeated 500 times. Subsequently, the predicted probabilities for adults' to exceed kidney and BM threshold of 29 Gy and 2 Gy were calculated. Similarly, predicted probabilities to exceed the defined threshold of kidney and BM dosimetry were calculated from the final dosimetry model based on pooled adult and adolescent data. The predicted probabilities were summarized by the median (5th, 95th percentiles) across the 500 simulated trials (Table 5 in the PK part of the Assessment Report above).

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

Assessment of PK of Lutathera in adolescent participants in NETTER-P study (observed and predicted values)

The Lutathera concentration-time profiles following the first dose administration in the NETTER-P study were comparable for both GEP-NET and PPGL disease cohorts, with the blood concentration showing a bi-exponential phase with a quick first phase until 24 hours and a slower second phase until 72 hours post-administration.

Observed PK metrics for adults and adolescents

In the underlying clinical studies (NETTER-P (adolescents) and NETTER-1 (adults)), the observed PK metrics for adults and adolescents indicated that AUClast was about 36% and Cmax about 24% higher in adolescents with GEP-NET and PPGL compared to adults with GEP-NET. Taking into account the high variability, results could be interpreted to show a great overlap (i.e. to be probably "overall consistent").

Modelled PK metrics for adults and adolescents

Based on the final popPK model, the exposure could be regarded as comparable between adolescents and adults. However, this conclusion was made based on n=11 adolescent patients which was in compliance with the sample size discussed for the PIP. Predicted AUC showed more similar exposures (31.01 ng.h/mL in adults vs. 32.34 ng.h/mL in adolescents) compared to observed results (30.08 ng.h/mL in adults vs. 41 ng.h/mL in adolescents). Upon request, the MAH provided boxplots for AUC and Cmax for predicted and observed exposures to be able to compare exposure between adolescents and adults. Observed AUC tended to be higher in adolescents compared to adults, the median of adolescents is around the 75th percentile of the adult values. But the range of adolescent's AUC values is comprised within adult AUC values. Model-based AUC predictions tended to be lower for adolescents and higher for adults. For Cmax, observed as well as predicted values were in a comparable range for adolescents and adults. In order to confirm an appropriate model fit across different bodyweights, upon request, the MAH also provided VPCs stratified by bodyweight (<60 kg). Considering the small patient numbers, model fit was considered acceptable.

Organ dosimetry

For adolescents investigated in NETTER-P, the mean dosage-normalised absorbed radiation doses (Mean (SD)) of Lutathera in the organs at risk, i.e., kidney and bone marrow (estimated using blood data), were 0.78 (±0.28) Gy/GBq and 0.026 (±0.005) Gy/GBq, respectively, in the 10 participants of the Dosimetry Analysis Set (DAS).

The organs receiving the largest mean theoretical cumulative absorbed dose (Mean (SD)) after 4 cycles of treatment with a theoretical cumulative dosage of 29.6 GBq of Lutathera were the pituitary glands (33 [±13] Gy), the kidneys (23 [±8.3] Gy), the spleen (22 [±8.1] Gy) and the urinary bladder wall (16 [±2.6] Gy). The theoretical cumulative absorbed dose in the red marrow by either blood- or by imaging-based methods were 0.78 (±0.15) and 1.7 (±0.79) Gy, respectively.

Overall, the results of the target organ dosimetry were comparable between GEP-NET and PPGL disease cohorts. There were some differences, e.g. the absorbed dose in the red marrow based on imaging was somewhat more pronounced in the PPGL cohort (mean of 0.043 Gy/GBq in GEP-NET vs 0.067 Gy/GBq in PPGL). This could, however, be a chance finding considering the multiple organs compared and the small sample size hampering a valid comparison.

For the comparative assessment of observed dosimetry results in adolescent and adults, overall, the dosimetry results of organs listed above in Table 3 were comparable between adolescent and adult participants treated with Lutathera. There were some minor exceptions, for example, for osteogenic cells absorbed doses are distinctly higher for adults (approximately 0.15 ± 0.27 Gy/GBq vs. 0.05 ± 0.02 Gy/GBq), this would, however, be expected taking into account the small cohorts, the variability of the results and the multiples sides which were compared.

Both studies (NETTER-1 and NETTER-P) employed the same hybrid methodology utilizing both serial planar images and a single time point SPECT/CT. It was highlighted that due to different vendors performing the dosimetry at different times with different dosimetry software version and reference phantoms (ICRP-89 vs. ORNL Adult Phantom), not all the same organ estimates were derived between the two studies. It was, however, concluded that the methodology can otherwise considered to be comparable for the same organs. It was highlighted that pituitary gland and red marrow dosimetry by imaging were not derived in NETTER-1, only in NETTER-P. The absorbed dose coefficients in the red

marrow by imaging were, on average, about 2-fold higher than blood-based estimates. Unfortunately, investigations for absorbed dose coefficients in the red marrow based on imaging were not performed in the NETTER-1 study and therefore no comparison with adult data from NETTER-1 is possible.

The MAH states that neither kidney nor bone marrow model estimates were affected by the addition of adolescent data confirming similar dosimetry estimates, similar probability of going beyond External Beam Radiation Therapy (EBRT) thresholds for adolescents and adults, and that the same empirical model could be used for both populations. It was concluded that both observed and predicted results of the simulation revealed that the probabilities of exceeding 29 Gy for kidneys and 2 Gy for bone marrow after 4 cycles of treatment with Lutathera were low and comparable between adolescent and adult populations (Table 5).

The probability for adolescents to exceed the 29 Gy threshold in kidneys was predicted to be twice as high in adolescents (20.9%; 5th, 95th percentile 7.7, 36.7) compared to adults (10.0%; 5th, 95th percentile 7.8, 12.2). In the modelling and simulation Report of August 2023 the median probability of an adolescent population with normal renal function to exceed 29 Gy was predicted to be 11.3%, which could not be confirmed using clinical data from adolescent patients (also discussed in chapter "organ dosimetry results"). It remains unclear, whether this observed higher risk to exceed 29 Gy kidney dosimetry could be related to differences in exposure or to other effects. However, the predicted median values for kidney dosimetry after the first dose (not cumulative) for adults and adolescents were 4.37 Gy and 5.39 Gy, respectively, which can be regarded as similar. In contrast to higher risk regarding kidney dosimetry, the probability to exceed >2 Gy in bone marrow is predicted to be lower in adolescents compared to adults. Conclusions should be made with caution as the analyses are based on n=10 adolescent patients.

In order to minimize the risk of potential radiation toxicities affecting bone marrow and kidney function for each study participant, an accelerated analysis of dosimetry and safety data was performed for each participant after the first dose of treatment (or as soon as feasible upon a later dose in the exceptional circumstances) to enable the Investigator to take a decision for the subsequent Lutathera doses. The results of dosimetry assessments (imaging and blood dosimetry) were provided to the Investigators for their evaluation before administering subsequent therapeutic cycles in each participant. In case that dosimetry results exceeded reference limits in individual participants, an independent DSMB was consulted to evaluate benefit-risk for the participant and advise on whether dosing could continue and at which level. Dosimetry assessment performed in 3 PPGL participants (all with normal kidney function but relatively small size/volume) displayed abnormally high absorbed doses in the kidneys. Two of the 3 participants had Lutathera dose reduced, based on extrapolation the cumulative absorbed dose for a total of 29.6 GBq would have crossed the predefined threshold of 29 Gy in the kidney.

Based on the fact that

I.) individual dosimetry was applied in the clinical study,

II.) Lutathera doses were reduced in 2 patients with abnormally high absorbed doses in the kidneys based on individual dosimetry,

III.) the currently available data set justifying the proposed unchanged dosing regimen in adolescents aged 12 years and older is very small,

IV.) the probability for adolescents to exceed the 29 Gy threshold in kidneys is predicted to be twice as high in adolescents (20.9%; 5th, 95th percentile 7.7, 36.7) compared to adults (10.0%; 5th, 95th percentile 7.8, 12.2).

the MAH was asked to critically discuss if a similar approach of applying "individual dosimetry assessments", e.g. comparable to what was done in the Clinical Study Protocol, was warranted and feasible in clinical praxis, and to update SmPC and corresponding sections of the PL to reflect the need for "individual dosimetry assessments" if justified .

Predicted probabilities and observed proportions of patients with kidney dosimetry >29 Gy were higher in adolescents (~20%) than in adults (10- 13%). The small sample size and the large prediction interval for adolescents as well as the fact that there is still an overlap between the range of predicted probabilities for both populations was highlighted by the MAH and is acknowledged.

Even though it can be agreed that, based on the now available results in the small dataset in adolescent patients from NETTER-P study, the collected dosimetry data do indicate that the target organ dosimetry from adolescent patients fell overall in the range of that of the adults, clinical data to conclude that the safety profile in adolescents (especially the long term safety profile) will be consistent with the safety profile in adults are still very limited. By monitoring organ exposure, especially to the kidneys and bone marrow, applicable dosimetry thresholds for organs could be better adhered to, and the risk of (radiation) dose-dependent adverse events could probably be reduced. This could be particularly important in patients with e.g. pre-existing or developing renal impairment or other pre-conditions making them more vulnerable to radiation. Following the MAH's decision not to pursue an extension of indication to paediatric patients, no specific recommendations on the option of performing individual dosimetry were included in sections 4.2 or 4.4 of the SmPC, as initially proposed. The dosimetry data generated during the NETTER-P study was kept in section 11.

Overall tumour absorbed doses of Lutathera:

In adolescents,

• For the GEP-NET cohort (N=4), the mean (SD) absorbed dose coefficient was 2.6 (1.2) Gy/GBq with a coefficient of variation (CV) of 46.1%, and a range of 1.4-5.1 Gy/GBq.

• For the PPGL cohort (N=6), the mean (SD) absorbed dose coefficient was 1.5 (1.1) Gy/GBq with a CV of 76.4%, and a range of 0.17-3.3 Gy/GBq.

The uptake of radioactivity at tumour sites was generally high in both disease cohorts compared to organs with a positive tumour-to-organ ratio. With regard to the observed dosimetry values for Lutathera in the tumour, the results were not completely comparable between GEP-NET and PPGL disease cohorts. The absorbed dose in the tumour was about 73% higher in GEP-NET patients (Table 6). This could be a chance finding and the small sample size hampering a valid comparison needs to be acknowledged.

When comparing the estimated tumour radiation absorbed dose for Lutathera in GEP-NET in adolescents (NETTER-P) and adults (NETTER-1), the mean (SD) absorbed dose in adults was considerably higher (2.6 ± 1.2 Gy/GbBq vs. 8.1 ± 10.8 Gy/GbBq, see Table 7).

The submitted Clinical Summary emphasised that tumour dosimetry was associated with large variability and due to the small numbers of patients and evaluable lesion, it would be difficult to draw any strong conclusions. It was stated that compared to adult GEP-NET data, the comparison is even more challenging given than only 8 lesions from 3 adolescent GEP-NET patients could be compared against 65 lesions from NETTER-1 from the 20 adult patients sub-set. The range of extrapolated cumulative tumour absorbed doses after 4 cycles observed in adolescents (41 to 150 Gy) overlaps with the wider range observed in adults (7 to 2174 Gy) (NETTER-1).

While the mean absorbed dose in tumour lesions is numerically lower in NETTER-P compared to NETTER-1, the mean observed cumulative absorbed dose may still provide sufficient volume reduction or tumour control probability based on published exposure-efficacy relationships for Lutathera in GEP-NET in line with early clinical signs from the NETTER-P study.

The sparse results on clinical effects on the tumour are discussed in the efficacy part.

PK/PD modelling

Population PK modelling

The final structural model was the same as the interim analysis, with the inclusion of two more patients in the current dataset. The covariate search using SCM approach suggested kidney mass and BSA effects on clearance. Therefore, a popPK model including both kidney mass and BSA as covariates was assessed. Although the inclusion of those covariates reduced the -2xLL and could explain the IIV on clearance, this was estimated with very low precision at RSE of 251.2%. Considering the reduced sample size and the lack of knowledge regarding kidney mass acquisition feasibility a second covariate search, horseshoe prior approach, was applied and no covariate was determined to be statistically significant. Consequently, the popPK model with no covariate was selected as the final model as clearance and its IIV were estimated with good precision at RSE of 5.43%, and 30.72%, respectively. The popPK parameters estimated for adolescents were within the range of popPK parameters estimated for adults (NETTER-1). Based on the final popPK model, the exposure was comparable across GEP-NET and PPGL patients in the NETTER-P study. In addition, the exposure metrics derived from the adolescent model were comparable to the adult exposure metrics, confirming similar exposure between the NETTER-P adolescent and NETTER-1 adult populations.

Dosimetry modelling

Considering the 5th and 95th percentile of the probabilities of predicted dosimetry for both organs, comparable kidney and BM dosimetry and exposure-response relationship between adults and adolescents were confirmed. Finally, the relationship between the kidney mass and kidney dosimetry was investigated using only NETTER-P (N=10) data. Based on this analysis, for adolescent patients with the kidney mass of ≤216 g, kidney dosimetry may exceed the 29 Gy theoretical threshold after receiving full 7.4 GBq Lutathera dose for 4 cycles. However, due to small sample size, the conclusion should be made with caution.

For the adult population (which remains unchanged from the first analysis), there was a significant correlation observed between BM dosimetry and weight (R= -0.37 and p= 0.0095), BMI (R= -0.37 and p= 0.0095), BMI (R= -0.36 and p= 0.012), BSA (R= -0.31 and p= 0.033), CrCl (R= -0.51 and p= 0.00022), and dose (R= 0.46 and p= 0.001). As body weight, BMI, and BSA are highly correlated, only body weight was further tested as a covariate for the BM dosimetry model.

The same model with dose (exposure-metric) and CrCl as covariates for kidney and BM dosimetry model, based on the previously developed model for pooled adults and adolescent was tested in this primary analysis. The adult and adolescent data fall within the same range as presented in Figure 6 and Figure 7 confirming comparable exposure-dosimetry between adults and adolescents. The impact of weight on the model derived for kidney and BM dosimetry was also assessed for adults and adolescents by grouping patients into 4 categories: ≤60 kg, >60-80 kg, >80-100 kg, or >100 kg. The kidney and BM dosimetry vs. CrCl and dose by weight categories were plotted (Figure 8). Most of the patients, regardless of the categories, fell within the 90% prediction interval.

Generally, as discussed in the PIP, the approach was to extrapolate efficacy based on limited PK and dosimetry data in adolescents i.e. an extrapolation of the adults data via modelling to be confirmed by the NETTER-P data. The PIP compliance check discusses the limited number of expected results in adolescents […] "*the total number of adolescents that will be included and by that the amount of data that will become available in support of the full extrapolation of adult data to adolescents is very limited, especially when considering the GEP-NET cohort independently. Yet, it is likely the best we can get within a reasonable time frame, also considering the rarity of the GEP-NETs (and PPGLs) in adolescents. Of note, it will eventually be up to the CHMP whether this data will be sufficient to grant a "paediatric" (adolescent) indication*. […]").

This approach has been reflected in section 5.2 of the approved SmPC:

"Pharmacokinetic data were collected from 11 adolescents aged 12 years and older with somatostatin receptor-positive GEP-NET or PPGL enrolled in the NETTER-P study using the adult dosage. These data were within the range of values in adults, with a mean AUC_{inf} of 35.8 ng.h/mL (CV 12.5%), a mean CL of 6.0 L/h (CV 11.5%) and a mean C_{max} of 10.3 ng/mL (CV 5.2%), which occurred at the end of the Lutathera infusion."

Regarding dosimetry, the section 11 of the SmPC states:

"Dosimetry of lutetium (177Lu) oxodotreotide in adolescents has been studied in 4 GEP-NET and 6 PPGL patients (age range: 12 to <18 years) enrolled in the phase II NETTER-P study. Dosimetry was collected to define the biodistribution profile of lutetium (177Lu) oxodotreotide and to calculate whole body and organ radiation dosimetry, with particular focus on the radiation absorbed dose to critical organs (e.g. kidney and bone marrow)."

The SmPC then tabulates the mean and SD of the estimated absorbed dose for adolescents receiving Lutathera.

Although the applicant decided not to pursue an extension of indication for paediatric patients, the summary above as proposed for the SmPC is regarded to be overall adequately reflecting the PK and dosimetry results and the respective conclusions drawn from the models.

2.3.6. Conclusions on clinical pharmacology

Results to support the full extrapolation of adult data to adolescents are very limited, especially when considering the GEP-NET cohort independently (N=4 patients). A very limited data set was, however, expected considering the rarity of the GEP-NETs (and PPGLs) in adolescents and this limitation was also discussed when discussing the PIP.

Based on the modelling data, a higher probability for adolescents to exceed the 29 Gy threshold in kidneys could not be excluded and the MAH was requested to discuss whether applying "individual dosimetry assessments", e.g. comparable to what was done in the Clinical Study Protocol, was warranted and feasible in the clinical practice. However, since the MAH decided to drop their claim for an extension of indication to paediatric patients, this matter was not further pursued.

2.4. Clinical efficacy

According to the PIP, it was agreed that due to the rarity of the disease in the paediatric population, one clinical study should be submitted to support the extension of indication.

Study CAAA601A32201 (also referred to as NETTER-P) is a multicenter, open-label, single-arm study that was conducted to evaluate safety and dosimetry of Lutathera in paediatric patients (12 to <18 years old) with somatostatin receptor (SSTR) positive GEP-NET and Pheochromocytoma and paragangliomas (PPGL).

The study aimed to enroll at least 8 adolescents (including at least 3 GEP-NET patients).

- **Tabular overview of clinical studies**

Protocol No, Countries & Study dates	Study design, Purpose & population studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status & Reports of Study Results

Protocol: CAAA601A32201 **Countries:** France, Poland, Spain, United Kingdom, United States **Start:** 31-Aug-2022 **Data Cut Off:** 12-Mar-2024 **End:** Ongoing	A multicenter open-label study to evaluate safety and dosimetry of Lutathera in adolescent patients with somatostatin receptor (SSTR)-positive gastroenteropancreatic neuroendocrine (GEP-NET) tumors, pheochromocytoma and paragangliomas (PPGL)	**Total**: 12 screened, 11 enrolled as of data cut-off 12-Mar-2024 **Age**: 13-17 (15) years **Groups**: 2 GEP-NET cohort: 4 PPGL cohort: 7	**Form(s)**: Lutathera radiopharmaceutical solution (7.4 GBq / 200 mCi of Lutathera per 30 ml vial), infusion **Duration**: Treatment period 24 weeks Follow-up period 5 years	**Study Status**: ongoing **Report no**. [NETTER-P Primary CSR-2024] full, final **Report date**: 25-Oct-2024 **Other reports**: **Report no**. NETTER-P Interim CSR-2023 full, final

2.4.1. Dose response study(ies)

The dose regimen proposed for use in the adolescent population is the same as that approved in adults based on modelling and simulation analysis. The treatment consisted of Lutathera (7.4 GBq (200 mCi) every 8 weeks ± 1 week) for a total of 4 doses. Due to the rarity of the disease, the similarity in organ absorbed radiation doses from PRRT with Lutathera in adolescent participants with SSTR-positive GEP-NETs and PPGLs in NETTER-P is essential for bridging efficacy and safety data in this application. Thus, this endpoint was defined as co-primary together with the evaluation of safety and tolerability of Lutathera in the adolescent target population.

2.4.2. Main study(ies)

Title of Study

NETTER-P

Protocol identification number: CAAA601A3**2201**, EudraCT no. 2020-002951-39

"A multicenter open-label study to evaluate safety and dosimetry of Lutathera in adolescent patients with somatostatin receptor (SSTR)-positive gastroenteropancreatic neuroendocrine (GEP-NET) tumors, pheochromocytoma and paragangliomas (PPGL)"

Study period:

Study initiation date: 31-Aug-2022 (first participant first visit) Data cut-off date: 12-Mar-2024 (ongoing)

Phase of development (phase of this clinical study): II

Indication studied: Somatostatin receptor-positive gastroenteropancreatic neuroendocrine (GEP-NET) tumours, pheochromocytoma and paragangliomas (PPGL)

Study Sponsor: Advanced Accelerator Applications, a Novartis company

Regulatory agency identifier number(s): EudraCT no. 2020-002951-39

Study initiation date: 31-Aug-2022 (first participant first visit)

Data cut-off date: 12-Mar-2024

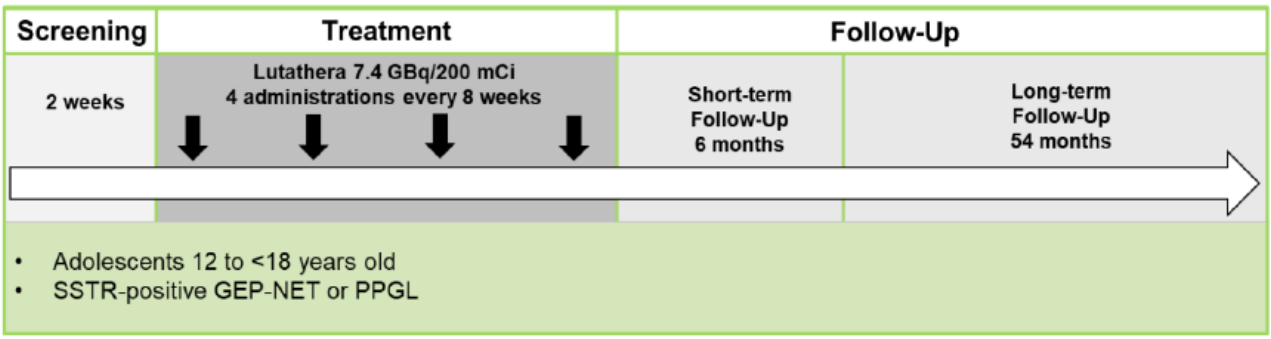
Coordinating Investigator: Dr. Markus N. Gaze, University College London Hospitals NHS Foundation Trust, 250 Euston Road, London NW1 2PG, United Kingdom

GCP: The Clinical trial was performed in accordance with GCP as claimed by the MAH

Methods

The study schedule for each participant consisted of the screening period (up to 2 weeks) followed by the treatment period (4 treatment administrations at 8 week intervals [±1 week]) and the follow-up period (5 years) (figure below).

Figure 9. Study design



Screening period: During the screening period of up to 2 weeks, participant eligibility was determined according to the protocol's pre-defined inclusion and exclusion criteria. Participants who met all eligibility criteria at screening were enrolled in the study. The enrollment and Lutathera order were performed immediately after all eligibility criteria were verified and the participant was confirmed to be eligible.

Treatment period: The treatment period consisted of 4 Lutathera treatments administered at 8 week intervals (±1 week). Lutathera administration occurred on Week 1, Day 1 of each cycle. Proposed treatment duration was 4 doses of Lutathera (7.4 GBq/200 mCi per administration; cumulative dose: 29.6 GBq/800 mCi). With each administration, participants also received sterile 2.5% Lys-Arg amino acid (AA) solution for infusion for renal protection. An antiemetic was administered prior to infusion of the AA solution for prevention of infusion-related nausea and vomiting.

The **dosimetry** and **pharmacokinetics (PK) assessments** were performed during the first week after the first Lutathera dose, i.e., one time during the study treatment period for each participant. In the circumstance when dosimetry could not be performed after the first Lutathera dose, it was completed as soon as feasible upon a later dose. The dosimetry analysis estimated the cumulative absorbed radiation dose from 4 Lutathera administrations using the radiation dose observed at the first or later Lutathera administration, to enable an informed decision on the next dose to be administered to the participant.

Safety assessments in the study included physical examinations, vital signs, electrocardiograms (ECG), standard clinical laboratory evaluations (haematology, blood chemistry, and urinalysis), safety biomarkers and AE monitoring. Safety assessments were performed in each treatment cycle to monitor potential toxicities, with clinical laboratory samples taken regularly after each Lutathera dose. A set of safety biomarkers of growth and development, bone development, reproductive and endocrine (pituitary) function was collected and analysed for each participant.

Tumour response assessments were considered exploratory in this study. Computed tomography (CT)/ magnetic resonance imaging (MRI) was done according to the assessment schedule to evaluate tumour response according to RECIST 1.1 criteria.

An external **Data and Safety Monitoring Board (DSMB)** was established in the study to evaluate accumulating safety and dosimetry data to ensure the safety of adolescents enrolled in the study. In case the resulting cumulative radiation dose exceeded the reference limits, the DSMB evaluated the benefit-risk for the participant and provided recommendations to the Investigator on whether dosing could continue and at which level.

In order to minimise the risk for each study participant, an accelerated analysis of dosimetry and safety data was performed for each participant to enable the Investigator to make a decision for subsequent Lutathera doses. The results of dosimetry assessments (imaging and blood dosimetry) were provided to the Investigators for their evaluation before administering subsequent therapeutic cycles in each participant.

Follow-up period: Each participant who received at least one dose of Lutathera was to be followed up for a total of 5 years (60 months) from the time the participant received the last Lutathera dose. This follow-up period comprises a short-term follow-up of 6 months in order to evaluate cumulative Lutathera toxicities, followed by a long-term follow-up of another 54 months.

Study participants

The study aimed to enroll at least 8 adolescents (including at least 3 GEP-NET patients).

The key **inclusion criteria** included:

- Participants from 12 to < 18 years of age at the time of enrollment.
- GEP-NET cohort: the presence of metastasized or locally advanced, inoperable (curative intent), histologically proven, G1 or G2 (Ki-67 index ≤20%), well-differentiated GEP-NET.
- PPGL cohort: the presence of metastasized or locally advanced, inoperable (curative intent), histologically proven PPGL.
- Expression of SSTRs confirmed by a SSTR imaging modality within 3 months prior to enrollment, with tumour uptake observed in the target lesions more or equal to the normal liver uptake.
- Performance status as determined by Karnofsky score ≥ 50 or Lansky Play-Performance Scale score ≥ 50.
- Parent's ability to understand and the willingness to sign a written informed consent document for adolescents as determined by local regulations. Adolescents will sign assent along with parental/legal guardian consent or will co-sign consent with parent/legal guardian in accordance with local regulation, prior to participation in the study.

The key **exclusion criteria** included:

- Laboratory parameters:
  - Estimated creatinine clearance calculated by the Cockroft-Gault method < 70 mL/min
  - Hemoglobin concentration <5.0 mmol/L (<8.0 g/dL); white blood cells (WBC) <2x109/L; platelets <75x109/L.
  - Total bilirubin >3 x upper limit of normal (ULN) for age.
  - Serum albumin <3.0 g/dL unless prothrombin time is within the normal range.
- Established or suspected pregnancy.
- Current spontaneous urinary incontinence.
- Other known co-existing malignancies except non-melanoma skin cancer and carcinoma in situ of the uterine cervix, unless definitively treated and proven no evidence of recurrence for 5 years.

- Hypersensitivity to the study drug active substance or to any of the excipients.
- Participants with any other significant medical, psychiatric, or surgical condition, currently uncontrolled by treatment, which may interfere with the completion of the study.
- Participants with known incompatibility to CT scans with IV contrast due to allergic reaction or renal insufficiency. If such a participant can be imaged with MRI, then the participant would not be excluded.

Treatments

The investigational drug used in this study is Lutathera (lutetium Lu 177 dotatate/ lutetium [177Lu] oxodotreotide). All participants were to receive a total of 4 administrations of Lutathera 7.4 GBq / 200 mCi every 8±1 weeks.

Lutathera was supplied to the Investigators as a radiopharmaceutical solution (7.4 GBq of Lutathera per 30 mL vial) for infusion. All test materials were supplied by Advanced Accelerator Applications in open-label vials.

Objectives and outcomes/endpoints

Primary objectives and endpoints

Objectives	Endpoints
Evaluate organ absorbed radiation doses from peptide receptor radionuclide therapy (PRRT) with Lutathera in adolescents with SSTR-positive GEP-NETs and PPGLs as a pooled cohort	Target organ (e.g., kidney and bone marrow) absorbed radiation doses in adolescents 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 PPGLs as a pooled cohort	The incidence of adverse event (AE) and laboratory toxicities after the 1st Lutathera administration in adolescents with SSTR-positive GEP-NETs and PPGLs as a pooled cohort

Secondary objectives and endpoints

Objectives	Endpoints
Evaluate cumulative safety of Lutathera in adolescents with SSTR-positive GEP-NETs and PPGLs as a pooled cohort	The incidence of AEs and laboratory toxicities until 6 months after the last Lutathera dose (short-term follow up) in adolescents with SSTR-positive GEP-NETs and PPGLs as a pooled cohort
Evaluate long-term safety of Lutathera in adolescents with SSTR-positive GEP-NETs and PPGLs as a pooled cohort	The incidence of AEs and laboratory abnormalities during the long-term follow-up of 5 years after the last Lutathera dose in adolescents with SSTR-positive GEP-NETs and PPGLs as a pooled cohort
Perform comparative assessment of dosimetry and PK between adolescents with GEP-NETs and PPGLs as a pooled cohort and adult participants using the extrapolation model developed for the clinical study	Calculated organ absorbed doses and PK parameters based on imaging/blood radioactivity concentration data from adolescents with SSTR-positive GEP-NETs and PPGLs as a pooled cohort compared to the predicted distribution / organ absorbed doses

Exploratory objectives and endpoints

Objectives	Endpoints
Evaluate organ absorbed radiation doses from PRRT with Lutathera in adolescent participants with SSTR-positive PPGLs and GEP-NETs as separate cohorts	Target organ (e.g., kidney and bone marrow) absorbed radiation doses in adolescents with SSTR-positive PPGLs and GEP-NETs as separate cohorts
Evaluate safety and tolerability (after 1st administration, cumulative and long-term) of Lutathera in adolescents with SSTR-positive PPGLs and GEP-NETs as separate cohorts	Incidence of AEs and laboratory toxicities after the 1st Lutathera administration in adolescents with SSTR-positive PPGLs and GEP-NETs as separate cohorts Incidence of AEs and laboratory toxicities until 6 months after the last Lutathera dose (short-term follow-up) in adolescents with SSTR-positive PPGLs and GEP-NETs as separate cohorts Incidence of AEs and laboratory abnormalities during the long-term follow-up of 5 years after the last Lutathera dose in adolescents with SSTR-positive PPGLs and GEPNETs as separate cohorts
Assess the objective response rate (ORR), PFS and overall survival (OS) in adolescent participants with SSTR-positive GEP-NETs and PPGLs as separate cohorts after treatment with Lutathera	ORR (rate of complete and partial responses), PFS (time from enrollment to the disease progression or death), and OS (time from enrollment to the day of death) in adolescent participants with SSTR-positive GEP-NETs or PPGLs as separate cohorts

Sample size

No formal sample size or power calculations were made. Simulations from adult kidney and bone marrow dosimetry models suggested that a clinical trial that has enrolled between 5 and 10 participants should have the ability to define the median dosimetry values without significant risk of exceeding pre-defined thresholds. For the primary analysis, the overall sample size of at least 8 participants was deemed sufficient to confirm similar organ dosimetry results in the adolescent population compared to the ones in adults.

Randomisation

No randomisation was performed in this study, as this was a single-arm, open-label study. All participants received Lutathera treatment, allocated upon site ordering for each administration.

Blinding (masking)

No blinding was performed in this study, as this was a single-arm, open-label study.

Statistical methods

All statistical analyses, unless otherwise specified, were performed by Novartis. The SAS (SAS Institute Inc., Cary, NC, USA) version 9.4 was used for the analyses.

An interim analysis was conducted based on all data collected in the database up to the data cutoff date of 08-May-2023 (i.e., when 5 participants, including 2 participants with GEP-NET and 3 participants with PPGL, have completed at least one cycle of treatment).

The primary analysis presented in this CSR was conducted after all participants completed the first cycle of Lutathera (or later when feasible in case dosimetry assessment was not done after the first dose), at which time both dosimetry and safety assessments were complete for the assessment of the primary objective.

A final analysis will be performed after all participants who have received at least one dose of Lutathera have completed 5 years of follow-up or have withdrawn from the study.

Analysis sets

The following analysis sets were used for the analysis of the study results:

- The Full Analysis Set (FAS) included all participants that received at least one dose of Lutathera. The FAS was used for all baseline and demographic summaries and listings unless otherwise specified.
- The Safety Set was identical to the FAS.
- The Dosimetry Analysis Set (DAS) consisted of all participants who had at least one valid (i.e., not flagged for exclusion by the dosimetrist) dosimetry measurement. The DAS was used for summaries (tables and figures) and listings of dosimetry data and modeling.
- The PK Analysis Set (PKAS) consisted of all participants who had at least one valid (i.e., not flagged for exclusion) PK measurement. The PKAS was used for summaries (tables and figures) and listings of PK data and modeling.

Analysis of the primary endpoints

The primary objectives of the study were to evaluate organ radiation doses as well as safety and tolerability of Lutathera in adolescents with SSTR-positive GEP-NETs and PPGL as a pooled cohort.

Definition of the primary endpoints

a.) Dosimetry

The primary dosimetry endpoint of the study is the target organ (e.g., kidney and bone marrow) absorbed radiation doses in adolescents with SSTR-positive GEP-NETs and PPGLs as a pooled cohort.

b.) Safety

The primary safety endpoint of the study is the incidence of AEs and laboratory toxicities during the first cycle of the pooled GEP-NET and PPGL cohorts.

Statistical hypothesis, model, and method of analysis: No statistical hypothesis was tested in the context of this descriptive study.

Dosimetry endpoint: The analysis of dosimetry primary endpoint consisted of descriptive summaries of the absorbed radiation doses in the target organs (e.g., kidney, bone marrow). Whole body planar, SPECT/CT imaging, blood, and urine radioactivity data (measured by gamma-counter) were used by the dosimetry vendor to calculate the absorbed radiation dose in the target organs.

The details of the dosimetry parameters derivations are given in the Imaging, Dosimetry and Pharmacokinetics Manual.

Safety endpoints: Adverse events and laboratory toxicities that occurred during the first cycle were summarised descriptively to evaluate the acute toxicities induced by a single full-dose Lutathera infusion (7.4 GBq).

Handling of missing values: Missing data were not replaced.

Analysis of secondary endpoints: Secondary objectives of the study included the evaluation of cumulative and long-term safety of Lutathera in the pooled GEP-NET/PPGL cohort and a comparative assessment of dosimetry and PK between adolescents with GEP-NETs or PPGL and adult patients with GEP-NET using the extrapolation model developed for the clinical study.

Interim analysis: Due to the slower than expected recruitment rate, and the proportionally higher-than-expected recruitment of adolescents with PPGL, an interim analysis was performed with a DCO of 08-May-2023 to provide early evaluation of dosimetry and safety when at least 5 adolescent participants (including 2 participants with GEP-NET and 3 participants with PPGL) have completed at least one cycle of treatment. The interim analysis permitted an evaluation across the indications in order to have sufficient number of participants to assess the similarity of dosimetry between adolescents and adults.

Results

Participant flow and Recruitment

At the DCO date (12-Mar-2024) for the primary analysis of NETTER-P, a total of 12 adolescent participants had been screened across 7 centers in UK, Poland, France, Spain, Italy and the USA.

Of the 12 screened participants, 11 were enrolled across 6 centers (the center in Italy did not enroll any participants) and received Lutathera during the study. This included 4 participants with GEP-NET and 7 participants with PPGL.

Table 12. Participant disposition (FAS)

	GEP-NET (N=4) n (%)	PPGL (N=7) n (%)	All participants (N=11) n (%)
Participants treated			
Completed treatment	4 (100)	5 (71.4)	9 (81.8)
Ongoing treatment	0	1 (14.3)	1 (9.1)
Discontinued treatment	0	1 (14.3)	1 (9.1)
Reason treatment discontinued			
Physician decision	0	1 (14.3)	1 (9.1)
Participants entered short term follow-up	4 (100)	5 (71.4)	9 (81.8)
Participants entered long-term follow-up	1 (25.0)	3 (42.9)	4 (36.4)
End of Study			
Completed study	0	0	0
Ongoing study	3 (75.0)	7 (100)	10 (90.9)
Not completed study	1 (25.0)	0	1 (9.1)
Reason for not completed			
Physician decision	1 (25.0)	0	1 (9.1)

Conduct of the study

Protocol amendments

The study protocol was amended three times. The table below summarises the key features of each amendment.

Table 13. Protocol amendments

Version and date	Summary of key changes
Amendment 1 (11-May-2022)	The primary purpose of this amendment was to implement the following modifications in contraception requirements in line with Lutathera Investigator's Brochure version 17 released on 09-Mar-2022: • The highly effective contraception period was extended from 6 months to 7 months for female participants. • The sponsor added a requirement for male participants to use condom with female partners of reproductive potential during treatment and for 4 months after last Lutathera dose.
Amendment 2 (24-May-2023)	The changes were not due to new data but based on Sponsor Guideline on Prevention of Pregnancies in Participants in Clinical Trials as well as the CTFG guideline on recommendations related to contraception and pregnancy testing in clinical trials. The primary purpose of Amendment 02 was to implement the following changes: • Added interim analysis for an early evaluation of dosimetry and safety data when 5 participants (including 2 participants with GEP-NET and 3 participants with PPGL) had been treated. • Due to the higher-than-expected screening rate of participants with PPGLs and to avoid imbalance between GEP-NET and PPGLs, enrolment was limited to a maximum of 8 participants for the PPGL cohort. • As per the recommendation of the DSMB regarding monitoring of microproteinuria during study treatment, spot urine test of urine protein creatinine ratio (UPCR) was added to the study assessments, in order to detect early signs of renal toxicity especially in light of treatment of participants with medical history of nephrectomy.
Amendment 3 (14-Dec-2023)	The primary purpose of Amendment 03 was to implement the following changes: • Pooling of data across indications for the primary analysis leading to at least 8 adolescent participants across indications including a minimum of 3 adolescents with GEP-NET. • Pooling of the GEP-NETs and PPGLs cohorts for the evaluation of the co-primary and secondary objectives to compare adolescent data with data from adult GEP-NET participants. • Assessments of exploratory objectives in GEP-NETs and PPGLs as separate cohorts. • Laboratory assessments on safety biomarkers of endocrine and gonadal function were added to long-term follow up visits.

No other changes to the study conduct occurred.

Protocol deviations

In the FAS, 9 participants (4 participants from the GEP-NET and 5 participants from the PPGL cohort) had at least one major protocol deviation at the time of the DCO date (Table 14). Investigational product (IP) administration and IP compliance (3 participants each) were the most frequent protocol deviations. Two participants (1 with GEP-NET and 1 with PPGL) did not have Lutathera doses reduced to 50% because of Grade 3 neutropenia and as required per protocol.

None of the protocol deviations were related to the COVID-19 pandemic. None of the protocol deviations had a significant effect on the participant's safety, rights or welfare and/ or the integrity of the study data.

Table 14. Major Protocol Deviations (FAS)

Category Protocol deviation	GEP_NET (N=4)	PPGL (N=7)	All participants (N=11)

	n (%)	n (%)	n (%)
Any major protocol deviation	4 (100)	5 (71.4)	9 (81.8)
IP administration	2 (50.0)	1 (14.3)	3 (27.3)
Lutathera dosing error: Participant received incorrect dose of	1 (25.0)	1 (14.3)	2 (18.2)
study medication Further deviations to study drug handling and administration	1 (25.0)	0	1 (9.1)
(outside of dose errors)			
Participant IP compliance	1 (25.0)	2 (28.6)	3 (27.3)
Lutathera Administration Visit did not occur in 8 weeks from the previous dose +- 1 week	1 (25.0)	2 (28.6)	3 (27.3)
Informed consent and process	1 (25.0)	0	1 (9.1)
Informed Consent Form collection delayed	1 (25.0)	0	1 (9.1)
Safety	0	1 (14.3)	1 (9.1)
Deviation to SAEs/AESIs reporting	0	1 (14.3)	1 (9.1)
Study procedures	0	1 (14.3)	1 (9.1)
During the dosimetry week, SPECT/CT and Whole Body Planar Imaging were not performed as per the schedule specified in the	0	1 (14.3)	1 (9.1)

Baseline data

Demographics and other baseline characteristics

Table 15. Demographics and other baseline characteristics (FAS)

Demographic variable	GEP-NET (N=4)	PPGL (N=7)	All participants (N=11)
Age (years)			
Mean (SD)	15.5 (0.58)	14.9 (1.77)	15.1 (1.45)
Median	15.5	14.0	15.0
Q1-Q3	15.0-16.0	13.0-17.0	14.0-16.0
Min-Max	15 - 16	13 - 17	13 - 17
Sex, n (%)			
Female	2 (50.0)	4 (57.1)	6 (54.5)
Able To Bear Children	2 (50.0)	4 (57.1)	6 (54.5)
Male	2 (50.0)	3 (42.9)	5 (45.5)
Race, n (%)			
White	2 (50.0)	3 (42.9)	5 (45.5)
Black or African American	1 (25.0)	0	1 (9.1)
Asian	0	1 (14.3)	1 (9.1)
Not Reported	1 (25.0)	2 (28.6)	3 (27.3)
Other	0	1 (14.3)	1 (9.1)
Ethnicity, n (%)			
Not Hispanic or Latino	3 (75.0)	4 (57.1)	7 (63.6)
Not Reported	1 (25.0)	3 (42.9)	4 (36.4)
Creatinine Clearance (mL/min)			
Mean (SD)	122.87 (28.920)	121.71 (23.335)	122.13 (24.041)
Median	124.75	124.00	124.00
Q1-Q3	103.00 - 142.75	99.00 - 135.00	99.00 - 135.00
Min-Max	86.0-156.0	90.0-160.0	86.0-160.0
Weight (kg)			
Mean (SD)	59.63 (9.223)	50.84 (8.951)	54.04 (9.655)
Median	58.35	50.20	54.30
Q1-Q3	53.00 - 66.25	43.00 - 59.60	44.00 - 60.70
Min-Max	50.0-71.8	40.6-64.2	40.6-71.8
Height (cm)			
Mean (SD)	164.9 (7.58)	161.5 (6.45)	162.7 (6.72)
Median	164.8	160.0	161.8

Demographic variable	GEP-NET (N=4)	PPGL (N=7)	All participants (N=11)
Q1-Q3	159.3 - 170.5	157.0 - 166.0	157.0 - 167.0
Min-Max	156-174	155-174	155-174
Body mass index (kg/m2)			
Mean (SD)	21.95 (3.098)	19.46 (2.936)	20.36 (3.103)
Median	22.46	19.18	21.21
Q1-Q3	19.57 - 24.33	16.90 - 21.33	17.44 - 23.72
Min-Max	17.9-24.9	16.0-24.2	16.0-24.9

Baseline values for weight, height, body mass index refer to value closest to Cycle 1 Day 1 visit.

Disease history

The primary tumour lesions had extended to adjacent structures at baseline in the majority of participants (T2 or T3 grading in 8 participants according to the TNM classification system; 6 PPGL participants with T2, 2 GEP-NET participants with T3) with only low levels of regional node involvement (≤ N1 grading in all participants). All participants had Stage IV disease.

All 4 participants with GEP-NET had received ≥ 1 line of prior antineoplastic treatments and 6 of 7 participants in the PPGL cohort had had no prior antineoplastic therapy. One participant with PPGL had received one prior treatment. Two of the PPGL patients had prior unilateral nephrectomy. The tumours in all participants had developed metastases, 6 participants (3 in each cohort) had ≥ 3 metastases. The median time since initial diagnosis to study entry was 32.0 (range: 1.1 to 54.3) months.

Table 16. Disease history for participants with GEP-NET (FAS)

GEP-NET Disease history	GEP-NET (N=4)
Primary site of cancer, n (%)	
Pancreas	2 (50.0)
Rectum	1 (25.0)
Stomach	1 (25.0)
Tumour Status, n (%)	
Functional	2 (50.0)
Non-Functional	2 (50.0)
Not Assessed	0
Missing	0
Grade of GEP-NET (according to Ki-67 index), n (%)	
G1 (<3%)	2 (50.0)
G2 (3-20%)	2 (50.0)
G3 (>20%)	0

Table 17. Disease history for the PPGL cohort only (FAS)

PPGL Disease history	(N=7)
Tumor type, n (%)	
Pheochromocytoma (adrenal)	2 (28.6)
Paraganglioma (extra-adrenal)	5 (71.4)
Primary origin, n (%)	
Abdominal cavity	4 (80.0)
Other	1 (20.0)
Chromaffin tissue, n (%)	
Sympathetic	4 (57.1)
Parasympathetic	0
Missing	3 (42.9)
123I-MIBG uptake, n (%)	
Positive	4 (57.1)

Negative	0
Not done	3 (42.9)

Prior and concomitant therapies

Prior (antineoplastic / non-antineoplastic) therapies and procedures were those therapies that started before the study treatment, irrespective of when it ended. A therapy starting prior to the start of study treatment and continuing after the start of study treatment was considered as both, prior and concomitant.

- **Prior antineoplastic therapy**

In the FAS, 10 participants received prior antineoplastic therapy/procedures of any type (all 4 participants in the GEP-NET cohort, 6 participants in the PPGL cohort). One participant with PPGL did not receive any prior antineoplastic therapy.

  - A total of 10 participants (4 participants in the GEP-NET and 6 participants in the PPGL cohort) underwent prior antineoplastic surgery. Mass excision and tumor excision were reported most frequently (each in 3 participants).
  - A total of 5 participants (4 participants in the GEP-NET cohort, 1 participant in the PPGL cohort) received prior antineoplastic medications. These included other alkylating agents (3 participants; 2 participants with GEP-NET and 1 participant with PPGL), SSAs (3 participants with GEP-NET) and pyrimidine analogues (2 participants with GEP-NET) as the most frequently administered prior antineoplastic therapies.
  - One participant received radiotherapy to the abdominal region and the lumbar vertebra.

- **Antineoplastic therapy since discontinuation of study drug**

Two participants have received antineoplastic treatment since discontinuation of study drug: One participant from the GEP-NET cohort received carbozantinib after Lutathera treatment was completed. One participant from the PPGL cohort withdrew study treatment after the first dose of Lutathera due to physician's decision. This participant received Lutathera and carbozantinib outside of the study.

- **Prior non-antineoplastic therapy**

In the FAS, 8 participants (3 participants in the GEP-NET and 5 participants in the PPGL cohort) had received at least one prior non-antineoplastic medication (i.e. starting and ending before the start of study treatment). Dihydropyridine derivatives (3 participants), α-adrenoreceptor antagonists (2 participants), other peripheral vasodilators (i.e. phenoxybenzamine, 2 participants), and proton pump inhibitors (2 participants) were received by ≥ 2 participants.

- **Concomitant non-antineoplastic medications**

All 11 participants in the FAS had received at least one concomitant non-antineoplastic medication (i.e. starting on or after the start of study treatment but not more than 56 days after the last administration of study treatment or starting prior to and continuing after the start of study treatment). Serotonin antagonists (11 participants), anilides (6 participants), combinations of sulfonamides and trimethoprim including derivatives (5 participants) were received most frequently (by ≥ 5 participants).

Numbers analysed

The FAS includes all participants who received at least one dose of Lutathera and comprises 11 participants (4 participants with GEP-NET, 7 participants with PPGL). The Safety Set is identical to the

FAS in this study. The PKAS consists of all patients who have at least one valid (i.e. not flagged for exclusion) PK measurement. The PKAS is equivalent to the FAS in this study.

One participant from the PPGL cohort was excluded from the Dosimetry Analysis Set (DAS), as there were issues when the whole-body planar and SPECT/CT images for this participant were collected such that SPECT/CT images could not be utilized for dosimetry analysis. Therefore, absorbed dose estimates could only be derived by planar methodology, and such values are associated with greater uncertainty than the hybrid methodology applied for the other participants.

Table 18. Analysis sets

	GEP-NET (N=4)	**PPGL (N=7)**	**All participants (N=11)**
Analysis set	**n (%)**	**n (%)**	**n (%)**
Full Analysis Set (FAS)	4 (100)	7 (100)	11 (100)
Safety Set	4 (100)	7 (100)	11 (100)
Dosimetry Analysis Set (DAS)	4 (100)	6 (85.7)	10 (90.9)
PK Analysis Set (PKAS)	4 (100)	7 (100)	11 (100)

The Safety Set is equivalent to the FAS in this study.

Outcomes and estimation

At the time of the primary analysis (cut-off date 12 March 2024), post-baseline tumor assessments and overall response data were available for 9 participants (3 participants with GEP-NET, 6 participants with PPGL).

Two participants did not have overall response data available: one participant from the PPGL cohort had no post-baseline tumour assessments due to premature discontinuation of the study treatment and withdrawal of the consent for further protocol assessments and another participant in the GEP-NET cohort had tumour not evaluable by CT/MRI scan.

All 9 participants evaluable for tumor assessments had stable disease as the best overall response. Stable disease was also indicated by percentage changes in the sum of diameters of the lesions in individual participants.

Table 19. Best Overall Response (FAS) in NETTER-P

	GEP-NET (N=4) **n (%)**	**PPGL (N=7)** **n (%)**
Number of participants with at least one baseline and post baseline valid assessment - m	3 (75.0)	6 (85.7)
Best overall response*		
Complete Response (CR)	0	0
Partial Response (PR)	0	0
Stable Disease (SD)	3 (100)	6 (100)
Progressive Disease	0	0
Unknown (UNK)	0	0
Objective response rate (ORR:CR + PR)*	0	0
Disease control rate (DCR:CR + PR + SD)*	3 (100)	6 (100)

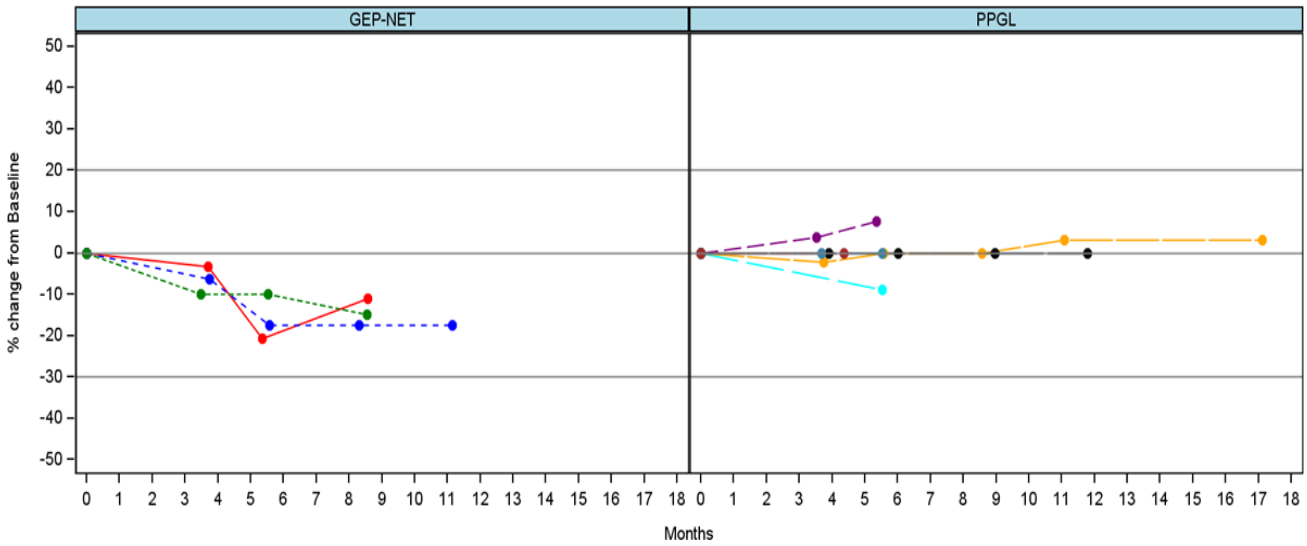
* Percentages are based on m (number of participants with at least one baseline and post baseline valid assessment)

The mean number of cycles of Lutathera administered was 3.6 (± 0.9), with 9 patients (4 GEP-NET, 5 PPGL) receiving 4 cycles, 1 PPGL patient receiving 3 cycles, and 1 PPGL patient receiving 1 cycle of Lutathera. As per NETTER-P study protocol dose modification criteria, a 50% dose reduction was

implemented in 2 PPGL patients after the first cycle due to the estimated cumulative organ absorbed dose for the kidney exceeding 29 Gy.

At the time of the DCO for the primary analysis, 10 of 11 participants remained in the study and were ongoing without tumor progression. One participant with GEP-NET had disease progression at 8.6 months, three months after the last dose was administered, and later discontinued from the study at 10.6 months due to physician's decision.

Figure 10. Percentage change from baseline in sum of longest diameters (FAS) in NETTER-P



Ancillary analyses

Lutathera has been investigated in children and adolescents with SSTR-positive tumors in a limited number of clinical studies to date which have been reviewed as part of the literature review report.

Based on the literature review, 4 pediatric patients with GEP-NET (including patients who were newly diagnosed as well as with progressive disease) who were treated with 2-5 cycles of Lutetium Lu 177 dotatate, had favorable efficacy outcomes including clinical symptoms improvement, metastatic mass decrease, partial remission, stable disease or disease-free status.

In addition, 6 pediatric patients with PPGL were treated with 3-4 cycles of Lutetium Lu 177 dotatate. Of these, efficacy outcomes were available for 4 patients. In one patient, median duration of complete response was 36 months. One patient achieved stable disease for up to 52 months without local symptoms. One patient had stable disease for 24 months and survival at a 66-month follow-up. One patient was clinically stable with no evidence of disease progression 4 years post-initial presentation.

No subgroup analyses were conducted, due to the limited sample size of NETTER-P study and so there is nothing to report in this section.

Summary of main study(ies)

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

Table 20. Summary of Efficacy for trial NETTER-P

Title: NETTER-P A multicenter open-label study to evaluate safety and dosimetry of Lutathera in adolescent patients with somatostatin receptor (SSTR)-positive gastroenteropancreatic neuroendocrine (GEP-NET) tumors, pheochromocytoma and paragangliomas (PPGL)				
Study identifier	CAAA601A32201, EudraCT no. 2020-002951-39			
Design	Multi-centre, open-label, single-arm, two-cohort			
	Duration of screening: Duration of treatment: Duration of Extension phase:		2 weeks 8 months (4 administrations every 8 weeks) 6 months (short term FU), 54 months (long term FU)	
Hypothesis	Exploratory: dosimetry and safety			
Treatments groups	Treatment arm		4 Lutathera administrations at 8 week intervals (±1 week)	
	Secondary endpoint: best overall response	BOR	Highest level of response	
Database lock	DCO: 12 March 2024			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set			
Descriptive statistics and estimate variability	Treatment group		GEP-NET	PPGL
	Number of subjects		4	7
	Best overall response			
	Complete response (CR)		0	0
	Partial response (PR)		0	0
	Stable disease (SD)		3	6
	Progressive disease		0	0
	Objective response rate (ORR: CR+PR)		0	0
	Disease control rate (DCR:CR+PR+SD)		3	6
Notes	One participant from the PPGL cohort had no post-baseline tumour assessments and another participant in the GEP-NET cohort had tumour not evaluable			
Analysis description	N/A			

Clinical studies in special populations

NETTER-P is a trial specifically undertaken in the paediatric special population.

Supportive study(ies)

Efficacy of Lutathera in the applied GEP-NET setting in adults was established during the NETTER-1 and ERASMUS. These trials were evaluated in previous or ongoing procedures and led to approval in the adult population according to the labelled indications.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

NETTER-P trial was conducted to collect safety, PK and dosimetry data in paediatric patients (12 to <18 years old) treated at the same dose as adults, to confirm the appropriateness of the dose regimen and by similarity in dosimetry and PK in order to extrapolate the clinical efficacy documented in adults with unresectable metastatic progressive GEP-NETs to the adolescent population. In line with the PIP of Lutathera, NETTER-P study aimed to enrol at least 8 adolescents with a minimum of 3 in the GEP-NET cohort.

As previously discussed, a PPGL indication was not sought as part of this application. The data provided from this cohort were intended exclusively to support the GEP-NET indication.

The comparability of both PK and organ dosimetry data between adolescents and adults for the use of the adult dosage of 7.4 GBq of Lutathera every 8 weeks ± 1 week for a total of 4 doses is currently uncertain. Neither Lutathera pharmacokinetics nor kidney and red marrow dosimetry were impacted by participants' age and body weight, confirming the appropriateness of flat dosing in the adolescent population, similar to the adult population (see Clinical pharmacology section above).

Efficacy data and additional analyses

The efficacy of Lutathera in GEP-NET in adults was established during the NETTER-1 and ERASMUS trial. These trials were evaluated in previous or ongoing procedures and led to approval in the adult population (see EPAR initial MAA).

Given the similarity of the disease between adults and adolescents which, in line with the paediatric extrapolation framework of ICH E11A guidance, the PK/dosimetry results of NETTER-P study could, in principle, support an extrapolation of the established clinical outcome benefits of Lutathera in adult patients to paediatric patients. Exploratory efficacy data from the primary analysis results of NETTER-P study could, fundamentally, be used as supplementary data to support PK/dosimetry data.

At the time of the primary analysis DCO (12-Mar-2024) for NETTER-P study, all 11 participants (4 with GEP-NET and 7 with PPGL) had received 1-4 cycles of treatment. Nine participants (3 with GEP-NET and 6 with PPGL) with at least 1 post-baseline tumour assessment had stable disease as best overall response (BOR) as per local assessment with no deaths reported during the study. Ten participants were ongoing in the study without disease progression while 1 participant with GEP-NET had disease progression 8.6 months after the first administration of Lutathera. PFS is not reported probably due to immature follow up.

Since efficacy outcomes based on classical cancer trial endpoints -such as OS, PFS, ORR- were only exploratory, and the available results indicate only stable disease, the selected bridging strategy for establishing efficacy in paediatric patients remains insufficiently proven. Nevertheless, this discussion will not be further pursued within the scope of this application, as the applicant has decided not to pursue an extension of indication for paediatric patients.

In conclusion, Lutathera' s established efficacy in adults could, in principle, be extrapolated to the adolescent population based on the similarity of disease, comparable drug exposure, and similar exposure-dosimetry relationship. Based on the results of the efficacy extrapolation as well as the exploratory efficacy results from NETTER-P study, Lutathera may offer a similar therapeutic benefit in adolescents aged 12 years and older with unresectable or metastatic, progressive, well-differentiated (G1 and G2), SSTR2 positive GEP-NETs. However, while the evaluation of this application was ongoing, the

applicant decided to withdraw their claim for an extension of indication to adolescent patients. At the time of withdrawal, unresolved issues remained that prevented the committee from reaching a definitive conclusion on the extrapolation of clinical efficacy from adults to adolescents.

Assessment of paediatric data on clinical efficacy

NETTER-P was a trial exclusively conducted in the paediatric population in the context of the agreed PIP for Lutathera.

2.4.4. Conclusions on the clinical efficacy

It remains currently uncertain whether data can confirm similar comparable exposure and similar exposure-dosimetry relationship. Thus, currently efficacy extrapolation of the available data from adults for the treatment of unresectable or metastatic, progressive, well-differentiated, SSTR-positive GEP-NETs in adolescents aged 12 years and older cannot be finally concluded.

Following the applicant's decision not to pursue an extension of indication, the adolescent population has not been included in section 4.1 of the SmPC.

2.5. Clinical safety

Introduction

NETTER-P is an ongoing multicenter open-label study conducted with the primary objectives to evaluate organ radiation doses as well as safety and tolerability of Lutathera in adolescents.

As per the secondary objectives, pharmacokinetic (PK) and kidney and red marrow (RM) or bone marrow (BM) dosimetry (both terms are used interchangeably) from both adults and adolescents was compared, pooled and analysed together.

Available data have shown that Lutathera has generally been well-tolerated in adults with GEP-NETs with limited, transient toxic events.

The following are the important identified and important potential risks associated with Lutathera, based on the data from adult patients. Some of the below-mentioned safety risks were chosen as adverse events of special interest (AESI) in the NETTER-P study.

Important identified risks

- Renal dysfunction
- Myelosuppression/cytopenias (immediate hematologic toxicity)
- Myelodysplastic syndrome (MDS)/acute leukemia (AL) (late hematologic toxicity)
- Hepatotoxicity
- Tumor lysis syndrome
- Hormonal release-induced crisis (HRIC)
- Hypogonadism, sexual dysfunction
- Drug interaction with somatostatin/somatostatin analogues (SSAs)

Important potential risks

- Radiotoxicity, including occupational exposure and inadvertent exposure
- Secondary malignancies (solid tumors)
- Embryo-fetal toxicity

Safety analysis in the paediatric population is mainly based on data from the NETTER-P study. The currently submitted safety analyses are based on the data collected up to the primary analysis, DCO date: 12-Mar-2024.

Comparisons to larger safety data derived from previous clinical trials in adults (NETTER-1 and NETTER-2) were done where applicable and meaningful.

Furthermore, to supplement the safety data from the NETTER-P study, additional information from a review of the safety of Lutetium Lu 177 dotatate and/or Yttrium Y 90 dotatoc in the paediatric population, based on publications and Novartis global safety database search for paediatric safety reports, with a data cut-off date of 30-Apr-2024 was provided.

Safety evaluations in the NETTER-P study included standard adverse event (AE) monitoring, vital signs, cardiac imaging by electrocardiogram (ECG), and clinical laboratory results. Additional potential safety concerns in the paediatric population were assessed via a set of safety biomarkers for growth and development, bone development, and reproductive and endocrine (pituitary) function. Safety data from both GEP-NET and PPGL cohorts were analysed.

The primary safety endpoint of NETTER-P was the incidence of AEs and laboratory toxicities during the first cycle for the pooled GEP-NET and PPGL cohorts. Safety data observed during the treatment period, up to the primary analysis DCO date were reported. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 and assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

The adverse event of special interest (AESI) categories in the study included:

- The main known risks of Lutathera for adults: secondary malignancies (solid tumors, myelodysplastic leukaemia (MDL), acute leukaemia (AL)), haematotoxicities (immediate and late haematotologic toxicities), nephrotoxicity (renal dysfunction)
- Known risks of amino acid (AA) treatment: cardiovascular and electrolyte disorders
- Theoretical risks in paediatric population: endocrine disorders and bone development disorders.

Patient exposure

As of the primary analysis DCO date (12-Mar-2024), 9 participants (81.8%; 4 with GEP-NET, 5 with PPGL) out of the 11 enrolled participants had completed all 4 cycles of treatment with Lutathera, 1 participant (9.1%) with PPGL completed 3 cycles of treatment and 1 participant (9.1%) discontinued treatment with Lutathera after the first cycle. The mean cumulative decay corrected dose was 24.2 (±7.1) GBq and the mean relative dose intensity was 88.7% (±14.1).

Table 21. Participant disposition (FAS)

Participants treated	GEP-NET (N=4) n (%)	PPGL (N=7) n (%)	All participants (N=11) n (%)
Completed treatment	4 (100)	5 (71.4)	9 (81.8)
Ongoing treatment	0	1 (14.3)	1 (9.1)
Discontinued treatment	0	1 (14.3)	1 (9.1)
(Reason treatment discontinued)			
- Physician decision	0	1 (14.3)	1 (9.1)
Participants entered short term follow-up	4 (100)	5 (71.4)	9 (81.8)
Participants entered long-term follow-up	1 (25.0)	3 (42.9)	4 (36.4)
End of Study			

Completed study	0	0	0
Ongoing study	3 (75.0)	7 (100)	10 (90.9)
Not completed study	1 (25.0)	0	1 (9.1)
(Reason for not completed)			
- Physician decision	1 (25.0)	0	1 (9.1)

Adverse events

Table 22. Overview of adverse events (Safety set)

	GEP-NET (N=4)		PPGL (N=7)		All participants (N=11)	
Category	**All grades**	**Grade≥3**	**All grades**	**Grade≥3**	**All grades**	**Grade≥3**
Adverse events (AEs)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
AEs during first Lutathera cycle	4 (100)	2 (50.0)	6 (85.7)	2 (28.6)	10 (90.9)	4 (36.4)
Lutathera-related AEs during first Lutathera cycle	3 (75.0)	1 (25.0)	6 (85.7)	1 (14.3)	9 (81.8)	2 (18.2)
AEs during Lutathera treatment	4 (100)	2 (50.0)	7 (100)	5 (71.4)	11 (100)	7 (63.6)
Lutathera-related AEs during Lutathera treatment	3 (75.0)	1 (25.0)	7 (100)	4 (57.1)	10 (90.9)	5 (45.5)
AEs during short-term follow-up	1 (25.0)	0	3 (42.9)	0	4 (36.4)	0
Lutathera-related AEs during short-term follow-up	1 (25.0)	0	2 (28.6)	0	3 (27.3)	0
AEs during long-term follow-up	0	0	1 (14.3)	1 (14.3)	1 (9.1)	1 (9.1)
Lutathera-related AEs during long-term follow-up	0	0	0	0	0	0

Table 23. Adverse events by system organ class during Lutathera treatment (Safety Set)

	GEP-NET (N=4)		PPGL (N=7)		All participants (N=11)	
Primary system organ class	**All grades**	**Grade≥3**	**All grades**	**Grade≥3**	**All grades**	**Grade≥3**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of participants with at least one event	**4 (100)**	**2 (50.0)**	**7 (100)**	**5 (71.4)**	**11 (100)**	**7 (63.6)**
Blood and lymphatic system disorders	3 (75.0)	2 (50.0)	4 (57.1)	2 (28.6)	7 (63.6)	4 (36.4)
General disorders and administration site conditions	3 (75.0)	0	4 (57.1)	0	7 (63.6)	0
Nervous system disorders	3 (75.0)	0	4 (57.1)	0	7 (63.6)	0
Infections and infestations	3 (75.0)	0	3 (42.9)	1 (14.3)	6 (54.5)	1 (9.1)
Gastrointestinal disorders	2 (50.0)	1 (25.0)	3 (42.9)	0	5 (45.5)	1 (9.1)
Investigations	2 (50.0)	1 (25.0)	3 (42.9)	2 (28.6)	5 (45.5)	3 (27.3)
Respiratory, thoracic and mediastinal disorders	3 (75.0)	0	1 (14.3)	0	4 (36.4)	0
Metabolism and nutrition disorders	1 (25.0)	1 (25.0)	2 (28.6)	0	3 (27.3)	1 (9.1)
Musculoskeletal and connective tissue disorders	1 (25.0)	0	2 (28.6)	0	3 (27.3)	0
Skin and subcutaneous tissue disorders	1 (25.0)	0	2 (28.6)	0	3 (27.3)	0
Psychiatric disorders	1 (25.0)	0	1 (14.3)	0	2 (18.2)	0
Renal and urinary disorders	0	0	2 (28.6)	1 (14.3)	2 (18.2)	1 (9.1)
Vascular disorders	0	0	2 (28.6)	1 (14.3)	2 (18.2)	1 (9.1)
Ear and labyrinth disorders	0	0	1 (14.3)	0	1 (9.1)	0
Eye disorders	0	0	1 (14.3)	0	1 (9.1)	0

	GEP-NET (N=4)		PPGL (N=7)		All participants (N=11)	
Primary system organ class	**All grades**	**Grade≥3**	**All grades**	**Grade≥3**	**All grades**	**Grade≥3**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hepatobiliary disorders	1 (25.0)	1 (25.0)	0	0	1 (9.1)	1 (9.1)
Injury, poisoning and procedural complications	1 (25.0)	0	0	0	1 (9.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (25.0)	0	0	0	1 (9.1)	0

Safety topics of interest

Table 24. Overview of adverse events of special interest during Lutathera treatment (Safety Set)

	GEP-NET (N=4)		PPGL (N=7)		All participants (N=11)	
	All grades	**Grade≥3**	**All grades**	**Grade≥3**	**All grades**	**Grade≥3**
Safety topic	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any	4 (100)	2 (50.0)	5(71.4)	5 (71.4)	9(81.8)	7 (63.6)
Hematotoxicities	3 (75.0)	2 (50.0)	5(71.4)	4 (57.1)	8(72.7)	6 (54.5)
Nephrotoxicities	1 (25.0)	1 (25.0)	1(14.3)	1 (14.3)	2(18.2)	2 (18.2)
Bone development disorders	1 (25.0)	1 (25.0)	0	0	1 (9.1)	1 (9.1)
Cardiovascular and electrolyte disorders	1 (25.0)	0	0	0	1 (9.1)	0

Numbers (n) represent counts of participants.

A participant with multiple severity grades for an AE is only counted under the maximum grade.

Two sources were used to identify AESI: from the eCRF as reported by the Investigator and using eCRS for a systematic search of terms

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

Table 25. SAEs in NETTER-P

	GEP-NET (N=4)		PPGL (N=7)		All participants (N=11)	
Category	**All grades**	**Grade≥3**	**All grades**	**Grade≥3**	**All grades**	**Grade≥3**
Adverse events (AEs)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
SAEs during first Lutathera cycle	1 (25.0)	1 (25.0)	0	0	1 (9.1)	1 (9.1)
Lutathera-related SAEs during first Lutathera cycle	0	0	0	0	0	0
SAEs during Lutathera treatment	1 (25.0)	1 (25.0)	1 (14.3)	1 (14.3)	2 (18.2)	2 (18.2)
Lutathera-related SAEs during Lutathera treatment	0	0	0	0	0	0

- One participant with GEP-NET had a Grade 3 SAE of lower GI hemorrhage during the first cycle of Lutathera, which resolved 4 days later upon receiving additional therapy. The participant also had a Grade 2 AE of hypercalcaemia during Cycle 4, which worsened to an SAE of Grade 3 severity after 4 days from the onset date. The SAE of Grade 3 hypercalcaemia improved to a Grade 2 AE within one day after additional therapy was given and was not resolved at the time of the primary analysis DCO. Both the events were assessed to be not related to Lutathera or AA treatment. No action was taken on Lutathera and AA dose and administration due to either event.

- Another participant with PPGL had a Grade 3 SAE of catheter-related infection starting on Day 99 that required prolonged hospitalization. The participant was treated with antibiotics (vancomycin and flucloxacillin) for this event. On Day 101, the SAE resolved, and the participant was discharged from hospital. The SAE was assessed to be not related to Lutathera or AA treatment. No action was taken on Lutathera and AA dose and administration due to the event.

Deaths

As of the primary analysis DCO date, there have been no deaths reported in the study.

Laboratory findings

Hematology

Most participants (over 90%) had at least 1 hematological abnormality during the first cycle of Lutathera and all participants had at least 1 hematological abnormality during the Lutathera treatment. The most frequently reported post-baseline hematological abnormalities during the first cycle of Lutathera were: Lymphocyte count decreased (10 participants, 90.9%), Anemia (8 participants, 72.7%) and WBC decreased (6 participants, 54.5%). Analyses of haematological abnormalities for the overall Lutathera treatment period also revealed similar observations.

Grade 3 hematological laboratory abnormalities were observed in 4 participants during the first cycle of Lutathera (2 with GEP-NET and 2 with PPGL) and 7 participants (2 with GEP-NET and 5 with PPGL) during the overall Lutathera treatment period.

Clinical chemistry

The most frequently reported post-baseline biochemistry abnormality during the first cycle of Lutathera was creatinine increase (3 participants, 27.3%). For the overall Lutathera treatment period, the most frequently reported post-baseline biochemistry abnormality was hypomagnesemia (6 participants, 54.5%), followed by creatinine increase (4 participants, 36.4%).

No Grade ≥3 post-baseline biochemistry abnormalities were reported during the first cycle of Lutathera, while 1 participant had a Grade ≥ 3 post-baseline biochemistry abnormality during the treatment period. One participant from the GEP-NET cohort experienced Grade 3 hypercalcemia during Cycle 2 and Cycle 4 of Lutathera. The Grade 3 hypercalcemia during Cycle 4 was also reported as an AESI of bone development disorder.

As of the primary analysis DCO date, there were no other clinical chemistry abnormalities that were clinically significant or reported as AEs during the study.

Liver enzymes

No post-baseline values of ALT or AST > 3 × ULN were reported. Total bilirubin > 2 × ULN was reported in 1 participant from the GEP-NET cohort. No cases that met the biochemical criteria (ALT or AST > 3 × ULN and bilirubin > 2 × ULN without ALP < 2× ULN) for Hy's law were reported during the study.

Renal function

Creatinine increase was the most frequent renal parameter abnormality, reported in 3 participants (27.3%, all Grade 1 or 2). These abnormalities were not considered clinically significant or reported as AEs. Similarly, there were no urinalysis abnormalities that were clinically significant during the study except for a transient elevation of urine protein creatinine ratio leading to proteinuria reported in one participant with PPGL, which was evaluated as not related to study treatment by the Investigator.

Safety biomarkers

Shifts in values of safety biomarkers (for growth and development, bone development, and reproductive and endocrine [pituitary] function) from baseline were infrequent in the safety set and were considered clinically non-significant.

Vital signs

Overall, there were no clinically meaningful observations for the post-baseline abnormalities in vital sign values during Lutathera treatment.

Safety in special populations

NETTER-P was a trial in the very rare paediatric subpopulation; thus, no additional subpopulations were analysed.

Safety related to drug-drug interactions and other interactions

Based on published literature and on clinical data from 11 adolescents with SSTR-positive GEP-NET or PPGL enrolled in NETTER-P, no new safety signals were reported. Hence there are no changes to the **adverse drug reactions** that are already described for Lutathera in the product information.

Discontinuation due to adverse events

No AEs led to treatment discontinuation at the time of the primary analysis DCO date.

Adverse events leading to dose interruptions/adjustments or infusion interruptions
AEs leading to Lutathera dose delay or infusion interruption were reported in 2 participants as detailed in the following table:

Table 26. Details regarding Adverse events leading to dose interruptions/adjustments or infusion interruptions

	GEP-NET (N=4)		PPGL (N=7)		All participants (N=11)	
	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
AEs leading to dose delay* (interruption) /adjustment						
During Lutathera treatment	4 (100)	2 (50.0)	6 (85.7)	2 (28.6)	10 (90.9)	4 (36.4)
Lutathera-related does delay (interruption)	3 (75.0)	1 (25.0)	6 (85.7)	1 (14.3)	9 (81.8)	2 (18.2)
AEs leading to infusion interruption						
During first Lutathera cycle	1 (25.0)	0	1 (14.3)	0	2 (18.2)	0
Lutathera-related during first cycle	1 (25.0)	0	1 (14.3)	0	2 (18.2)	0
During Lutathera treatment	1 (25.0)	0	1 (14.3)	0	2 (18.2)	0
Lutathera-related during Lutathera treatment	1 (25.0)	0	1 (14.3)	0	2 (18.2)	0
AEs requiring additional therapy						
During first Lutathera cycle	3 (75.0)	1 (25.0)	4 (57.1)	0	7 (63.6)	1 (9.1)

	GEP-NET (N=4)		PPGL (N=7)		All participants (N=11)	
	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Lutathera-related during first Lutathera cycle	1 (25.0)	0	4 (57.1)	0	5 (45.5)	0
During Lutathera treatment	4 (100)	2 (50.0)	6 (85.7)	3 (42.9)	10 (90.9)	5 (45.5)
Lutathera-related during Lutathera treatment	2 (50.0)	1 (25.0)	6 (85.7)	2 (28.6)	8 (72.7)	3 (27.3)

- One participant (GEP-NET cohort) had an AE of Grade 1 infusion related reaction (flush, headache, nausea, and weakness) during Cycle 1 Day 1. The event was assessed to be related to Lutathera, and Lutathera infusion was interrupted due to the event. The event was resolved on the same day without additional medication and the infusion was resumed at the same dose.
- Another participant (PPGL cohort) had three AEs leading to infusion interruption: one AE of Grade 1 headache during Cycle 1 (Day 1), one AE of Grade 1 headache during Cycle 2 (Day 57), and one AE of Grade 1 hot flush during Cycle 3 (Day 113). All the events were assessed to be related to both Lutathera and AAs, while headache on Day 1 was also considered to be related to AAs. All the events were resolved on the same day without additional medication and the infusions were resumed at the same dose.

AEs leading to Lutathera dose reduction were reported in 1 participant:

- One participant (PPGL cohort) had an AE of Grade 3 neutropenia during Cycle 3, which was assessed to be related to Lutathera, and lead to a reduction of the next Lutathera dose by 50% as per protocol. The participant received Lutathera in Cycle 4 at a decay-corrected dose of 3.8 GBq instead of the planned 7.4 GBq. The event resolved after 1 week following treatment with folic acid and Vitamin B6.

Post marketing experience

Lutathera is currently approved in 40 countries (i.e., Canada, European Economic Area countries, Hong Kong, Israel, Japan, Singapore, South Korea, Switzerland, Taiwan, United Kingdom, and USA) for the treatment of SSTR-positive GEP-NETs in adults and has been marketed since the International Birth Date (IBD) of 26-Sep-2017.

With respect to the adolescent population, the MAH has performed two separate literature searches for Lutetium Lu 177 dotatate and Yttrium Y 90 dotatoc to identify case reports, clinical studies, and review articles where these radioligand therapy (RLT) were used to treat paediatric patients with SSTR-positive GEP-NET tumors as well as other tumor types from 1946 onwards with a data cut-off date of 30-Apr-2024. There were no additional limits placed on time period or language.

The intention of these reviews was to provide supportive data to the NETTER-P study. The safety data from the NETTER-P study (7 cases) were excluded from this analysis and presented in the CSR. The search (excluding NETTER-P cases) yielded 23 case reports in paediatric patients, of which 13 cases were reported as serious and 10 as non-serious. Of the 13 serious cases, 5 were reported as suspected. Of the 10 non-serious cases, 8 cases reported off-label use without AEs.

Based on the limited safety information available from the published literature and the Lutathera safety database, there were no new safety signals that would highlight concerns of Lutathera use in the paediatric population.

The safety events following Lutathera treatment in paediatric patients with SSTR-positive tumours consisted mostly of hematological toxicities (primarily thrombocytopenia), with the majority occurring in the presence of progressive bone disease or associated with prior or concomitant treatments. The types, frequency, and severity of events reported in the paediatric population appeared to be similar to the tolerability and safety profile established for the adult population. Safety data from published studies of Yttrium Y 90 dotatoc, a β-emitter with higher maximum energy and longer range than Lutathera, in patients with SSTR-positive tumors, including SSTR-positive NETs, also suggested no specific concerns for the paediatric population.

In addition, based on limited safety follow-up of up to 5 years in a small number of studies, there were no reports of long-term safety risks, such as myelodysplastic syndrome or secondary malignancies in paediatric patients. However, considering the mechanism of action it is likely that such event may also occur in the paediatric population applied.

2.5.1. Discussion on clinical safety

Based on the safety data collected from NETTER-P up to the primary analysis DCO date, no new safety signals have been identified.

Lutathera administered to the few adolescents with GEP-NET or PPGL at the same dose as the adults dose of 7.4 GBq every 8 ± 1 weeks administered over 4 cycles (cumulative dose: 29.6 GBq) showed a similar safety and tolerability profile in GEP-NET and PPGL patients as in adults.

As of the primary analysis DCO date, 9 participants out of the 11 enrolled participants had completed all 4 cycles of treatment with Lutathera, 1 participant had treatment ongoing (completed 3 cycles of Lutathera), and 1 participant prematurely discontinued treatment with Lutathera after the first cycle. Follow up is currently limited.

Overall, 10 of the 11 participants (90.9%) in the safety set experienced at least 1 AE during the first cycle of Lutathera, and all 11 participants (100%) experienced at least 1 AE during the overall treatment period. Lutathera-related AEs were reported in 9 participants (81.8%) during the first cycle of Lutathera and 10 participants (90.9%) during the overall treatment period. Grade $\geq$ 3 AEs occurred in 4 participants (36.4%) during the first cycle of Lutathera and 7 participants (63.6%) overall during the Lutathera treatment in NETTER-P. The AE profile was comparable between the 2 disease cohorts.

AEs suspected to be related to Lutathera treatment during the first treatment cycle included nausea, fatigue (in 3 participants each), lymphopenia and lymphocyte count decreased (in 2 participants each). This pattern did not substantially change with subsequent cycles (up to 4 cycles) of Lutathera and may be at least partially reflect also the adverse events of the needed renal protection with an amino acid infusion solution (data not shown).

Adverse events of special interest were reported in 9 participants (81.8%) during the study period, with haematotoxicities being the most frequently reported AESIs (occurred in 8 participants, 72.7%). This was expected based on the known risk of radiation induced haematotoxicites with Lutathera treatment. There was 1 participant with bone development disorder AESI (Grade 3 hypercalcemia). This AESI was assessed by the investigator to be not related to Lutathera, and the laboratory assessments of bone development biomarkers for this participant were considered clinically non-significant. There were no events reported for the AESI categories of secondary malignancies and endocrine (pituitary) disorders.

There were no deaths or AEs leading to study treatment discontinuation until the primary analysis DCO. Three SAEs were reported in 2 participants (18.2%): one SAE (Grade 3 lower GI haemorrhage) during the first cycle of Lutathera and two SAEs (Grade 3 hypercalcemia, Grade 3 catheter-related infection) in later cycles. None of the SAEs were related to the study treatment, as assessed by the Investigator.

Three participants (27.3%) experienced at least one AE leading to dose reduction or infusion interruption during the Lutathera treatment period. Three participants had a dose reduction, including 1 participant due to Grade 3 neutropenia that occurred after the third cycle of treatment and 2 participants based on dosimetry results to reduce dose after the first cycle.

Overall, no clinically meaningful differences in laboratory toxicity events were observed in NETTER-P. There were no clinically meaningful observations for the post-baseline abnormalities in haematology, clinical chemistry (including renal and liver parameters), urinalysis, safety biomarkers, vital signs, and ECGs. Most participants (over 90%) had at least 1 hematological abnormality during the first cycle of Lutathera and all participants had at least 1 hematological abnormality during the Lutathera treatment. This was expected considering the mechanism of action of Lutathera.

Based on published literature and on the limited available short-term clinical data from paediatric patients aged 12 to < 18 years and treated with Lutathera in NETTER-P, no new or changing safety signals were identified. This is also confirmed by the overall assessment of post-marketing safety information available from 26-Sep-2017 to 19-Dec-2022, as well as cumulative data.

However, for Lutathera as a therapeutic radiopharmaceutical, long-term safety data should be collected in the paediatric population for whom a longer life expectancy could be expected. The MAH was initially requested to discuss and propose details of a long-term safety follow-up trial (PASS) in patients with newly diagnosed tumours including the paediatric patients initially claimed in this application, including the use of existing EU registry-based study (with special attention to those where administered treatment and dosimetry data are collected). However, following the MAH's decision not to pursue an extension of indication to the adolescent population, the issue was not pursued. The Applicant confirmed that the long-term safety follow-up in NETTER-P study has been extended to 10 years regardless of the application conversion.

It was claimed that organ dosimetry observed in adolescents was comparable between the GEP-NET and PPGL cohorts, and similar to organ dosimetry observed in adults. However, modelling data indicated that the predicted probability of kidney dosimetry exceeding 29 Gy was higher in adolescents (~20%) compared to adults (10–13%). Given the probability of exceeding 29 Gy after four treatment cycles approached 20%—the accepted safety limit—the MAH was requested to include a warning regarding the predicted kidney dosimetry in the paediatric population in section 4.4 of the SmPC. Nevertheless, following the MAH's decision to withdraw their claim for a paediatric indication, this matter was not further pursued.

Dosimetry data indicate that the absorbed doses to the spleen (cumulative >20Gy) and pituitary (cumulative >30Gy) are of concern, irrespective of a high SD and the uncertainties in comparing with External beam RT. Further, hyposplenism (and its consequences) cannot be considered solely a long-term risk. The MAH was therefore requested to amend the RMP to include "hyposplenism" and "hypopituitarism" as missing information, with additional pharmacovigilance activities proposed. However, following the MAH's decision not to pursue a paediatric indication, changes in the RMP are no longer warranted.

While no cases of hypogonadism or, sexual dysfunction were reported in the adolescent patients in the NETTER-P study, it is based on only 11 patients. The MAH was therefore asked to discuss whether hyposplenism, primary hypopituitarism and temporary or permanent infertility should be included as important potential risks in the RMP. It was noted, however, that "Hypogonadism, sexual dysfunction" was already listed as an important identified risk in the Lutathera RMP, and therefore no additional pharmacovigilance measures were considered necessary.

The applicant was invited to discuss and suggest wording to section 4.4 of the SmPC, including recommendations for adequate follow-up with laboratories and consideration of (re)vaccination in

paediatric patients. Reference was also made to the recommendation from SIOP (International Society of Paediatric Oncology) working group on External Beam RT and the spleen as Organ at Risk (PMID: 33271483). However, following the MAH's decision not to pursue a paediatric indication, this issue no longer considered relevant for inclusion in the PI.

Assessment of paediatric data on clinical safety

NETTER-P trial is part of the agreed PIP and was performed with the main intention to establish safety in adolescents and to show tolerability in the paediatric population.

2.5.2. Conclusions on clinical safety

From the limited available data, the safety profile of Lutathera in the investigated adolescent patients with GEP-NET could be similar to that reported in the adult population. No new signals were identified specific to the paediatric population.

2.5.3. PSUR cycle

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

2.6. Update of the Product information

As a consequence of this application, sections 4.2, 4.8, 5.1, 5.2 and 11 of the SmPC have been updated.

2.6.1. User consultation

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

"Given that the proposed changes to the Lutathera PL are not significant and were already tested in a previous user consultation of the Lutathera PL, a new user consultation is not deemed necessary"

2.6.2. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Lutathera (Lutetium (177Lu) oxodotreotide) is removed from the additional monitoring list as the product has been authorised for more than 5 years (since September 2017).

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

Lutathera is currently approved for the following indication

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

The originally proposed indication for this application was: *Lutathera is indicated for the treatment of unresectable or metastatic, somatostatin receptor-positive GEP-NETs in adolescents aged 12 years and older.*

At the time of submission of the present application, a variation to extend the indication to broaden the adult indication to newly diagnosed, unresectable or metastatic, well-differentiated (G2 and G3), somatostatin receptor-positive GEP-NETs was ongoing. However, at the time of conclusion of the current application, this procedure was withdrawn (see WPAR Lutathera II/52).

Following the withdrawal of the Lutathera II/52 procedure, the applicant decided not to further pursue an extension of indication to paediatric patients (type C.I.6 variation), and to continue as an SmPC label update (type C.I.4 variation). Paediatric data collected during NETTER-P study was therefore included in sections 4.8, 5.1, 5.2 and 11 of the Lutathera SmPC, but no changes to section 4.1 (therapeutic indication) were made.

3.1.1. Disease or condition

Neuroendocrine tumours (NETs) are a relatively rare, clinically diverse group of epithelial malignancies that originate most commonly from the gastrointestinal tract and the pancreas (GEP-NETs). The natural history of GEP-NETs is heterogeneous and appears to be affected by the primary site of disease, degree of differentiation, expression of somatostatin receptors (SSTRs), and presence of metastases at diagnosis (Díez et al., 2013).

GEP-NETs usually have high levels of SSTR type 2 (SSTR2) expression, typically in >80% of the patients (Krenning et al 1993, Reubi et al 2000). Peptide receptor radionuclide therapy (PRRT) has been considered most appropriate in patients with well-differentiated tumours as SSTR expression appears to decrease as tumours become less differentiated (Kayani et al 2008).

3.1.2. Available therapies and unmet medical need

Management of paediatric NETs depends on tumour location, grade, growth rate, extent of disease, and symptoms. Surgical resection for local or locoregional disease is the standard of care and is associated with long-term survival in most patients. For the subset of patients with unresectable, metastatic disease, the approach to diagnosis, staging, and treatment is similar to that of adult NETs. No systemic pharmacological therapies are currently approved for paediatric patients with GEP-NET in EU. Peptide receptor radionuclide therapy, targeted agents, or chemotherapy are the most frequently used off-label treatments in the paediatric population. Thus, GEP-NETs in paediatric patients 12 to < 18 years of age represent an area of unmet medical need.

3.1.3. Main clinical studies

This type II variation application relates to paediatric studies included in Lutathera paediatric investigation plan (EMEA-002950-PIP01-20-M01). It is supported by:

- A modelling and simulation analysis performed to justify the appropriateness of the adult dose for use in the adolescent population based on extrapolation of adult dosimetry data from kidney and bone marrow.

- The full extrapolation approach for clinical efficacy from adults to adolescents (that was principally agreed with EMA based on the PIP, see above) based on i) similar disease characteristics and potential response to Lutathera treatment; ii) same mechanism of action; iii) similar exposure/response relationship; and iv) that the drug amount (i.e. dose, concentration, exposure) is measurable and predictive of clinical response.

- Results of a modelling and simulation analysis of PK and dosimetry data of Lutathera in adolescents based on both PopPK model and empirical kidney and bone marrow dosimetry models as well as NETTER-P data.

- A review of published literature and spontaneous reports on the safety and efficacy of lutetium Lu 177 dotatate and yttrium Y 90 dotatoc in the paediatric population.

- The primary analysis results from CAAA601A32201 study (also referred to as NETTER-P), a multicenter open-label study which evaluated safety and dosimetry of Lutathera in adolescent patients with somatostatin receptor positive GEP-NETs or PPGLs. The study aimed to enrol at least 8 adolescents (including at least 3 GEP-NET patients).

As a note, a PPGL indication was not sought as part of this application. The data provided from this cohort were intended exclusively to support the GEP-NET indication.

The study schedule for each participant consisted of the screening period (up to 2 weeks) followed by the treatment period (4 treatment administrations (7.4 GBq/200 mCi per administration; cumulative dose: 29.6 GBq/800 mCi) at 8 week intervals [±1 week]) and the follow-up period (5 years).

The dosimetry and pharmacokinetics (PK) assessments were performed during the first week after the first Lutathera dose, i.e., one time during the study treatment period for each participant. The dosimetry analysis estimated the cumulative absorbed radiation dose from 4 Lutathera administrations using the radiation dose observed at the first or later Lutathera administration, to enable an informed decision on the next dose to be administered to the participant.

Blood samples for radioactivity measurement were collected for PK and dosimetry assessments.

Dosimetry estimates for Lutathera were determined based on bio-distribution found using whole body conjugate planar image data, SPECT/CT image data, blood assay data, and urinary excretion data collected in 11 enrolled participants.

Safety assessments in the study included physical examinations, vital signs, electrocardiograms (ECG), standard clinical laboratory evaluations (haematology, blood chemistry, and urinalysis), safety biomarkers, and AE monitoring.

Tumour response assessments were considered exploratory in this study. Computed tomography (CT)/ magnetic resonance imaging (MRI) was done according to the assessment schedule to evaluate tumour response according to RECIST 1.1 criteria.

3.2. Favourable effects

Extrapolation for clinical efficacy of Lutathera from adults to adolescents with GEP-NETs with high levels of SSTR2 expression was accepted in the PIP by PDCO based on i) similar disease characteristics and potential response to Lutathera treatment; ii) same mechanism of action; iii) similar exposure/response relationship; and iv) that the drug amount (i.e. dose, concentration, exposure) is measurable and predictive of clinical response. This was shown by the data provided from the NETTER-P study.

Based on the observed **PK metrics** for adults (NETTER-1) and adolescents (NETTER-P), and the final popPK model, the exposure between the two populations could be regarded as comparable. Observed AUClast was about 36% and Cmax about 24% higher in adolescents with GEP-NET and PPGL compared to adults with GEP-NET. Taking into account the high variability, results could be interpreted to show a great overlap.

Since GEP-NETs are very rare in the paediatric population, **explorative efficacy data** reported for 4 GEP-NETs (and 7 subjects with PPGL; not applied here) from NETTER-P could be considered appropriate to extrapolate the clinical efficacy documented in adults to adolescent population, in line with the PIP of Lutathera. At the time of the primary analysis DCO (12-Mar-2024) for NETTER-P study, all 11 participants (4 with GEP-NET and 7 with PPGL) had received 1-4 cycles of treatment. Nine participants (3 with GEP-NET and 6 with PPGL) with at least 1 post-baseline tumour assessment had stable disease as best overall response (BOR) as per local assessment with no deaths reported during the study, while 1 participant with GEP-NET had disease progression 8.6 months after the first administration of Lutathera.

3.3. Uncertainties and limitations about favourable effects

The observed dosimetry results were comparable between adolescent and adult participants treated with Lutathera. There were some minor exemptions, e.g. for osteogenic cells, absorbed doses were higher for adults (approximately 0.15 ± 0.27 Gy/GBq vs. 0.05 ± 0.02 Gy/GBq), this could, however, be explained by the small cohorts, the variable results and the multiples sites which were compared. Notably, observed kidney dosimetry was comparable (0.78 ± 0.28 Gy/GBq in adolescents vs. 0.65 ± 0.30 Gy/GBq in adults).

Kidney and BM dosimetry relationships with dose and CrClBL were investigated via modelling and comparability was assessed between adults and adolescents. The probability for adolescents to exceed the 29 Gy threshold in kidneys was predicted to be twice as high (20.9%; 5th, 95th percentile 7.7, 36.7) compared to adults (10.0%; 5th, 95th percentile 7.8, 12.2). In the modelling and simulation Report of August 2023 the median probability of an adolescent population with normal renal function to exceed 29 Gy was predicted to be 11.3%, which could not be confirmed using clinical data from adolescent patients (also discussed in chapter "organ dosimetry results"). It remains unclear, whether this observed higher risk to exceed 29 Gy kidney dosimetry could be related to differences in exposure or to other effects. However, the predicted median values for kidney dosimetry for adults and adolescents after the first dose (not cumulative) were 4.37 Gy and 5.39 Gy, respectively, which can be regarded as similar. In contrast to higher risk regarding kidney dosimetry, the probability to exceed >2 Gy in bone marrow is predicted to be lower in adolescents compared to adults. Conclusions should be made with caution as the analyses are based on n=10 adolescent patients only.

Efficacy assessment appears premature at the time of the primary analysis, since PFS is assessable from 1 patient only and all other subjects are reported with stable disease BOR. No information was provided regarding standard tumour specific endpoints as PFS, ORR and OS.

3.4. Unfavourable effects

The overall safety profile of Lutathera was established in adult patients in the NETTER-1 phase III and ERASMUS phase I/II (Dutch patients) and from compassionate use programmes. The established safety profile in adult patients was recently confirmed by additional data derived from NETTER-2 trial, these data were pivotal in the recently withdrawn procedure applying for inclusion of the first line GEP-NET population (Lutathera II/52).

Overall, 10 of the 11 paediatric participants (90.9%) in the safety set experienced at least 1 AE during the first cycle of Lutathera, and all 11 participants (100%) experienced at least 1 AE during the overall treatment period. Lutathera-related AEs were reported in 9 participants (81.8%) during the first cycle of Lutathera and 10 participants (90.9%) during the overall treatment period. Grade $\geq$ 3 AEs occurred in 4 participants (36.4%) during the first cycle of Lutathera and 7 participants (63.6%) overall during the Lutathera treatment in NETTER-P.

There were no deaths or AEs leading to study treatment discontinuation until the primary analysis DCO. Three SAEs were reported in 2 participants (18.2%): one SAE (Grade 3 lower GI haemorrhage) during the first cycle of Lutathera and two SAEs (Grade 3 hypercalcemia, Grade 3 catheter-related infection) in later cycles). None of the SAEs were related to the study treatment, as assessed by the Investigator.

Based on published literature and on the available clinical data from paediatric patients aged 12 to < 18 years and treated with Lutathera in NETTER-P, no new or changing safety signals were identified at present form the available short-term data. Lutathera showed a similar safety and tolerability profile in adolescent GEP-NET and PPGL patients as in adults.

3.5. Uncertainties and limitations about unfavourable effects

Considering the very limited data, the MAH was requested to discuss and propose details for a long-term safety follow-up trial (PASS) in paediatric patients with GEP-NET tumours. For Lutathera as a therapeutic radiopharmaceutical, long-term safety data should be collected in the paediatric population for whom a longer life expectancy could be expected. The MAH was initially requested to discuss and propose details of a long-term safety follow-up trial (PASS) in patients with newly diagnosed tumours including the paediatric patients initially claimed in this application, including the use of existing EU registry-based study (with special attention to those where administered treatment and dosimetry data are collected). However, since the MAH eventually decided not to pursue a paediatric indication, further discussion on additional risk minimisation measures is no longer relevant.

The dosimetry indicates that the absorbed doses to the spleen (cumulative >20Gy) and pituitary (cumulative >30Gy) are of concern, irrespective of a high SD and irrespective of the uncertainties in comparing with External beam RT. Further, hyposplenism (and its consequences) cannot be considered solely a long-term risk. While no cases of "Hypogonadism or, sexual dysfunction" were reported in the adolescent patients of the NETTER-P study, this is only based on 11 patients. However, as "hypogonadism and sexual dysfunction" are already listed as important identified risks in the RMP of Lutathera, no further actions were deemed necessary. While no cases of hyposplenism have been identified so far, both in clinical trials and post-marketing setting, given the very low number of treated paediatric patients, the risk of hyposplenism was requested to be listed as missing information in the RMP of Lutathera with additional pharmacovigilance activity proposed. The same paradigm applies to hypopituitarism. However, as the MAH is no longer pursuing the paediatric indication, no update of the RMP were considered necessary.

3.6. Effects Table

Not provided, given the limited sample size (N=11) and the uncontrolled design of the NETTER-P study.

3.7. Benefit-risk assessment and discussion

In light of the NETTER-2 application withdrawal (see WPAR EMEA/H/C/004123/II/0052) the MAH reassessed the strategy for a paediatric indication and decided that the extension of Lutathera therapeutic indication to unresectable or metastatic, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) adolescents aged 12 years and older would be no longer pursued.

The MAH applied instead to convert the current application from a new indication (type C.I.6) to a SmPC label update (type C.I.4) and to continue under the ongoing procedure with the paediatric data available from the NETTER-P study proposed for inclusion in sections 4.8, 5.1, 5.2 and 11 of the Lutathera SmPC. Section 4.2 was updated as per SmPC guideline (EMA 2009).

3.7.1. Importance of favourable and unfavourable effects

There is a large amount of clinical experience with the use of peptide receptor radionuclide therapy in adult patients with unresectable or metastatic, progressive, well-differentiated SSTR2 positive GEP-NETs. The pivotal phase III study NETTER-1 data in adults showed a statistically significant and clinically relevant benefit with improved response rates and improvements in progression free survival in adults (see Lutathera EPAR initial MAA).

In agreement with PDCO, efficacy and safety bridging for the paediatric population, specifically for the adolescent patients above an age of 12 years and below the age of 18 years, may be based on the reasoned assumption of a similar disease treated with comparable exposure and similar exposure-dosimetry relationship.

3.7.2. Balance of benefits and risks

The clinical benefits demonstrated by the extrapolation of the clinical efficacy of Lutathera from adults to adolescents could have outweighed the safety risks provided that additional amendments to the SmPC had been implemented: ensuring that the paediatric indication would not be broader than the approved adult indication and including warnings specific to paediatric population in section 4.4. Furthermore, the introduction of additional risk minimisation measures, such as an EU registry-based study for the collection of long-term safety data, would have strengthened the overall benefit-risk profile.

However, as the MAH decided to convert the current application from a new indication (type C.I.6) to a SmPC label update (type C.I.4), no conclusion can be drawn regarding the benefit-risk profile for Lutathera in the adolescent population.

3.7.3. Additional considerations on the benefit-risk balance

Results to support the full extrapolation of adult data to adolescents are very limited, especially when considering the GEP-NET cohort independently (N=4 patients). Numbers are also limited even with the addition of the PPGL cohort (N=7 patients). A very limited data set was, however, expected and foreseen in the PIP of Lutathera considering the rarity of the GEP-NETs (and PPGLs) in adolescents.

No conclusion can be drawn regarding the benefit-risk profile for Lutathera in the GEP-NET adolescent population, as the MAH decided to withdraw their claim for an extension of indication and opted to proceed with the application as an SmPC label update.

3.8. Conclusions

The overall B/R of Lutathera in the previous approved therapeutic indication *for the treatment of unresectable or metastatic, progressive, well-differentiated (G1 and G2), somatostatin receptor-positive GEP-NETs in adults* remains unchanged positive.

The extension of Lutathera therapeutic indication to unresectable or metastatic, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) adolescents aged 12 years and older is no longer pursued.

Selected paediatric data available from the NETTER-P study have been included in sections 4.8, 5.1, 5.2 and 11 of the Lutathera SmPC.

This proposed update of the SmPC according to some aspects derived from the NETTER P trial is **approvable** in the CHMP's view.

No conclusion can be drawn regarding the benefit-risk profile for Lutathera in the GEP-NET adolescent population, as the MAH decided to withdraw their claim for an extension of indication and opted to proceed with the application as an SmPC label update.

4. Recommendations

Outcome

The MAH submitted a variation application under category C.1.6 of the variation classification Guideline with the scope to include the treatment of unresectable or metastatic, somatostatin receptor-positive GEP-NETs in adolescents aged 12 years and older for Lutathera based on the NETTER-P study.

Following the second round of assessment, the applicant decided not to further pursue the extension of indication but to include information regarding paediatric populations in sections 4.2, 4.8, 5.1, 5.2 and 11 of the SmPC. These changes fall under category C.1.4 of the variation classification Guideline.

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

To update sections 4.2, 4.8, 5.1, 5.2 and 11 of the SmPC to include efficacy, safety, pharmacokinetic and dosimetry data of Lutathera in adolescents based on primary analysis results from study CAAA601A32201 (NETTER-P). NETTER-P study is a Phase II, multicenter open-label study which evaluated the safety and dosimetry of Lutathera in adolescent patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) and pheochromocytoma and paragangliomas (PPGLs).

In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0461/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC).