Advanced Accelerator Applications

Research and Development

LUTATHERA® (lutetium Lu 177 dotatate)

Clinical Trial Protocol CAAA601A32201 / NCT04711135

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

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List of abbreviations

AA	Amino Acid
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT/ALAT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST/ASAT	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AxMP	Auxiliary Medicinal Product
BALP	Bone Alkaline Phosphatase
BCRP	Breast Cancer Resistance Protein
BUN	Blood Urea Nitrogen
CI	Confidence Interval
Cl	Clearance
Cr	Creatinine
CRO	Contract Research Organization
CSR	Clinical study report
CTC	Common Terminology Criteria
CT	Computed Tomography
CTFG	Clinical Trials Facilitation and Coordination Group
CTIS	Clinical Trials Information System
CTR	Clinical Trials Register
CTX	C-terminal cross-linked telopeptide of type I collagen
DICOM	Digital Imaging and Communications in Medicine
DMT	Dose Modifying Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEA	European Economic Area
EMA	European Medicines Agency
EoT	End of Treatment
EoS	End of Study
eSource	Electronic Source
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
FUP	Follow-up period
GBq	Giga becquerel
GCP	Good Clinical Practice
GEP-NETs	Gastroenteropancreatic Neuroendocrine Tumors
G1/2	Grade1/2
Gy	Gray
h	Hour
Hb	Hemoglobin
i.v.	Intravenous
IB	Investigator’s Brochure

ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IEC	Independent Ethics Committee
IGF1	Insulin-like Growth Factor 1
IRB	Institutional Review Board
LAR	Long-Acting Release (Octreotide LAR)
LH	Luteinizing Hormone
^{177}Lu	Lutetium-177
mCi	Millicurie
MCV	Mean Cell Volume
MDS	Myelodysplastic Syndrome
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram(s)
M&S	Modelling and simulation
mL	Milliliter(s)
MRI	Magnetic Resonance Imaging
NETs	Neuroendocrine Tumors
NTX	N-terminal cross-linked telopeptide of type I collagen
PFS	Progression-free Survival
PK	Pharmacokinetic(s)
PLT	Platelets
PPGL	Pheochromocytoma and paraganglioma
PRRT	Peptide Receptor Radionuclide Therapy
[redacted]	[redacted]
ROI	Region Of Interest
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	standard deviation
SEER	Surveillance Epidemiology and End Results Program of the US National Cancer Institute
SmPC	Summary of Product Characteristics
SPECT	Single Photon Emission Computed Tomography
SRI	Somatostatin Receptor Imaging
SSTR2	Somatostatin Subtype 2 Receptors
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAC	Time Activity Curves
TIAC	Integrated Activity Coefficient
TSH	Thyroid Stimulating Hormone
ULN	Upper limit of normal
UPCR	Urine protein creatinine ratio
US	United States of America
USPI	United States Prescribing Information
WBC	White blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
WOCBP	Women of Childbearing Potential

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Auxiliary Medicinal Product (AxMP)	Medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., rescue medication, challenge agents, background treatment or medicinal products used to assess endpoints in the clinical trial). Concomitant therapy is not considered as AxMP.
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Control drug	A study drug (active) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days or weeks.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time when eligibility criteria are confirmed and study treatment is prescribed
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Advanced Accelerator Applications for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Participant number	A unique identifier assigned to each screened participant
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Screening	Point of time when participant entry into the study at which informed consent must be obtained
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body

Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Protocol summary

Protocol number	CAAA601A32201
Full Title	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 (PPGL)
Brief title	Study to evaluate safety and dosimetry of Lutathera in adolescent patients with GEP-NETs and PPGLs
Sponsor and Clinical Phase	Sponsor: Advanced Accelerator Applications Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	There are currently no approved therapies for GEP-NETs in the pediatric population. As observed in adults, the diagnosis of NETs in children is often delayed due to the indolent nature of the disease. It has been reported that 10% to 20% of pediatric patients present with metastatic disease at diagnosis (Parham 2001, Sarvida et al 2011). While surgical intervention is favored as first-line treatment for patients with early-stage disease, metastatic NETs in the pediatric population, as in adults, are unresectable. Non-surgical treatment modalities for the pediatric population include those used in adults, namely, somatostatin analogues, chemotherapy, everolimus, and peptide receptor radionuclide therapy (PRRTs.) There is very limited published data on the use of Lutathera in the pediatric population with GEP-NETs (case reports Yesil et al 2016 and Potter et al 2018). A small number of published studies have reported data on the use of Lutathera in children and adolescents with neuroblastomas (Gains 2011, Kong 2016, Chen 2018, Gains 2020), or with 90Y-DOTATOC in pediatric GEP-NETs (Menda 2010, Menda 2018). Given the lack of approved therapeutic options for the pediatric population and the scarcity of pediatric data, GEP-NETs in adolescents constitute an area of high unmet need. This clinical study aims to address this unmet need and to accelerate access of Lutathera as a potential treatment for adolescent patients with GEP-NETs. In this context, a full extrapolation of the clinical efficacy of Lutathera already established in adults to the adolescent population (12 to <18 years old) approach is made by [redacted] Furthermore, it is based on the assumption that [redacted] This full efficacy extrapolation approach for adolescent patients with GEP-NET is conducted based primarily on the following 4 aspects: 1. Similar disease characteristics, including manifestation, progression and course (Spunt et al 2000, Dall'Igna et al 2005, Farooqui and Chauhan 2019, Bethel et al 1997, Fernandez et al 2015, Johnson 2014) as well as [redacted] and adolescent patients with GEP-NETs to Lutathera treatment. 2. Similar mechanism of action of Lutathera in adult and adolescent patients with GEP-NET, including [redacted] 3. Similarity in [redacted] between adult and adolescent. 4. Results of [redacted] which has established the dose for adolescent population based on [redacted] registration clinical studies). The extrapolation approach aims to provide evidence for the safe and effective use of Lutathera in adolescents with GEP-NETs and has been verified by the results of a modelling and simulation (M&S) analysis that confirmed that the Lutathera dose for the adolescent population 12 to <18 years old is the same as used in adults. The main objective of the current clinical study is to confirm the defined dose by assessing the safety, tolerability and dosimetry of Lutathera in adolescents with GEP-NETs or PPGLs. Similarly to GEP-NETs, there are limited non-surgical treatment modalities in pediatric patients with progressive PPGLs. Recently, Azedra (iobenguane I 131) has been approved by FDA for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic

	pheochromocytoma or paraganglioma who require systemic anticancer therapy. Increased somatostatin receptor (SSTR) expression, particularly that of SSTR2, in PPGLs has been demonstrated by uptake on somatostatin receptor scintigraphy providing the rationale for the use of PRRT with radiolabeled somatostatin analogues in this patient population (Reubi et al 2001, Reubi 2003). Published adult data from SSTR-positive PPGL patients treated with Lutathera shows clinical efficacy and improvement of quality of life (Satapathy 2019). Only few case reports have been published on the use of Lutathera in children with PPGLs (Cassano 2019, Yadav 2019, Roll 2020, Pinato 2016), with single patients treated in each of the reports. Due to the rarity of pediatric data in PPGL and unmet need in this indication, this study includes a cohort for enrolment of adolescent patients with somatostatin receptor positive PPGLs. In conclusion, this clinical study evaluating PRRT with Lutathera in the adolescent population will be essential to bring a new potential therapeutic option for adolescent GEP-NET and PPGL patients.

Primary Objectives	• Evaluate organ absorbed radiation doses from PRRT with Lutathera in adolescent patients with SSTR-positive GEP-NETs and PPGLs as a pooled cohort
	  • Endpoint: 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
	  • Endpoint: The incidence of adverse events (AEs) and laboratory toxicities after the 1st Lutathera administration in adolescents with SSTR-positive GEP-NETs and PPGLs as a pooled cohort

Secondary Objectives	• Evaluate cumulative safety of Lutathera in adolescents with SSTR-positive GEP-NETs and PPGLs as a pooled cohort
	  • Endpoint: The incidence of adverse events (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
	  • Endpoint: The incidence of adverse events (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 pharmacokinetics (PK) between adolescent patients with GEP-NETs and PPGLs as a pooled cohort and adult patients using the extrapolation model developed for the clinical study.
	  • Endpoint: Calculated organ absorbed doses and PK parameters based on imaging/blood radioactivity concentration data from adolescent patients with SSTR-positive GEP-NETs and PPGLs as a pooled cohort compared to the predicted distribution / organ absorbed doses

[redacted]	

Study design	This is a multicenter, open-label, single-arm study to evaluate the safety and dosimetry of Lutathera in adolescent patients 12 to <18 years old with somatostatin receptor positive GEP-NETs and PPGLs. The study will enroll at least 8 adolescent patients across GEP-NETs and PPGLs, including a minimum of 3 adolescents with GEP-NETs . The study schedule for each patient consists of the screening period (up to 2 weeks) followed by the treatment period (4 treatment administrations at 8-week intervals), and the follow-up period (5 years). During the screening period of up to 2 weeks, patient eligibility will be determined according to the protocol's pre-defined inclusion and exclusion criteria. Patients who meet all eligibility criteria at screening can be enrolled in the study. The enrollment and Lutathera order must be performed immediately after all eligibility criteria are verified and the patient is confirmed to be eligible. The treatment period will consist of 4 Lutathera treatments administered at 8-week intervals. Lutathera administration will occur on Week 1 Day 1 of each cycle. Each patient will receive a total of 4 doses of Lutathera (7.4 GBq/200 mCi x 4 administrations every 8 weeks; cumulative dose: 29.6 GBq/800 mCi). An infusion of sterile 2.5% Lysine - Arginine amino acid (AA) solution will be co-administered with each Lutathera dose for renal protection according to the approved Lutathera local prescribing information. An antiemetic will be administered prior to infusion of the AA solution for prevention of infusion-related nausea and vomiting. The dosimetry and PK assessments will be performed during the first week after the 1st Lutathera dose, i.e. one time during the study treatment period for each patient. The dosimetry analysis will allow for estimation from the 1st Lutathera administration of the cumulative absorbed radiation dose from 4 Lutathera doses and also for taking a decision on the next dose levels. In the exceptional circumstances when dosimetry cannot be performed in a particular patient after the first Lutathera dose, it should be completed as soon as feasible upon a later dose. In order to minimize risk for each study subject, an accelerated analysis of dosimetry and safety data will be performed for each patient in the study, to enable the Investigator to take a decision for the subsequent Lutathera doses. The results of dosimetry assessments (imaging and blood dosimetry) will be provided to the investigators for their evaluation prior to administration of subsequent therapeutic cycles in each patient. See Section 6.5.1 for further information on the criteria for evaluating the need for dose modification based on safety and dosimetry data. A total follow-up period of 5 years (60 months) after the last Lutathera dose will take place for each patient who received at least one dose of Lutathera. This follow-up period will be comprised of a short-term follow-up of 6 months to evaluate cumulative Lutathera toxicities, followed by a long-term follow up of another 54 months. An external Data and Safety Monitoring Board (DSMB) will also operate in the study to evaluate accumulating safety and dosimetry data, to ensure the safety of adolescents enrolled in the study, and to provide recommendations to investigators as well as to the clinical team in charge of conducting the study.
Study population	This study will enroll at least 8 adolescent patients 12 to < 18 years old with somatostatin receptor-positive GEP-NETs or PPGLs, including a minimum of 3 adolescents with GEP-NETs.
Key Inclusion criteria	1. GEP-NET cohort: presence of metastasized or locally advanced, inoperable (curative intent), histologically proven, G1 or G2 (Ki-67 index ≤20%), well differentiated GEP-NET. PPGL cohort: presence of metastasized or locally advanced, inoperable (curative intent), histologically proven PPGL. 2. Patients from 12 to < 18 years of age at the time of enrollment.

	3. Expression of somatostatin receptors confirmed by a somatostatin receptor imaging (SRI) modality within 3 months prior to enrollment, with tumor uptake observed in the target lesions more or equal to the normal liver uptake. 4. Performance status as determined by Karnofsky score ≥ 50 or Lansky Play-Performance Scale score ≥ 50. 5. 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.
Key Exclusion criteria	1. Laboratory parameters: • Estimated creatinine clearance calculated by the Cockroft-Gault method < 70 mL/min • Hb concentration <5.0 mmol/L (<8.0 g/dL); WBC <2x10^9/L; platelets <75x10^9/L. • Total bilirubin >3 x ULN for age. • Serum albumin <3.0 g/dL unless prothrombin time is within the normal range. 2. Established or suspected pregnancy. 3. Breastfeeding female patients unless they accept to discontinue breastfeeding from the 1st dose until 3 months after the last administration of study drug. 4. Female patients of child-bearing potential, unless they are using highly effective methods of contraception during treatment and for 7 months after the last dose of Lutathera (see details in the Appendix 1). 5. Sexually active male patients, unless they agree to remain abstinent or be willing to use condoms and highly effective methods of contraception during treatment and for 4 months after the last Lutathera dose. 6. Patients for whom in the opinion of the investigator other therapeutic options are considered more appropriate than the therapy offered in the study, based on patient and disease characteristics. 7. Current spontaneous urinary incontinence. 8. 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. 9. Hypersensitivity to the study drug active substance or to any of the excipients. 10. Patients with any other significant medical, psychiatric, or surgical condition, currently uncontrolled by treatment, which may interfere with the completion of the study. 11. Patient with known incompatibility to CT scans with I.V. contrast due to allergic reaction or renal insufficiency. If such a patient can be imaged with MRI, then the patient would not be excluded. 12. Patients who received any investigational agent within the last 30 days. 13. Prior therapies and procedures as detailed in Section 5.2.
Study treatment	Lutathera (7.4 GBq/200 mCi x 4 administrations every 8 weeks; cumulative dose: 29.6 GBq/800 mCi), with a concomitant administration of 2.5% Lysine - Arginine amino acid (AA) solution
Key safety assessments	Safety assessments in the study will include physical examinations, vital signs, ECGs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), safety biomarkers and adverse event monitoring. To monitor for potential Lutathera toxicities, safety assessments will be performed in each treatment cycle, with clinical laboratory samples taken regularly after each Lutathera dose. A set of safety biomarkers of growth and development, reproductive and endocrine function will be collected and analyzed for each patient.
Dosimetry and pharmacokinetic assessments	Patients will have whole body and organ radiation dosimetry (including the critical organs, i.e. bone marrow and kidney) determined following the first Lutathera treatment using planar imaging and blood radioactivity data. In the exceptional

	circumstances when dosimetry cannot be done in a particular patient after the first dose, it should be done as soon as feasible upon a later dose. For each patient, dosimetry will be performed only once throughout the study. Dosimetry assessments will include: - Whole body planar images - SPECT/CT scan - Blood samples for radioactivity measurement - Urine sample for radioactivity measurement (all excreted urine from the start of Lutathera infusion until the first whole body planar imaging) The absorbed radiation dose in organs will be the ultimate output dosimetry parameter that will be provided to Investigators for each patient, and to DSMB, if necessary. Pharmacokinetic parameters such as the maximum blood concentrations (C_{max}), the sampling time at which C_{max} is reached (t_{max}), in addition to the area under the curve ($AUC_{0-\infty}$), systemic clearance (Cl), volume of distribution (V1 and V2) will be determined using model based methods. Other parameter estimates may be determined as deemed appropriate.
[redacted]	
Data analysis	The data will be analyzed by the Sponsor and/or designated CRO. All statistical analyses will be descriptive in nature and will include summaries and graphical presentations of data. No statistical hypothesis will be tested. Interim analyses will be performed to evaluate dosimetry and safety when at least five patients (including at least two GEP-NET patients) have completed at least one cycle of treatment. The data from all completed treatment cycles will be presented. Analysis will be presented across both indications, as well as for GEP-NET and PPGL separately. The primary analysis will be conducted after at least 8 patients (including at least 3 GEP-NET patients) have completed the first cycle (cut-off before the second dose of Lutathera), at which time both dosimetry and safety assessments of the first cycle will be complete for the assessment of the primary objective. Should the dosimetry assessments be done at a later cycle instead of first cycle, the primary analysis will be done after the dosimetry assessments are performed. All data available at the time of primary analysis will be collected for the assessment of the primary, secondary [redacted] objectives including the analysis of the PPGL cohort. A final analysis will be performed after all subjects who have received at least one dose of Lutathera have completed the 5 years of follow-up or have withdrawn from the study.
Key words	GEP-NET, pheochromocytoma, paraganglioma, PPGL, adolescents, pediatric, Lutathera, lutetium (^{177}Lu) oxodotreotide, lutetium Lu 177 dotatate, PRRT

Protocol Amendment 03

As of 14-Dec-2023, 11 patients including 4 GEP-NET and 7 PPGL patients have been enrolled in the study.

Amendment rationale

The primary purpose of Amendment 03 is to align the protocol with the amended FDA Written Request and PDCO positive opinion on the request for modification of the agreed PIP for Lutathera issued on 28-Jun-2023 and 13-Oct-2023 respectively. On 01-Dec-2023, the final EMA Decision/Acceptance for the modification of the agreed pediatric investigation plan for Lutathera (EMEA-002950-PIP01-20-M01) was received. It was agreed with both Health Authorities that the primary analysis of organ dosimetry, pharmacokinetic (PK) and safety data will be carried out across adolescent patients with GEP-NETs and PPGLs, as these parameters are not expected to vary substantially depending on tumor type. The main risks arising from treatment with Lutathera are radiation toxicities affecting either kidney function o(r bone marrow, which applies to both GEP-NET and PPGL. Biodistribution to organs and normal tissues and thus organ dosimetry and safety is not anticipated to be affected by the disease. Therefore, the data from both GEP-NET and PPGL patients can support the overall comparison between adolescents and adult GEP-NET patients during the primary analysis.

Based on the above rationale, the study design, study objectives and endpoints are modified as follows:

- The total number of patients required for the primary analysis remains the same, with at least 8 adolescent patients evaluable for the primary endpoints, but the primary analysis will be pooled across indications. Consequently, this change leads to an updated sample size from 8 GEP-NET patients to 8 adolescent patients across indications including a minimum of 3 adolescents with GEP-NET. With the enrolled number of patients, the updated recruitment target has already been met.
- The co-primary and secondary objectives will be evaluated in GEP-NETs and PPGLs as a pooled cohort instead of GEP-NETs cohort alone, serving the same purpose to compare adolescent data with data from adult GEP-NET patients.
- [redacted]

In addition, the protocol amendment included the following changes:

- Laboratory assessments on safety biomarkers of endocrine and gonadal function were added to long-term follow up visits. This implements FDA written request requirements that safety follow up should include monitoring for pituitary dysfunction given the potential risk for toxicity to the pituitary gland.
- Added text to clarify the safety reporting requirements for Auxiliary Medicinal Products (AxMPs), regulatory and ethical compliance, and publication of the study protocol and results per EU Clinical Trial Regulation 536/2014 in view of the future study transition to EU CTR.

The Amendment also includes editorial changes and text corrections made for clarification, where required.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through and red font for deletions and red underline for insertions.

The following sections and/or tables were changed/updated:

- Section 1, Section 2, Section 3, Section 4, Section 12.4, Section 12.5, Section 12.6, and Section 12.8: Updated the primary and secondary objectives of the study to use pooled data derived from the GEP-NET and PPGL cohorts. [redacted]
- Section 3: Updated the text to clarify that the study will enroll at least 8 adolescents across the GEP-NET and PPGL cohorts and a minimum of 3 adolescents in the GEP-NET cohort. The maximum number of 8 PPGL patients was deleted as it no longer applies.
- Section 6.1.2 and Table 6-2: Updated the text to provide additional details regarding the sterile 2.5% Lys-Arg amino acid solution and clarification of anti-emetics as AxMP.
- Table 8-2: Added an EOS visit to the assessment schedule and included a footnote to clarify that the last FU visit would be the EOS visit for patients who completed the long-term FU period, and that a separate EOS should be planned for patients who discontinued from the study prior to completion of the long-term FU period.

  Added assessments for biomarkers of endocrine and gonadal function during the long-term FU visit.

  Also included a footnote to clarify the collection of concomitant medications and new anticancer therapies administered during the FU period.
- Section 9.1.1.1: Updated text, in line with the changes to the primary dosimetry analysis.
- Section 10.1.1 and Section 10.1.6: Updated the text to clarify the AE reporting responsibility and causality assessment with regards to A(x)MPs following the EU CTR.
- Section 10.1.2: Added text to clarify Hy's law reporting.
- Section 12.8: Updated text to clarify that the overall sample size calculated for the study is 8 patients overall, across indications.
- Section 13.1 and Section 13.3: Added wording to align with the EU CTR requirements.
- Section 13.4: Added wording regarding the retention of records and documents, including signed ICFs.
- Protocol summary was updated to reflect change to the protocol body.

  Other minor changes/corrections were made for consistency and/or clarifications.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol Amendment 02

As of May the 8th 2023, 5 patients including 2 GEP-NET and 3 PPGL patients have been enrolled in the study.

Amendment rationale

The primary purpose of Amendment 02 is to implement interim analyses for an early evaluation of dosimetry and safety data when at least five patients (including at least two GEP-NET patients) have been treated. This formal interim analysis is introduced due to the slower than expected recruitment rate, and proportionally higher than expected recruitment of PPGL patients. The interim analysis will combine patients with GEP-NET and PPGL based on the consideration from clinical perspective there are no expected differences from dosimetry or critical organ toxicity across these two indications, which will permit an evaluation across the indication in order to test modelling assumptions of similar dosimetry between adolescents and adults. Taking the slow recruitment into account, the result of interim analysis with at least 5 patients across these two indications could provide support for full extrapolation.

Due to higher-than-expected screening rate of patients with PPGLs, this amendment will limit enrolment to a maximum of 8 PPGL patients to avoid recruitment bias between GEP-NET and PPGLs.

In addition, the recommendation of the Data and Safety Monitoring Board (DSMB) regarding monitoring of microproteinuria during the course of study treatment is now formally implemented in the protocol in order to detect early signs of renal toxicity especially in light of treatment of patients with medical history of nephrectomy in the study. Therefore, spot urine test of urine protein creatinine ratio (UPCR) is added in the Assessment schedule (Table 8-2) before each Lutathera infusion and 3 weeks after each infusion.

The Amendment 02 also includes editorial changes and text corrections made for clarification, where required.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through and red font for deletions and red underline for insertions.

1. Protocol summary: Data analysis section updated to reflect the implementation of interim analyses. Study design and Study population updated to clarify the enrollment target in PPGL patients.
2. Section 1.1: updated reference and data from NETTER-1 study.
3. Section 3: updated to add a paragraph on the interim analyses and include modified enrollment target in PPGL patients.
4. Section 4.1: updated to indicate that “the investigator is advised to follow DSMB recommendation on dose modification”.
5. Section 4.3: updated data from NETTER-1 study.
6. Section 5: Added clarification on enrollment target for GEP-NET and PPGL patients.
7. Section 6.1.1: +/-1 week visit window was added to be consistent with the footnote in Table 8-2.
8. Added Section 6.2.4 “SARS-CoV-2 vaccination” to provide clarifications on the risk/benefit assessment in regard to SARS-CoV-2 vaccination and vaccination data collection.

9. Table 6.4: added footnote "1 No dose modification required for hematological toxicities Grade 3 or Grade 4 solely due to lymphopenia "in line with ongoing labeling updates.
10. Section 8: Table 8-2 and related foot notes updated as follows:
    a. Added height measurement at week 1 of cycle 4 and at the last visit of short-term FUP to ensure height monitoring twice a year throughout the course of the study.
    b. Added spot urine test of urine protein creatinine ratio (UPCR).
    c. Footnote 1: AE collection related to "End of Treatment Visit" was clarified.
11. Section 8.4.: Table 8-4 updated to include UPCR analysis as part of the Urinalysis.
12. Section 8.4.7: wording updated to align with UPCR test addition.
13. Section 10.1.1: clarification added to refer to section 10.1.5 for details related to adverse events of special interest (AESI).
14. Section 10.1.5: wording updated to clarify that during screening only AESI meeting seriousness criteria should be reported to the Sponsor.
15. Section 10.1.6: wording updated to clarify AESI reporting rules.
16. Section 10.1.9: wording related to SAE reporting rules adjusted for consistency.
17. Section 12: added wording related to the interim analyses and to PK modeling and simulation.
18. Section 12.7: added wording related to interim analyses and removed language for primary and final analysis.
19. Section 12.8: added maximum number of PPGL adolescents will be enrolled.
20. Section 15: added a new reference.
21. Section 16: removed Appendix 2 "Recommendations to patients treated with Lutathera" in Protocol Amendment 01 to align with other sponsored trial protocols. Instead this appendix will be attached to the Global Informed Consent Form.

Protocol Amendment 01

Amendment rationale

The primary purpose of amendment 01 is to implement modifications in contraception requirements in line with Lutathera Investigator's Brochure version 17 released on 09 March 2022. The changes are not due to new data but based on Sponsor Guideline on Prevention of Pregnancies in Participants in Clinical Trials as well as the Clinical Trials Facilitation and Coordination Group (CTFG) guideline on recommendations related to contraception and pregnancy testing in clinical trials. According to these guidelines, for radioligand therapies, highly effective contraception should be used during treatment and for (5 x T ½ + 6 months) after treatment in women of childbearing potential, and condom should be used during treatment and contraception period in male patients. For Lutathera, the effective half-life is 49 hours, and therefore, as per the calculation, the period of contraception for female patients should continue for 6 months and 10 days after the last dose. However, as a precautionary measure, the Sponsor decided to extend the highly effective contraception period from 6 months to 7 months for female patients. In addition, the sponsor propose to add a requirement for male patients to use condom with female partners of reproductive potential during treatment and for 4 months after last Lutathera dose. This duration is based on an exposure of 5 terminal half-lives (49 hours for Lutathera) plus 90 day (life span of spermatozoa of 60–75 days for sperm production + 10–14 days for transport to epididymis) ().

Based on its mechanism of action as a radioligand therapy, Lutathera can cause fetal harm when administered to a pregnant women and this information is now clarified in the Informed Consent Form.

The Amendment 01 also includes the following updates:

- Monitoring approach of women of childbearing potential (WOCBP) for pregnancy. Based on Sponsor Guideline on Prevention of Pregnancies in Participants in Clinical Trials, pregnancy testing is added monthly during treatment and during short-term follow up.
- Integration of local protocol amendments in UK (v00-UK01, 12 Jan 2021) into the global amendment:
    - Contraception requirements have been updated to reflect that sexually active male patients must agree to remain abstinent (refrain from heterosexual intercourse) or be willing to use condoms and highly effective methods of contraception with female partners of childbearing potential, and to use condoms with pregnant female partners during the treatment period and for 4 months after the last Lutathera dose.
    - Female and male patients must be informed that the study treatment may potentially have temporary toxic effects on female and male gonads. Genetic consultation is recommended if the patient wishes to have children after treatment. Cryopreservation of sperm or eggs can be discussed as an option to patients before the treatment.
    - In alignment with Lutathera and amino acids SmPC, a recommendation has been added to monitor vital signs during the infusion.
    - Body temperature has been added to the vital sign measurements due to concern of potential hematological toxicity and resultant infection during treatment of Lutathera.
- Specifying sterile condition of amino acid solution in order to emphasize that sterile solution is required for infusion.
- Correction of an error in the Cockcroft-Gault formula for calculation of creatinine clearance.
- Providing guidance to document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.
- Adding details of data protection under Ethical Considerations and Administrative procedures.
- Aligning with Lutathera USPI and updating the infusion rate from “400 mL/hr” to “up to 400 mL/hr”.
- Editorial changes and text corrections made for clarification, where required.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through and red font for deletions and red underline for insertions.

1. Protocol summary:
    a. Key Exclusion criteria #4: updated to reflect that female patients of child- bearing potential must use highly effective contraception during treatment and **for 7 months** (instead of 6 months) after the last Lutathera dose.
    b. Key exclusion criteria #5: use of **“condoms and highly”** effective methods of contraception **“during treatment and for 4 months after the last Lutathera dose”** inserted.

c. **"Sterile"** added before amino acid solution.

2. Section 5.2:
   a. Exclusion criteria #4:
      i. Language revised as follows: using highly effective methods of contraception during treatment and **for 7 months** after the last dose of Lutathera.
   b. Exclusion criteria #5:
      i. Language revised as follows: use of **"condoms and highly"** effective methods of contraception.
      ii. Language revised as follows: **"and to use condoms with"** pregnant female partners.
      iii. For UK and Poland only: "**6 months after the last Lutathera dose"** updated to **"4 months after the last Lutathera dose"**
3. Section 3, section 6.1.2, section 6.1.3, section 6.7 and section 10.1.5: "sterile" added before amino acid solution.
4. Section 6.7: Lutathera infusion rate updated from "400" to "Up to 400" in the table 6-5.
5. Section 7:
   a. Study treatment "may involve unknown risks to the fetus if pregnancy were to occur during the study" replaced by "can cause fetal harm when administered to a pregnant woman".
   b. Added following paragraph: **"Female and male patients must be informed that the study treatment may potentially have temporary toxic effects on female and male gonads. Genetic consultation is recommended if the patient wishes to have children after treatment. Cryopreservation of sperm or eggs can be discussed as an option to patients before the treatment."**
6. Section 8: Table 8-2 and related foot notes updated as follows:
   a. Added "body temperature" measurement as part of the vital signs assessment. Blood pressure and pulse rate monitoring during Lutathera and amino acid infusion is recommended.
   b. Pregnancy tests split into one row for blood pregnancy tests and one row for urine pregnancy tests with updated timepoints in alignment with Sponsor Guideline on Prevention of Pregnancies in Participants in Clinical Trials.
   c. Footnote 2: AE collection related to "End of Treatment Visit" was clarified.
   d. Footnote 6: clarification about data collection related to AEs, SAEs and AESI added.
7. Section 8.4.1: "reported" replaced by "recorded" for consistency.
8. Section 8.4.3: language revised to include the following:
   a. "Body temperature" as part of the vital signs assessment,
   b. Blood pressure and pulse rate monitoring during Lutathera and amino acid infusion is recommended,
   c. Body temperature measurement can be either oral or tympanic and method should be maintained throughout the study.
9. Section 8.4.6: update of the Cockcroft-Gault formula for calculation of creatinine clearance.
10. Section 8.4.8: wording updated to align with Sponsor Guideline on Prevention of Pregnancies in Participants in Clinical Trials.

11. Section 9.1.2: updated wording related to withdrawal of informed consent.
12. Section 9.1.3: slight update of the wording in line with Withdrawal of informed consent" section.
13. Section 10.1.9: wording related to AE reporting rules adjusted for consistency.
14. Section 13.5: added Data Protection section.
15. Appendix 1:
    a. Updated to reflect that female patients of child-bearing potential must use highly effective contraception during treatment and "**for 7 months"** (instead of 6 months) after the last Lutathera dose.
    b. Use of **"condoms and highly"** effective methods of contraception **"during treatment and for 4 months after the last Lutathera dose"** inserted.
    c. For UK and Poland only, male contraception language revised as follows: "**6 months after the last Lutathera dose"** updated to **"4 months after the last Lutathera dose".**
16. Appendix 2: language revised as follows:
    a. Female patients of child-bearing potential must use highly effective contraception during treatment and "**for 7 months"** (instead of 6 months) after the last Lutathera dose.
    b. Male patients should use **"condoms and highly"** effective "**methods**" of contraception with female partners of reproductive potential, **"and to use condoms with"** pregnant female partners.
    c. For UK and Poland only, male contraception language revised as follows: "**6 months after the last Lutathera dose"** updated to **"4 months after the last Lutathera dose".**

IRBs/IECs

A copy of this global amended protocol will be sent to Institutional Review Boards

(IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

1 Introduction

1.1 Background

Lutathera was FDA-approved on 26 January 2018 for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults. In the European Union, Lutathera was approved on 26 September 2017 for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive GEP-NETs in adults.

Lutetium (^{177}Lu) oxodotreotide (INN) or lutetium Lu 177 dotatate (USAN) has the trade name Lutathera® and is referred to as "lutetium (^{177}Lu) oxodotreotide" throughout this document. Lutetium (^{177}Lu) oxodotreotide is a radiolabeled somatostatin analog that has high affinity for SSTR2. It is comprised of the somatostatin peptide analog Octreotate, coupled to the metal-ion chelating moiety DOTA. It can be efficiently labelled with the beta-emitting radionuclide Lutetium-177 (^{177}Lu) and binds to cells, which express somatostatin receptors (SSTR). ^{177}Lu has a maximum penetration range in tissue of 2.2 mm (mean 0.67 mm), which is sufficient to kill targeted tumor cells with a limited effect on neighboring normal cells.

SSTR are members of the 7-segment G-protein coupled receptor family and are expressed in many tissues and organs in the body (Reubi et al 2000a). Of the 5 known receptor subtypes (Reubi et al 2001), the SSTR2 is considered the most important subtype for neuroendocrine tumors (Reubi et al 2000b, Reubi et al 2000a). The SSTR2 receptor is frequently overexpressed in neuroendocrine tumors and is central to the mode of action of a number of pharmaceutical agents, including somatostatin agonists for the control of symptoms in GEP-NET patients. Somatostatin analogs are used as targeted delivery vehicles for radionuclides in diagnostic imaging or therapy.

The biological basis for the use of peptide receptor radionuclide therapy (PRRT) in GEP-NETs is the receptor-mediated internalization and intracellular retention of radiolabeled somatostatin analogs. The SSTR2 is an attractive target for PRRT because the receptor density is higher on tumors than on non-tumor tissue (Reubi et al 2001, Reubi 2003), and because SSTR2 internalize into cells after ligand binding. After binding to SSTR2, the radiopeptide delivers tumoricidal radiation to the tumor tissue.

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) constitute a heterogeneous group of neoplasms arising from the diffuse neuroendocrine system, known tofrequently over-express somatostatin subtype 2 receptors (SSTR2) (Reubi et al 2000b). GEP-NETs are recognized as an orphan disease by the National Cancer Institute.

GEP-NETs are rarely seen in childhood. The estimated annual incidence of GEP-NETs in the pediatric population is extremely low — less than 1 per 100,000 person-years based on EU data from two published studies (Pastore et al., 2009; Diets et al., 2017), which is similar to estimates from several European cancer databases, including RARECARENet (RARECARENet, 2018), and ITACAN (Airtum Working Group et al., 2016). The age-adjusted annual incidence rate for all GEP-NETs estimated from the Surveillance, Epidemiology, and End Results Program of the US National Cancer Institute (SEER) using 18 cancer registries in the pediatric population was 0.08 per 100,000 population. The rate per 100,000 population was 0 for the group aged 0 to <12 years, and 0.21 for those aged 12 to < 17 years. The incidence increases in GEP-NET patients aged >17 years.

The most commonly reported location of GEP-NETs in children is the midgut, specifically the appendix (SEER database). The appendiceal NET in children is usually diagnosed at stage I,

the presentation with metastases is rare and survival is high. Conversely, published studies suggest that pancreatic NETs in the pediatric population are usually diagnosed at more advanced stages than NETs arising in the appendix, and their prognosis is poor (Johnson 2014).

Pheochromocytoma and paraganglioma (PPGLs) are rare neuroendocrine tumors arising from the chromaffin cells of the adrenal medulla or sympathetic/parasympathetic ganglia. The incidence of PPGLs in pediatric patients is extremely low with only single cases recorded in SEER registry in 2019, corresponding to a rate lower than 0.03 per 100,000 population (SEER database). Similar to GEP-NET, the incidence of PPGL increases in adult patients compared to adolescents.

The pathophysiology of PPGL is not substantially different in adolescents compared to adult patients. The symptomatology of PPGL is related to an excessive release of catecholamines produced by the tumor causing significant cardiovascular and gastrointestinal morbidity and representing the cause of hypertension in 0.5–2% of pediatric cases (Bholah 2017). A combined α- and β-adrenergic blockade is standard treatment for PPGL patients with pheochromocytoma in order to control blood pressure (Neumann 2019). While PPGLs in most patients are localized and can be treated by surgery, metastatic disease is diagnosed in 10% of pheochromocytomas and 15-35% of extra-adrenal paragangliomas (Martins 2014). Only metastases are the proof for a malignant PPGL, and it has been reflected in the updated WHO classification of endocrine tumors, which replaced the term “malignant pheochromocytoma” with “metastatic pheochromocytoma” (Tischler 2017). Patients with metastatic disease in non-chromaffin tissue have poorer prognosis and shorter overall survival than those with nonmetastatic disease (Jimenez 2018, Satapathy 2019). Increased SSTR expression, particularly that of SSTR2, in PPGLs has been demonstrated by uptake on somatostatin receptor scintigraphy providing the rationale for the use of Lutathera in this patient population (Reubi et al 2001, Reubi 2003,Fishbein et al 2021).

The approval of Lutathera was supported by two studies. The first was the Phase III NETTER-1 study, which compared treatment with Lutathera plus best supportive care (30 mg octreotide long-acting) to treatment with high dose (60 mg) octreotide long-acting in patients with inoperable, somatostatin receptor positive, histologically proven midgut carcinoid tumors, progressive under octreotide long-acting therapy (Strosberg 2017). The primary endpoint analysis was conducted after 74 progression-free survival (PFS) events and included 229 randomized patients. The median PFS was 8.5 months for the control arm (60 mg Octreotide LAR) and had not been reached for the Lutathera arm at the time of the primary endpoint analysis. The hazard ratio for the Lutathera arm compared to the high-dose octreotide LAR arm was 0.18 (95% CI: 0.11; 0.29), indicating 82% reduction in the risk of disease progression or death in favor of the Lutathera arm. The improvement in PFS was accompanied by a significant quality of life benefit (Strosberg et al, 2018).

The second study was a single-institution, single-arm, open-label trial based on data from 1,214 patients with somatostatin receptor-positive tumors, including GEP-NETs and PPGLs, who received Lutathera at the Erasmus Medical Centre in the Netherlands (Kwekkeboom 2008, Brabander 2017). The treatment effect observed across patients with GEP-NET in the Erasmus MC study was consistent with what was seen in NETTER-1 study.

Data from the Erasmus MC study and other studies in PPGL patients (reviewed in Satapathy 2019) demonstrated that Lutathera is an efficacious treatment option for patients with advanced PPGLs. Among patients with SSTR-positive tumors included in the Erasmus MC study, 38 patients with paragangliomas were enrolled. The full efficacy analysis included 18 patients with paragangliomas who showed a median PFS of 50.8 months (95% CI 15.4 – n/a).

Lutathera demonstrated a favorable safety profile in adults. The target organs for radiation toxicities are bone marrow and kidneys (Bergsma 2016a, Bergsma 2016b). The kidney related toxicity is largely eliminated by the co-infusion of 2.5% Lysine – Arginine (Lys-Arg) amino acid solutions during administration of Lutathera, which reduces the radiation dose to the kidney by approximately 45% (Rolleman 2003). In the Erasmus MC trial, 8 patients (<1%) developed renal failure 3 to 36 months following Lutathera administration. [redacted] of these patients either had underlying renal impairment or risk factors for renal failure (e.g., diabetes or hypertension) and required dialysis. Bone marrow toxicities include anemia, thrombocytopenia, lymphopenia and neutropenia which are usually mild, transient and monitorable by hematological and biochemical assessments between treatments (8 ± 1 week interval between doses).

Data on Lutathera use in patients with PPGL from the Erasmus MC study and from a number of other recent studies (reviewed in Satapathy 2019) suggest that the safety of Lutathera in adult patients with PPGL is similar to safety established in GEP-NET population. During Lutathera treatment, the frequency of adverse events related to toxicities in radiosensitive organs do not seem to be dependent on the tumor type, and in PPGL patients described so far the drug toxicities were represented by a low number of Grade 3/4 haematotoxicities and no cases of significant nephrotoxicity (Satapathy 2019).

While a wealth of adult data has been collected for Lutathera use, there is very limited published data on the use of Lutathera in the pediatric population, and no prospective pediatric clinical trials of Lutathera in GEP-NET or PPGL have been performed to date. The efficacy and safety of Lutathera and other PRRTs in the pediatric population have been investigated in a small number of studies, mostly in children with neuroblastomas (Gains 2011, Kong 2016, Chen 2018, Gains 2020).

Overall, based on the available safety information from pediatric patients, there have been no new safety signals compared to adults that would highlight concerns of Lutathera use specific for the pediatric population. The safety events following Lutathera treatment in children with neuroblastoma 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 (Gains 2011, Kong 2016, Chen 2018, Gains 2020). Few significant dose-limiting renal toxicities were reported. The types, frequency, and severity of events reported in the pediatric population appeared to be similar to the tolerability and safety profile established for the adult population. Safety data from published studies of other PPRTs in children and young adults with SSTR-positive tumors, including SSTR-positive NETs, also suggested no concerns specific for the pediatric population (Menda 2010, Menda 2018). In addition, based on limited safety follow-up of up to 3 years in a small number of studies, there were no reports of long-term safety risks, such as myelodysplastic syndrome or secondary malignancies in pediatric patients treated with Lutathera to date. For the detailed benefit-risk assessment see Section 4.5.

1.2 Purpose

There are currently no approved therapies for GEP-NETs in the pediatric population. As observed in adults, the diagnosis of NETs in children is often delayed due to the indolent nature of the disease. It has been reported that 10% to 20% of pediatric patients present with metastatic disease at diagnosis (Parham 2001, Sarvida et al 2011). While surgical intervention is favored as first-line treatment for patients with early-stage disease, metastatic GEP-NETs in the pediatric population, as in adults, are often unresectable. Non-surgical treatment modalities for the pediatric population include those used in adults, namely, somatostatin analogues,

chemotherapy, everolimus, and PRRTs. There are reports of confirmed response in pediatric patients to combination therapy of chemotherapy given concomitantly with cyclophosphamide, vincristine, and dacarbazine (Farooqui and Chauhan 2019). There is very limited published data on the use of Lutathera in the pediatric population with GEP-NETs (case reports Yesil et al 2016 and Potter et al 2018). A small number of published studies have reported data on the use of Lutathera in children and adolescents with neuroblastomas (Gains 2011, Kong 2016, Chen 2018, Gains 2020), or with 90Y-DOTATOC in pediatric GEP-NETs (Menda 2010, Menda 2018).

Similarly to GEP-NETs, there are limited non-surgical treatment modalities in pediatric patients with progressive PPGLs. Recently, Azedra (iobenguane I 131) has been approved by FDA for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy. Increased somatostatin receptor (SSTR) expression, particularly that of SSTR2, in PPGLs has been demonstrated by uptake on somatostatin receptor scintigraphy providing the rationale for the use of Lutathera in this patient population (Reubi et al 2001, Reubi 2003). Only few case reports have been published on the use of Lutathera in children with PPGLs (Cassano 2019, Yadav 2019, Roll 2020, Pinato 2016), with single patients treated in each of the reports.

Given the limitations of approved therapeutic options for the GEP-NET and PPGL pediatric population, these diseases in adolescents constitute an area of high unmet need. This clinical study aims to address this unmet need and to accelerate access of Lutathera as a potential treatment for adolescent patients with a primary focus on GEP-NETs. Due to the rarity of pediatric data in PPGL and unmet need in this indication, a separate cohort will be open for enrolment of adolescent patients with somatostatin receptor positive PPGLs.

For GEP-NET, a full extrapolation of the clinical efficacy of Lutathera already established in adults to the adolescent population (12 to <18 years old) approach is made by [redacted] Furthermore, it is based on the assumption that [redacted] This full efficacy extrapolation approach for adolescent patients with GEP-NET is conducted based primarily on the following 4 aspects:

1. Similar disease characteristics, including manifestation, progression and course (Spunt et al 2000, Dall'Igna et al 2005, Farooqui and Chauhan 2019, Bethel et al 1997, Fernandez et al 2015, Johnson 2014) as well as [redacted] and adolescent patients with GEP-NETs to Lutathera treatment.
2. Similar mechanism of action of Lutathera in adult and adolescent patients with GEP-NET, including [redacted]
3. Similarity in [redacted] between adult and adolescent.
4. Results of [redacted] which has established the dose for adolescent population based on [redacted] registration clinical studies).

The extrapolation approach aims to provide evidence for the safe and effective use of Lutathera in adolescents with GEP-NETs and has been verified by the results of a modelling and simulation (M&S) analysis that confirmed that the Lutathera dose for the adolescent population 12 to <18 years old is the same as used in adults (see Section 4.2 below for results of this M&S analysis and dose rationale). The main objective of the current clinical study is to confirm the

defined dose by assessing the safety, tolerability and dosimetry of Lutathera in adolescents with GEP-NETs or PPGLs.

In conclusion, this sponsored clinical study evaluating PRRT with Lutathera in the adolescent population will be essential to bring new potential therapeutic option for adolescent GEP-NET and PPGL patients.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

	Objectives	Endpoints
Primary	• Evaluate organ absorbed radiation doses from PRRT with Lutathera in adolescent patients with SSTR-positive GEP-NETs and PPGLs as a pooled cohort • Evaluate safety and tolerability of Lutathera in adolescents with SSTR-positive GEP-NETs and 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 • The incidence of adverse events (AEs) and laboratory toxicities after the 1st Lutathera administration in adolescents with SSTR-positive GEP-NETs and PPGLs as a pooled cohort
Secondary	• Evaluate cumulative safety of Lutathera 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 • Perform comparative assessment of dosimetry and pharmacokinetics (PK) between adolescent patients with GEP-NETs and PPGLs as a pooled cohort and adult patients using the extrapolation model developed for the clinical study	• The incidence of adverse events (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 • The incidence of adverse events (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 • Calculated organ absorbed doses and PK parameters based on imaging/blood radioactivity concentration data from adolescent with SSTR-positive GEP-NETs and PPGLs as a pooled cohort patients compared to the predicted distribution / organ absorbed doses
[redacted]	[redacted]	[redacted]

3 Study design

This is a multicenter, open-label, single-arm study to evaluate the safety and dosimetry of Lutathera in adolescent patients 12 to <18 years old with somatostatin receptor positive GEP-NETs and PPGLs. The study will enroll at least 8 adolescent patients across GEP-NETs and PPGLs, including a minimum of 3 adolescents with GEP-NETs .

The study schedule for each patient consists of the screening period (up to 2 weeks) followed by the treatment period (4 treatment administrations at 8-week interval), and the follow-up period (5 years).

During the screening period of up to 2 weeks, patient eligibility will be determined according to the protocol's pre-defined inclusion and exclusion criteria. All screening assessments should be performed according to Table 8-2.

Patients who meet all eligibility criteria at screening can be enrolled in the study. The enrollment and Lutathera order must be performed immediately after all eligibility criteria are verified and the patient is confirmed to be eligible.

There will be no study visits after screening and before the 1st Lutathera administration. Somatostatin receptor imaging (SRI) performed before the screening (within 3 months prior to enrollment) can be used for the assessment of patient eligibility. Laboratory tests completed before the screening can be used for the assessment of patient eligibility if performed within 2 weeks prior to enrollment.

The treatment period will consist of 4 Lutathera treatments administered at 8-week intervals. Lutathera administration will occur on Week 1 Day 1 of each cycle. Each patient will receive a total of 4 doses of Lutathera (7.4 GBq/200 mCi x 4 administrations every 8 weeks; cumulative dose: 29.6 GBq/800 mCi).

An infusion of sterile 2.5% Lysine - Arginine amino acid (AA) solution will be co-administered with each Lutathera dose for renal protection according to the approved Lutathera local prescribing information. An antiemetic will be administered for prevention of infusion-related nausea and vomiting (Section 6.1.2).

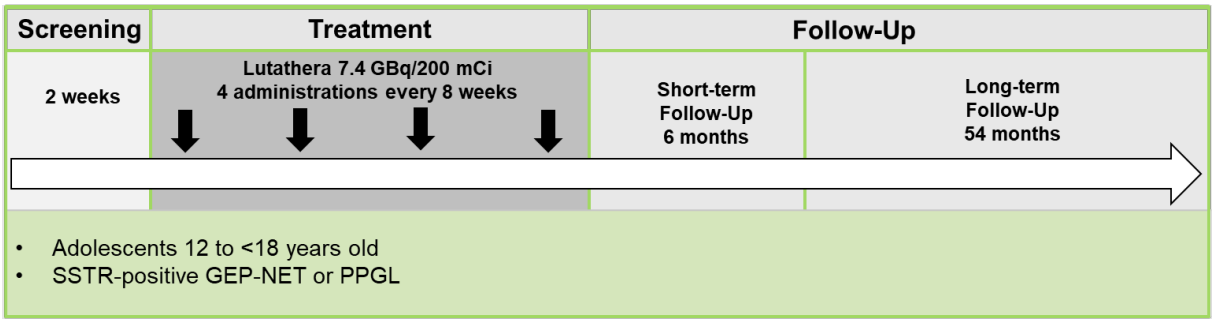
The dosimetry and PK assessments will be performed during the first week after the 1st Lutathera dose as per Table 8-2 and Table 8-3, i.e. one time during the study treatment period for each patient. The dosimetry analysis will allow for estimation from the 1st Lutathera administration the cumulative absorbed radiation dose from 4 Lutathera doses and taking a decision on the next dose levels (see Section 6.5.1.2). In the exceptional circumstances when dosimetry cannot be performed in a particular patient after the first Lutathera dose, it should be completed as soon as feasible upon a later dose.

Safety assessments in the study will include physical examinations, vital signs, ECGs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), safety biomarkers and adverse event monitoring (see Section 8). To monitor for potential Lutathera toxicities, safety assessments will be performed in each treatment cycle, with clinical laboratory samples taken regularly after each Lutathera dose (see Table 8-2). A set of safety biomarkers of growth and development, reproductive and endocrine function will be collected and analyzed for each patient (see Section 8.4.7).

[redacted]

Patients might need to stay overnight at the hospital or another facility for the days with intensive assessment schedule (e.g. for Lutathera administration, blood sampling and imaging). The decision on the overnight stay is up to Investigator, as appropriate according to local regulations, medical judgment, and the patient's preference.

Figure 3-1. Study design



In order to minimize risk for each study subject, an accelerated analysis of dosimetry and safety data will be performed for each patient in the study, to enable the Investigator to take a decision for the subsequent Lutathera doses. The results of dosimetry assessments (imaging and blood dosimetry) will be provided to the investigators for their evaluation prior to administration of subsequent therapeutic cycles in each patient. See Section 6.5.1 for further information on the criteria for evaluating the need for dose modification based on safety and dosimetry data.

A total follow-up period of 5 years (60 months) after the last Lutathera dose will take place for each patient who received at least one dose of Lutathera. This follow-up period will be comprised of a short-term follow-up of 6 months to evaluate cumulative Lutathera toxicities, followed by a long-term follow up of another 54 months.

An external Data and Safety Monitoring Board (DSMB) will also operate in the study to evaluate accumulating safety and dosimetry data, to ensure the safety of adolescents enrolled in the study, and to provide recommendations to investigators as well as to the clinical team in charge of conducting the study (see Section 10.2.1).

Interim analyses was added to evaluate dosimetry and safety when at least five patients (including at least two GEP-NET patients) have completed at least one cycle of treatment. This analysis is introduced due to the slower than expected recruitment rate, and proportionally higher than expected recruitment of PPGL patients. The interim analysis would permit an evaluation across the indication in order to confirm modelling assumptions of similar dosimetry between adolescents and adults. The data from all completed treatment cycles will be presented. Analysis will be presented across both indications, as well as for GEP-NET and PPGL separately.

The primary analysis to address the primary objective will be performed after at least 8 patients (including at least 3 GEP-NET patients) have completed the first cycle (up to cycle 2 pre-dose assessments) at which time both dosimetry and safety assessments of the first cycle will have been completed for all patients. In case the last subject has dosimetry assessments after the 2nd or a later dose, the data cut-off will be performed after that dose (and before the subsequent cycle pre-dose assessments). The primary analysis in the study will be of descriptive nature and no statistical hypothesis will be tested. All data available at that time from pooled cohorts will be used for the assessment of the primary and secondary objectives. [redacted]

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

4 Rationale

4.1 Rationale for study design

Lutathera is approved in the United States for the treatment of somatostatin receptor-positive GEP-NETs, including foregut, midgut, and hindgut neuroendocrine tumors in adults. It is also approved in other regions, including EU, for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive GEP NETs in adults. There are currently no approved therapies for GEP-NETs in the pediatric population.

As described in Section 1.2, and in line with the US and EU recommendations on extrapolation in the development of medicines for paediatrics (FDA *General Clinical Pharmacology Considerations for Pediatric Studies for Drug and Biological Products*, December 2014; EMA *Reflection paper on the use of extrapolation in the development of medicines for paediatrics*, October 2018), the development of Lutathera for adolescent patients with GEP-NETs follows a full efficacy extrapolation approach.

Increased SSTR expression, particularly that of SSTR2, in PPGLs has been demonstrated by uptake on somatostatin receptor scintigraphy providing the rationale for the use of PRRT with radiolabeled somatostatin analogues in this patient population (Reubi et al 2001, Reubi 2003). Although Lutathera has not been approved in adults with PPGL, there is evidence of significant clinical benefit demonstrated by Lu177 dotatate use in this indication (Satapathy 2019). Only few case reports have been published on the use of Lutathera in children with PPGLs (Cassano 2019, Yadav 2019, Roll 2020, Pinato 2016), with single patients treated in each of the reports. Due to the scarcity of pediatric data in PPGL and unmet need in this indication, a cohort will be open for enrolment of adolescent patients with somatostatin receptor positive PPGLs.

A modelling and simulation study analysis [redacted] has been conducted to define the dose in adolescent patients based on observed Lutathera dosimetry values in adults, and literature based physiological values [redacted] from

adolescents. The dose assessment was based primarily on the target organs for radiation toxicities (kidney and bone marrow) ensuring that the selected dose gave kidney dosimetry values below 29 Gy and bone marrow dosimetry values below 2 Gy (see Section 4.2). Analysis has indicated that the full adult regimen, i.e. 4 doses of Lutathera administered every 8 weeks (7.4 GBq/200 mCi x 4 administrations every 8 weeks; cumulative dose: 29.6 GBq/800 mCi) is appropriate in the adolescent population to keep the median kidney dosimetry within the values outlined above. Importantly, clinical data from the pivotal adult efficacy trials have shown that this full adult cumulative radioactive dose from 4 administrations correlated with efficacy in adult population.

In this adolescent study, dosimetry assessments will be performed in each patient after the first Lutathera dose (or in exceptional circumstances after a later dose in case dosimetry cannot be performed in a particular patient after the first Lutathera dose) to confirm dosimetry values with regard to reference limits (Section 6.5.1.2) and ensure continuation of safe dosing. In case that the resulting cumulative radiation dose exceeds the reference limits, the DSMB will evaluate benefit risk for the patient and give recommendation on whether dosing can continue and at which level (see Section 6.5.1). Although the ultimate decision on dose modification remains with the investigator, it is strongly recommended that the investigator follows DSMB recommendations.

The co-primary objectives and endpoints have been selected to meet the main goal of the clinical study to validate the dose extrapolation approach for adolescent patients with GEP-NETs or PPGLs. The clinical study will confirm the safety, tolerability and dosimetry findings of the adolescent dose modelled based on the original adult data. Of note, dosimetry is considered as a primary endpoint instead of PK parameters based on the Lutathera mechanism of action.

The secondary objectives and endpoints were selected to evaluate all safety data from cumulative dosing, as well as long-term safety in adolescents (see the rationale for duration of follow-up in Section 4.3). In addition to safety analysis, a comparative assessment of dosimetry in adolescent patients and adults (from the NETTER-1 study) is selected as a secondary objective in order to evaluate the predicted organ absorbed dose and the accuracy of the model.

The evaluation of primary and secondary objectives will be performed in GEP-NET and PPGL pooled cohort, [redacted]

This study is designed in a non-randomized open-label fashion, which is considered appropriate when specifically studying a very small sample size of patients with a rare indication. Due to the rarity of disease, the study will be conducted at multiple centers across several countries.

In summary, in line with the full efficacy extrapolation approach, this multicenter open-label clinical study will confirm the proposed Lutathera dosing strategy in adolescent patients 12 to <18 years old with SSTR-positive GEP-NETs or PPGLs by assessing the safety, tolerability and dosimetry of the dose/exposure matched Lutathera dose. [redacted]

4.2 Rationale for dose/regimen and duration of treatment

The modelling and simulation analysis to define the dose in the adolescent population was based on the clinical data from two adult clinical trials, [redacted] and approximately 50 subjects were available for analysis. As the principal Lutathera risks are related to renal and bone marrow toxicities, the key objective in this analysis was to investigate the factors influencing the absorbed dose to the kidneys and bone marrow in adults and extrapolate this to the adolescent population (12 to <18 years old) accounting for adolescent specific factors determined from the adult dosimetry model.

The amount of ^{177}Lu radioactivity administered to an adult patient has to achieve an optimal therapeutic effect of PRRT in the tumors with limited side effects to radiosensitive organs, namely the kidneys and bone marrow. The true threshold of the kidney-absorbed dose that predisposes patients to toxicity has not been accurately determined. Based on data from external beam radiation, commonly accepted values vary from 18 to 23 Gy (Marks et al 2010, Wessels et al 2008, Emami et al 1991, Emami 2013). However, there is growing evidence that PRRT with lutetium (^{177}Lu) oxodotreotide is less nephrotoxic (Konijnenberg et al 2007, Bodei et al 2008, Sundlöv et al 2017, Bergsma et al 2016b, and Löser et al 2018). As an example, results by Sundlöv et al 2017 support the dose limit proposed for high risk patients (concomitant risk factors) of 27 ± 2 Gy, while suggesting that patients without risk factors may support a higher kidney dosimetry value. In a study of 323 patients described by Bergsma et al 2016b, where a median number of four 7.4 GBq cycles of lutetium (^{177}Lu) oxodotreotide have been administered, no subacute grade 3 or 4 nephrotoxicity was observed. The mean kidney absorbed radiation dose in this study was 20.1 ± 4.9 Gy. No correlation was observed between radiation-absorbed dose to the kidneys and worsening creatinine clearance on long-term follow-up. A similar outcome was obtained also in the NETTER-1 Phase III study, in which the kidney absorbed radiation dose was 19.4 ± 8.7 Gy, with no clinically relevant kidney toxicity observed and no evidence of correlation between creatinine clearance level and kidney absorbed dose.

For bone marrow, the commonly accepted threshold is 2 Gy (based on historical cohorts of patients treated with 131I (Bergsma et al 2016b), and here too the clinical relevance for PRRT with lutetium (^{177}Lu) oxodotreotide has not been established. Bergsma et al 2016a described the hematological toxicity findings in 320 patients treated with 4 cycles of lutetium (^{177}Lu) oxodotreotide (7.4 Gy each). The bone marrow dosimetry was evaluated in a subset of patients (obtaining a mean bone marrow absorbed dose of 2.0 ± 0.2 Gy) and no correlation was found between cumulative bone marrow-absorbed dose and therapy-related persistent hematologic disorder. Similarly, in the NETTER-1 study, in which the estimated mean bone marrow absorbed dose was 1.0 ± 0.8 Gy, no correlation was found between these two parameters. Moreover, a wide heterogeneity between authors in the methodology of bone marrow dosimetry (planar imaging, SPECT imaging, blood samples) makes it difficult to compare between studies.

In view of the above, it is considered that the total doses of ≤ 29 Gy and ≤ 2 Gy of lutetium (^{177}Lu) oxodotreotide, constitute appropriate thresholds for the kidney and bone marrow-absorbed dose by subject, respectively.

The modelling and simulation analyses were therefore conducted to estimate the projected dose in the adolescent population ensuring that median dosimetry estimates are ≤ 29 Gy for the kidney or ≤ 2 Gy for the bone for four treatment cycles. Results indicate that the covariates important in explaining kidney dosimetry across the adult population [redacted] These findings were also supported by the prior analysis of Svensson et al 2015 who indicated that patients with inferior

renal function were exposed to higher renal dosimetry values, and also developed hematological toxicity.

Reference values taken from the literature for creatinine clearance levels in an adolescent population suggested limits from approximately 70 – 108 ml/min (Piepsz 2008), which are in line with adult values when adjusted by body surface area (Pottel 2017) indicating similar renal function in these two groups.

Simulations (estimation and re-estimation, n=500) from the model [redacted] developed in adults with adjustment for adolescent renal function indicated that after a full adult dose of Lutathera (7.4 GBq over 4 cycles, a total of 29.6 GBq) median kidney dosimetry and bone marrow dosimetry would be similar to those of adults with [redacted] values of [redacted] for kidney and [redacted] for bone marrow, i.e. [redacted] Therefore, the full adult regimen, i.e. 4 doses of Lutathera administered every 8 weeks (7.4 GBq/200 mCi x 4 administrations every 8 weeks; cumulative dose: 29.6 GBq / 800 mCi) is appropriate to be used in this study in adolescent population 12 - <18 years of age.

Data on Lutathera use in patients with PPGL from the Erasmus MC study and from a number of other recent studies (reviewed in Satapathy 2019) suggest that the safety of Lutathera administered as a full regimen (i.e. 4 cycles of 7.4 GBq each) in patients with PPGL is similar to safety established in GEP-NET population. During Lutathera treatment, the frequency of adverse events related to toxicities in radiosensitive organs do not seem to be dependent on the tumor type, and in PPGL patients described so far the drug toxicities were represented by a low number of Grade 3/4 haematotoxicities and no cases of significant nephrotoxicity (Satapathy 2019).

Both Erasmus MC study and other studies in PPGL patients (reviewed in Satapathy 2019) demonstrated that Lutathera is an efficacious treatment option for patients with advanced PPGLs. As the pathophysiology of PPGL is not substantially different in adolescents compared to adult patients, there is no evidence that adolescent patients with PPGL would exhibit different safety or efficacy profile after Lutathera treatment to what has been shown in adults with PPGL

As such, extrapolation is considered to be appropriate in PPGL indication similar to GEP-NET indication and a full flat dose of Lutathera will be administered to adolescent patients with PPGL in this study. All enrolled patients will be closely monitored for safety in real-time during the whole treatment period and will be followed up for any long-term effects after the last dose (Section 4.3). Stopping rules and DMT rules will apply for both GEP-NET and PPGL cohorts, and DSMB will ensure safety of all adolescents enrolled in the study and evaluate accumulating safety and dosimetry data for both indications.

4.3 Rationale for duration of follow-up

This study includes a total follow-up of 5 years (60 months) after the last Lutathera administration, including a 6-month short-term and a 54-month long-term follow-up periods.

Based on Lutathera's mechanism of action and pharmacological characteristics, the principal risks arising from treatment with Lutathera are potential radiation toxicities affecting bone marrow and kidney function (Bergsma et al 2016a, Bergsma et al 2016b, Lutathera USPI).

Kidney related toxicity is largely eliminated by the co-infusion of 2.5% Lysine – Arginine amino acid solutions during administration of Lutathera, which reduces the radiation dose to the kidney by approximately 45% (Rolleman et al 2003, Lutathera USPI). In the NETTER-1 study, no difference in renal long-term toxic effects between two arms was observed within the

period of observation (Strosberg et al 2017). In the Erasmus MC trial, 8 patients (<1%) developed renal failure 3 to 36 months following Lutathera administration. [redacted] of these patients had underlying renal impairment or risk factors for renal failure (e.g., diabetes or hypertension) and required dialysis. In the post-marketing safety surveillance of Lutathera, 43 cases had been reported in 5,968 patients with any preferred term covered by Standardised MedDRA Query of "Renal dysfunction" until 19 December 2019. Time to onset was reported for 41% of cases and ranged from 1 to 180 days after first Lutathera treatment cycle (median 20 days). Seventeen percent of cases were reported as resolved at the time of the last update.

In this study, in addition to the administration of an amino acid solution for kidney protection, renal function will be monitored during and after the treatment with Lutathera, with the assessment of serum creatinine, creatinine clearance, uric acid, BUN, and urine protein after each dose.

The observed effects of short-term bone marrow toxicity after Lutathera treatment are anemia, thrombocytopenia, leukopenia, lymphopenia and neutropenia, which are usually mild and transient (Strosberg at al 2017, Lutathera USPI). In the Lutathera arm of the NETTER-1 study, grade 3 or 4 anemia, thrombocytopenia, leukopenia, lymphopenia and neutropenia occurred in 0%, 1%, 2%, 44% and 3% of patients, respectively (Lutathera USPI). Lymphopenia in the Lutathera arm was not associated with an increased rate of infections compared to the control arm. Overall, it is important to note that the observed lymphopenia following PRRT is not a major concern regarding risk of infections, since only B lymphocytes are transiently affected, a subtype which is not directly involved in infection defense (Sierra et al 2009). The median time to onset of hematological toxicities was during the 2nd - 3rd cycle of Lutathera, while the median time of resolution was within 6 months after the last Lutathera cycle. When hematological toxicity occurred, a trend towards stabilization followed by improvement in patients with longer follow-up was observed.

Based on the median time to onset and the resolution time of hematological toxicities observed in adults in the NETTER-1 study, the short-term follow-up period in this study is 6 months after the last dose of Lutathera. This will allow for evaluation of cumulative toxicities after 4 cycles of Lutathera and for the detailed observation of resolution of hematological toxicity cases.

As for any radiotherapy, one of the long-term safety risks of Lutathera treatment is secondary malignancies. In the NETTER-1 study, with a median follow-up time of 24 months, myelodysplastic syndrome (MDS) was reported in 3 patients (2.3%) receiving Lutathera with long-acting octreotide compared to no patients receiving high-dose long-acting octreotide. In the Erasmus MC study, 16 patients (2%) developed MDS and 4 (0.5%) developed acute leukemia. The median time to the development of MDS was 28 months (9 to 41 months) for MDS and 55 months (32 to 125 months) for acute leukemia (EU SmPC).

Therefore, to enable a follow-up on long-term safety risks in adolescent patients treated with Lutathera, a follow-up period of 5 years is included in the study. During the long-term follow-up, patient visits will occur every 6 months to collect information on adverse events, secondary malignancies, further anticancer treatments, as well as to draw laboratory samples for chemistry, hematology and safety biomarkers of growth and development, reproductive and endocrine function as well as bone formation.

4.4 Rationale for study population

Per Section 1.1 above, the epidemiology search has shown that the incidence of patients with GEP-NETs per 100,000 population is 0 for the group aged 0 to <12 years, and 0.21 for those aged 12 to < 17 years. The incidence of PPGLs in pediatric patients is even smaller with only single cases recorded in SEER registry in 2019, corresponding to a rate lower than 0.03 per 100,000 population (SEER registry). In view of these epidemiology data, the study population will include adolescent patients 12 to <18 years of age.

Patients will be included in the GEP-NET cohort if there is a presence of metastasized or locally advanced, inoperable (curative intent) histologically proven, well differentiated GEP-NET. This population was chosen in line with the indication approved for the adult population.

For PPGL cohort, patients with metastasized or locally advanced, inoperable (curative intent), histologically proven PPGL will be enrolled. This population was selected based on unmet need and mimics adult population with PPGL that has been treated with Lutathera so far.

As Lutathera binds to SSTR2 to deliver tumoricidal radiation to the tumor tissue, the SSTR expression will be confirmed before the 1st Lutathera dose by an SRI modality.

As this is the first prospective clinical study of Lutathera in the pediatric GEP-NET and PPGL populations, a set of safety eligibility criteria will be implemented in the trial to exclude patients with significant hematological, renal and liver impairment, defined as:

- Estimated creatinine clearance calculated by the Cockroft-Gault method < 70 mL/min
- Hb concentration <5.0 mmol/L (<8.0 g/dL); WBC <2x10^9/L; platelets <75x10^9/L
- Total bilirubin >3 x ULN for age
- Serum albumin <3.0 g/dL unless prothrombin time is within the normal range

These exclusion criteria were chosen in line with the criteria used in the adult NETTER-1 study, except for the estimated creatinine clearance. In the NETTER-1 study, subjects were excluded if creatinine clearance was below 50 mL/min calculated by the Cockroft-Gault method. As a precaution and as this is the first study in the pediatric population, a higher creatinine threshold was chosen in order to reduce the risk to reach a cumulative renal absorbed dose above 29 Gy (assumed limit for kidney toxicity).

4.5 Risks and benefits

In this pediatric study conducted in a vulnerable participant population (adolescents 12 - <18 years of age) it will be ensured that the rights, safety and well-being of study subjects are protected.

In order to minimize pain, distress, and fear in participants, this study will use facilities appropriate to pediatric care, and the personnel will be trained to look after children and supervised by experienced health care professionals. Staff will be trained to communicate with both parents (or legal representative) and adolescent patients. Study patients will be hosted in a familiar environment and their concerns will be addressed by skilled personnel.

Appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific dose modification and stopping rules, are included in this protocol. The risk to participants in this trial is minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, per the schedule in Table 8-2.

Although this is an adolescent study, all female patients of child-bearing potential and sexually active males must be informed that the administration of Lutathera may involve unknown risks

to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria (Section 5.2) and Appendix 1. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

As described in Section 4.1, the highest risks arising from treatment with Lutathera are radiation toxicities affecting bone marrow or kidney function.

- The potential kidney related toxicities are largely eliminated by the co-infusion of 2.5% Lysine – Arginine amino acid solutions during administration of Lutathera, which reduces the radiation dose to the kidney by approximately 45% (Rolleman et al 2003, Lutathera USPI). In this study, in addition to AA administration for kidney protection, renal function will be monitored during and after the treatment with Lutathera, with the assessment of serum creatinine, creatinine clearance, uric acid, BUN, and urine protein after each Lutathera dose.
- The potential observed effects of short-term bone marrow toxicity after Lutathera treatment are decreased blood cell counts (anemia, thrombocytopenia, leukopenia, lymphopenia and neutropenia), which are usually mild and transient. A careful monitoring of hematological parameters will be conducted in this study after each Lutathera dose allowing for a prompt identification of possible acute effects. The large interval between the Lutathera treatments (8 weeks) allows for a possible recovery or for a modification of the dose, according to the protocol-defined scheme.

In order to minimize risk for each study subject, an accelerated analysis of dosimetry and safety data will be performed for each individual patient in the study, to enable the Investigator to take a decision for the next Lutathera dose. The results of dosimetry assessments (imaging and blood dosimetry) conducted in the 1st Lutathera cycle will be provided to and evaluated by investigators prior to administration of the next therapeutic cycle (Section 6.5.1.2).

With regard to long term safety effects, secondary myelodysplastic syndrome and leukemia are potential serious adverse effects of Lutathera, similar to any radioligand therapy. All secondary malignancies are considered adverse events of special interest (AESI) in this study and will be reported during and after the treatment with Lutathera and during the long-term follow-up period (Section 10.1.5).

Common adverse effects of Lutathera include vomiting and nausea which are usually mild and transient. In the vast majority of cases these side effects can be prevented by the use of antiemetics. The use of antiemetics is mandatory in this study, with the preventive administration given before each amino acid infusion and Lutathera treatment (Section 6.1.2).

For the patients enrolled in the PPGL cohort, a monitoring for development of hormonal crisis symptoms due to potential tumor lysis and excessive catecholamine release (such as hypertension, pallor, sweating, palpitations) (see Section 1.1) will be performed after each Lutathera dose. A combined α- and β-adrenergic blockade is a standard treatment for PPGL patents with pheochromocytoma in order to control blood pressure (Neumann 2019), and any additional medications will be administered in this study by investigator if necessary per the medical judgment and local standards. In a study of 20 adult PPGL patients treated with 177Lu-dotatate PRRT, hypertension flare was observed in only one patient, who had inadequate alpha- and beta-blockade before treatment resulting from patient nonadherence to prescribed therapy (Kong 2017). An appropriate adrenergic blockade, safety monitoring and patient control will be carried out in all adolescents with PPGL enrolled in the NETTER-P study.

Considering the age of participants, additional potential safety concerns in the pediatric population will be controlled via assessment of safety biomarkers. This includes potential effects of treatment with Lutathera on endocrine (hypothalamic-pituitary) function, gonadal function, growth and bone development that will be controlled during and after the treatment with Lutathera (Section 8.4.9).

All safety effects of Lutathera will be carefully assessed in this study, and patients will be closely monitored.

As this is the first study of Lutathera in adolescents with GEP-NETs and PPGLs, its efficacy and safety has not been established in this population yet. However, based on adult efficacy and similarities between adolescents and adults, it is expected that Lutathera administered in the study may bring therapeutic benefit to adolescents with GEP-NETs and PPGLs. This study will be essential to bring new potential therapeutic options for adolescent GEP-NET and PPGL patients.

4.5.1 Blood sample volume

Blood samples for clinical safety monitoring, safety biomarkers and radioactive dosimetry will be collected in this study from each patient, consistent with study objectives. The schedule of sampling has been designed to minimize the blood sample volume for adolescent participants, balancing it with required safety monitoring as described in Section 4.5.

The total blood volume taken from each patient will be in line with WHO Key recommendations regarding blood sampling in children involved in clinical research (Howie 2011), and will comply with local regulations/restrictions.

Timings of blood sample collection are outlined in the assessment schedule (Table 8-2). Additional unscheduled samples may be required for safety monitoring in case of adverse events.

Exact blood volumes will be provided in the informed consent form (ICF) for each participant. Instructions for sample collection, processing, storage and shipment information are also available in the laboratory manual.

5 Study Population

This study will enroll at least 8 adolescent patients 12 to < 18 years old with somatostatin receptor-positive GEP NETs or PPGLs, including a minimum of 3 GEP-NET patients.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. GEP-NET cohort: Presence of metastasized or locally advanced, inoperable (curative intent), histologically proven, G1 or G2 (Ki-67 index ≤20%), well differentiated GEP-NET.

   PPGL cohort: presence of metastasized or locally advanced, inoperable (curative intent), histologically proven PPGL.
2. Patients from 12 to < 18 years of age at the time of enrollment.
3. Expression of somatostatin receptors confirmed by a somatostatin receptor imaging (SRI) modality within 3 months prior to enrollment, with tumor uptake observed in the target lesions more or equal to the normal liver uptake.

4. Performance status as determined by Karnofsky score ≥ 50 or Lansky Play-Performance Scale score ≥ 50.
5. 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.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Laboratory parameters:
   - Estimated creatinine clearance calculated by the Cockroft-Gault method < 70 mL/min
   - Hb concentration <5.0 mmol/L (<8.0 g/dL); WBC <$2x10^9$/L; platelets <$75x10^9$/L.
   - Total bilirubin >3 x ULN for age.
   - Serum albumin <3.0 g/dL unless prothrombin time is within the normal range.
2. Established or suspected pregnancy.
3. Breastfeeding female patients unless they accept to discontinue breastfeeding from the 1st dose until 3 months after the last administration of study drug.
4. Female patients of child-bearing potential (female pediatric patients who are menarchal or who become menarchal during the study), unless they are using highly effective methods of contraception during treatment and for 7 months after the last dose of Lutathera (see details in the Appendix 1). If local regulations deviate from the listed contraception methods to prevent pregnancy, local regulations apply and will be described in the ICF.
5. Sexually active male patients, unless they agree to remain abstinent (refrain from heterosexual intercourse) or be willing to use condoms and highly effective methods of contraception with female partners of childbearing potential, and to use condoms with pregnant female partners during the treatment period and for at least 4 months after the last dose of Lutathera (see details in Appendix 1). In addition, male patients must refrain from donating sperm during this same period.
6. Patients for whom in the opinion of the investigator other therapeutic options are considered more appropriate than the therapy offered in the study, based on patient and disease characteristics.
7. Current spontaneous urinary incontinence.
8. 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.
9. Hypersensitivity to the study drug active substance or to any of the excipients.
10. Patients with any other significant medical, psychiatric, or surgical condition, currently uncontrolled by treatment, which may interfere with the completion of the study.
11. Patient with known incompatibility to CT Scans with I.V. contrast due to allergic reaction or renal insufficiency. If such a patient can be imaged with MRI, then the patient would not be excluded.
12. Patients who received any investigational agent within the last 30 days.
13. Prior therapies and procedures:

- External beam radiation therapy to more than 25% of the bone marrow.
- PRRT for GEP-NET or PPGL within 12 months prior to the first Lutathera administration in the study.
- Long acting somatostatin analogs within 28 days or short acting octreotide within 24 hrs prior to Lutathera administration.
- Prior solid organ transplantation.
- Any previous radioembolization, chemoembolization and radiofrequency ablation for GEP-NET and any surgery within 12 weeks prior to randomization in the study.
- Corticosteroids: Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible. If used to modify immune adverse events related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.
- Cytotoxic chemotherapy or other anti-cancer agents known to be myelosuppressive within 21 days prior to Lutathera administration (42 days for nitrosourea).
- Anti-cancer systemic agents not known to be myelosuppressive within 7 days prior to Lutathera administration.
- Antibodies, Interleukins, Interferons and Cytokines within 21 days prior to Lutathera administration or any toxicity related to prior antibody therapy not recovered to Grade ≤ 1.
- Hematopoietic growth factors within 14 days prior to Lutathera administration for a long-acting growth factor or within 7 days prior to Lutathera administration for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.
- Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including donor lymphocyte infusion or boost infusion within 84 days prior to Lutathera administration.
- Autologous stem cell infusion or cellular therapy within 42 days prior to Lutathera administration.

6 Treatment

6.1 Study treatment

As this is a single-arm, open-label, non-randomized study, no control drug will be used in the study.

Details on the requirements for storage and management of study treatment, and instructions to be followed for participant numbering, prescribing/dispensing, and administration of study treatment are outlined in the accompanying Pharmacy Manual.

6.1.1 Investigational drug

The investigational drug Lutathera® (lutetium Lu 177 dotatate/ lutetium (^{177}Lu) oxodotreotide) will be provided by the Sponsor (Table 6-1). Patients will receive a total of 4 administrations of Lutathera 7.4 GBq / 200 mCi every 8 ±1 weeks.

Table 6-1 Investigational drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply type	Supplier
Lutathera®	Radiopharmaceutical solution for infusion (7.4 GBq of Lutathera per 30 ml vial)	Intravenous use	Open label; vials	Sponsor

6.1.2 Additional study treatments

Patients will receive a sterile 2.5% Lys-Arg amino acid solution for infusion for renal protection for each Lutathera administration; and an anti-emetic before each amino acid infusion and Lutathera administration, for prevention of infusion-related nausea and vomiting (Table 6-2).

Table 6-2 Additional Study Treatment

Treatment Title	Sterile 2.5% Lys-Arg solution	Anti-emetics (ATC A04A and A03FA01)
Type	drug	drug
Dose Formulation	Solution for infusion	various
Unit Dose Strength(s)	25 g of L-arginine hydrochloride and 25 g of L-lysine hydrochloride	various
Dosage Level(s)	One bag concomitantly with Lutathera administration	various
Route of Administration	IV infusion	various
Use	Reduction of renal radiation exposure	Reduction of nausea/vomiting induced by 2.5% Lys-Arg
Authorization status of the AxMP in EEA	Yes	Yes
Sourcing	Provided locally by the study site or by the Sponsor where compounded amino acid is not made available	Provided locally by the study site
Packaging and Labeling	Will be provided in a 1-L bag. Each bag will be labeled as required per country requirement.	As locally available

The sterile 2.5% Lys-Arg solution must be administered intravenously with the infusion rate of 250 ml/h. The infusion should start 30 minutes prior to the start of the Lutathera infusion and continue for a total of 4 hours (extension up to 6 h is allowed in case of adverse reactions that require infusion interruption or slowing the infusion rate). Hyperkaleamia must be corrected prior to sterile 2.5% Lys-Arg infusion if >6.0 mmol/L.

The composition of the sterile 2.5% Lys-Arg solution is shown in Table 6-3 below.

Table 6-3 Sterile 2.5% Lys-Arg solution composition

Component	Quantity/1000 ml
L-lysine HCL	25g*
L-arginine HCl	25g**
Sodium chloride 9 mg/mL (0.9%) solution for injection, or water for injection	1 L
*equivalent to 20.0 g lysine **equivalent to 20.7 g arginine	

On the day of each Lutathera treatment, before the infusion with sterile 2.5% Lys-Arg solution is started, an intravenous bolus of anti-emetic must be given with sufficient lead time as per local prescribing information. The choice of antiemetics is at the discretion of investigator in accordance with institutional regulations (suggested options: Granisetron (3 mg), or Ondansetron (8 mg), or Tropisetron (5 mg)). Steroids must be avoided as preventive anti-emetic treatment because of potential somatostatin receptor down-regulation.

In case of development of nausea and vomiting during the infusion, a repeated administration of antiemetics should be performed at the physician judgment. In general, investigators are advised to use antiemetics which are commonly prescribed in their institutions for treatment of nausea induced by chemotherapeutic drugs. Among such antiemetics, the use of Aprepitant (Emend®) should be considered. Haloperidol (Haldol®) could also be considered as an adjunct treatment (either i.v. or oral) in case the advised antiemetic regimens are not successful and patients continue to vomit, as well as Lorazepam (Ativan®). All administered antiemetics must be documented in the appropriate eCRF page.

In case where the treatments previously provided for nausea and vomiting are insufficient, a single dose of corticosteroids can be used, as long as it is not given before initiating or within one hour after the end of Lutathera infusion.

For further details on the amino acid solution and Lutathera administration, see Section 6.7 and Pharmacy Manual.

6.1.3 Supply of study treatment

Lutathera® (lutetium Lu 177 dotatate/ lutetium (^{177}Lu) oxodotreotide) will be supplied by the Sponsor.

As Lutathera production and shipment takes approximately 12 days, Lutathera first dose must be ordered immediately after confirming patient eligibility and enrollment.

The sterile 2.5% Lys-Arg solution will be provided by the Sponsor or compounded by the appointed Pharmacy (hospital or local pharmacy).

Antiemetics, SRI imaging agents, somatostatin analogues or any other supportive care medication are not considered investigational drugs and will not be supplied by the Sponsor.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies administered after the patient was enrolled into the study must be recorded on the appropriate Case Report Forms, including somatostatin analogues, amino acid solution and antiemetic administration.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication list. If in doubt, the investigator should contact the Sponsor before enrolling a patient or allowing a new medication to be started. If the patient is already enrolled, contact the Sponsor to determine if the patient should continue participation in the study.

6.2.2 Prohibited medication

Patients may not receive any other systemic therapy for the treatment of GEP-NET or PPGL (chemotherapeutic, biologic, or any investigational agent) other than Lutathera and somatostatin analogues during the study treatment period.

Localized therapy such as surgery or external beam irradiation may be performed on additional site(s), provided that it does not affect study endpoint assessment. For a major surgery, treatment with Lutathera must be temporarily discontinued and can be restarted after 12 weeks from the date of surgery.

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

There is some evidence that corticosteroids can induce down-regulation of SST2 receptors. Therefore, as a matter of caution, repeated administration of high doses of glucocorticosteroids should be avoided during Lutathera treatment. The use of glucocorticosteroids should also be avoided as preventive anti-emetic treatment. In the case where the treatments previously provided for nausea and vomiting are insufficient, a single dose of corticosteroids can be used, as long as it is not given before initiating or within one hour after the end of Lutathera infusion.

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

There is no restriction for concomitant medications during the follow-up period.

6.2.3 Rescue medication

In GEP-NET cohort, subcutaneous, short-acting octreotide injections may be indicated for control of GEP-NET symptoms (i.e. diarrhoea and flushing) at the judgment of investigator in accordance with the manufacturer's prescribing information. Short-acting octreotide for symptom control may be administered (at home) at investigator's discretion and recommendation provided in Section 6.2.2 should be considered. Short-acting octreotide will not be supplied by the Sponsor.

In the PPGL cohort, an adequate alpha- and beta-blockade should be maintained to avoid acute symptoms of catecholamine release (i.e. hypertension, pallor, sweating, palpitations). The treatment of such symptoms should be done as per standard local practice and physician judgment according to prescribing information (Section 4.5).

6.2.4 SARS-CoV-2 vaccination

Patients are allowed to receive approved SARS-CoV-2 vaccines (inactivated, viral-vector-, or mRNA based Sars-CoV-2 vaccines approved by the Health Authorities in the country). The decision for vaccination should be done on a case-by-case basis and at the discretion of the treating physician, with patient consent, and in alignment with institutional guidelines, if available.

Investigators are expected to evaluate potential risks/benefits in the context of individual patient characteristics and make an individualized decision for vaccination. Investigators should refer to the prescribing information for the SARS-CoV-2 vaccine planned to be used and/or follow local Health Authorities or institutional guidelines, if available.

Patients should be instructed to contact their GP and/or the study site in case of side effects after vaccination.

Vaccine must be reported as a prior/concomitant medication according to the protocol guidelines. Any AEs after vaccination must be monitored and reported in eCRF.

6.2.5 Restriction for study participants

Before leaving the clinical site after Lutathera administration, patients will be instructed about radioactivity protection measures.

6.3 Participant numbering, treatment allocation

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is screened and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent re-screening. The Participant No. consists of the Center Number (Center No.) (as assigned by the Sponsor to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

6.3.2 Treatment allocation

No randomization will be performed in this study as this is a single-arm open-label study. All patients will receive Lutathera treatment, which will be allocated upon site ordering for each individual administration. Sites will be resupplied with amino acid solution based on recruitment rate.

6.4 Treatment blinding

This is a single-arm open-label study: No treatment blinding will be implemented.

6.5 Dose escalation and dose modification

No dose escalation is permitted in the study. For dose modification, see below.

6.5.1 Dose modification

In order to minimize risk for each study subject, an accelerated analysis of dosimetry and safety data will be performed for each individual patient in the study, to enable the Investigator to take a decision for the next Lutathera dose(s).

Dose modification recommendations for toxicities (DMT) and dose modification recommendations according to dosimetry results will apply as discussed in Section 6.5.1.1 and Section 6.5.1.2, respectively. The results of dosimetry assessments (imaging and blood dosimetry) and safety assessments will be provided to and evaluated by investigators prior to administration of next therapeutic cycle to decide on a need for dose modification based on the rules described below.

Patients, whose treatment is interrupted or permanently discontinued, must be followed up at regular intervals. In case of treatment interruption, the frequency of follow-up visits until treatment is resumed is at the discretion of Investigator depending on the DMT type and severity. In case of permanent treatment discontinuation, patients will enter the Follow-up Period (see Section 9.1.1), with visits frequency as specified in the Assessment Schedule.

In case that dosimetry results exceed reference limits in individual patient(s) (Section 4.2), DSMB must be consulted to evaluate benefit risk for the patient and advise on whether dosing

can continue and at which level (Section 6.5.1.2). The DSMB charter will include the reference information needed for dose decision making (including data collected from the M&S study).

Appropriate clinical experts such as cardiologists, endocrinologists, hepatologists, nephrologists etc. should be consulted as deemed necessary.

6.5.1.1 Dose modifying toxicities (DMTs)

Management of severe or intolerable adverse drug reactions may require temporary dose interruption, extending the dosing interval from 8 weeks up to 16 weeks, dose reduction, or discontinuation of treatment with Lutathera.

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted to allow the patient to continue the study treatment.

The criteria for dose modifications of Lutathera for toxicities are outlined in Table 6-4. The evaluation for potential DMTs will be done by Investigator based on local laboratory results from hematology and biochemistry tests done after each Lutathera treatment.

If a patient requires a dose delay of > 16 consecutive weeks of Lutathera from the intended day of the next scheduled dose, then the patient should be discontinued from the study treatment. In exceptional situations, if the patient is clearly benefitting from the study treatment (i.e. stable disease, partial response, complete response), and in the opinion of the investigator no safety concerns are present, after discussion with Sponsor Medical Monitor and/or DSMB, the patient may remain on the study treatment.

For each patient, a maximum of one dose reduction will be allowed after which the patient will be discontinued from the study.

All dose changes must be recorded on the appropriate electronic case report form (eCRF).

Table 6-4 Recommended Dose Modifications of Lutathera for Adverse Events

Adverse Reaction	Worst Toxicity CTCAE Grade (unless otherwise specified)	Dose Modification
Thrombocytopenia	First occurrence of: Grade 2 (PLT < 75 - 50 x 10^9/L) Grade 3 (PLT < 50 - 25 x 10^9/L) Grade 4 (PLT < 25 x 10^9/L)	Withhold dose until complete or partial resolution (Grade 0 to 1). Resume Lutathera at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 2, 3 or 4 thrombocytopenia, administer Lutathera at 7.4 GBq (200 mCi) for next dose.
	Recurrent Grade 2, 3 or 4	Permanently discontinue Lutathera.
Anemia	First occurrence of: Grade 3 (Hgb < 8.0 g/dL); transfusion indicated Grade 4 (life threatening consequences)	Withhold dose until complete or partial resolution (Grade 0, 1, or 2). Resume Lutathera at 3.7 GBq (100 mCi) in

Adverse Reaction	Worst Toxicity CTCAE Grade (unless otherwise specified)	Dose Modification
		patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 anemia, administer Lutathera at 7.4 GBq (200 mCi) for next dose.
	Recurrent Grade 3 or 4	Permanently discontinue Lutathera.
Neutropenia	First occurrence of: Grade 3 (ANC < 1.0 - 0.5 x 10^9/L) Grade 4 (ANC < 0.5 x 10^9/L)	Withhold dose until complete or partial resolution (Grade 0, 1, or 2). Resume Lutathera at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 neutropenia, administer Lutathera at 7.4 GBq (200 mCi) for next dose.
	Recurrent Grade 3 or 4	Permanently discontinue Lutathera.
Renal Toxicity	Defined as: First occurrence of: Creatinine clearance less than 60 mL/min; calculate using Cockcroft Gault with actual body weight, or 40% increase in baseline serum creatinine, or 40% decrease in baseline creatinine clearance; calculate using Cockcroft Gault with actual body weight.	Withhold dose until complete resolution. Resume Lutathera at 3.7 GBq (100 mCi) in patients with complete resolution. If reduced dose does not result in renal toxicity, administer Lutathera at 7.4 GBq (200 mCi) for next dose.
	Recurrent renal toxicity as described above	Permanently discontinue Lutathera.
Hepatotoxicity	Defined as: First occurrence of: • Bilirubinemia >3 times the upper limit of normal (Grade 3 or 4), or • Hypoalbuminemia less than 30 g/L with a decreased prothrombin ratio less than 70%.	Withhold dose until complete or partial resolution (Grade 0, 1 or 2). Resume Lutathera at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced Lutathera dose does not result in G3 or 4 bilirubinemia, administer Lutathera at 7.4 GBq (200 mCi) for next dose.
	Recurrent hepatotoxicity	Permanently discontinue Lutathera.

Adverse Reaction	Worst Toxicity CTCAE Grade (unless otherwise specified)	Dose Modification
Any other CTCAE* Grade 3 or Grade 4 AE[1]	First occurrence of: Grade 3 or 4	Withhold dose until complete or partial resolution (Grade 0 to 2). Resume Lutathera at 3.7 GBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 toxicity, administer Lutathera at 7.4 GBq (200 mCi) for next dose.
	Recurrent Grade 3 or 4	Permanently discontinue Lutathera.
[1] No dose modification required for hematological toxicities Grade 3 or Grade 4 solely due to lymphopenia *CTCAE: Common Terminology Criteria for Adverse Events, National Cancer Institute		

In addition,

- permanently discontinue treatment with Lutathera if hypersensitivity due to the active substance or any of the excipients of Lutathera is observed;
- temporarily discontinue treatment with Lutathera, until resolution or stabilisation before treatment can be resumed:
  - Occurrence of an intercurrent disease (e.g. urinary tract infection);
  - Major surgery: wait 12 weeks after the date of surgery, then restart the treatment with Lutathera.

If a patient experiences DMT during Lutathera therapy, subsequent treatments with Lutathera are permissible, provided the DMT resolves within 16 weeks following the non-tolerated administration. After resolution of a DMT, a patient may receive subsequent planned treatment(s) at 50% of the standard treatment dose, if this is felt to be safe for the patient, or the risk-benefit assessment is favourable. If the same DMT recurs after treatment with the reduced Lutathera dose, no further Lutathera treatment will be given. If the DMT event does not reoccur, the next treatment is at full dose, if it is considered to be safe for the patient, or the risk-benefit assessment is favourable.

Dose modification recommendations for toxicities might be overruled by dose modification recommendations based on dosimetry, and vice versa, i.e. a dose modification should be applied based on toxicity grading, even if dosimetry values are within limits.

6.5.1.2 Dose modification based on dosimetry

Patients will have bone marrow and kidney dosimetry (as well as that in other organs) determined following the first treatment using planar imaging and blood clearance (for bone marrow) data. In the exceptional circumstances when dosimetry cannot be done in a particular patient after the first dose, it should be done as soon as feasible upon a later dose.

As discussed in Section 4.2, the dosimetry reference limits are 2 Gy and 29 Gy based on bone marrow and kidney dosimetry, respectively.

Dosimetry data will be analysed by a central lab in an expedited manner, and the result of cumulative radiation dose will be provided to the Investigator for each patient to confirm that

the cumulative absorbed dose for subsequent treatments does not exceed the reference limits indicated above for kidney and bone marrow absorbed radiation doses.

For each patient, the Investigator will receive the results of dosimetry analysis (cumulative radiation dose) before the administration of next Lutathera dose (i.e. before the 2nd Lutathera administration if the dosimetry is done after the 1st dose). In parallel, the Investigator will assess safety data for potential DMTs as described in the Section 6.5.1.1 based on local laboratory test results.

In case that the resulting cumulative radiation dose is within the reference limits specified above, and no DMT criteria are met, the Investigator can administer full Lutathera dose for the next administration. DSMB does not need to be consulted in such case.

In case that the resulting cumulative radiation dose (calculated based on dosimetry analysis) exceeds the reference limits specified above, the DSMB will evaluate the totality of dosimetry, PK and safety data (See Section 8.3 and Section 8.4) to assess benefit risk for the patient and advise on whether dosing can continue and at which level. In such cases, the Investigator will be informed of the DSMB recommendation (including documented justification based on all data reviewed) prior to the next Lutathera administration. The ultimate decision on dose modification in such cases will remain with the Investigator.

The detailed guidance on dosimetry assessments will be provided in the dosimetry and imaging manuals. The detailed guidance for assessment of patient data and decision-making process for DSMB will be provided in the DSMB charter.

6.5.1.3 Overdose

Lutathera overdose has a very low probability of occurring since it will be supplied as a single dose "ready to use product" in order to avoid any manipulation outside the production facilities. In addition, the infusion system methods do not allow the concurrent use of two separate Lutathera solution vials. No doubling of the administered radioactivity is ever allowed either in absolute amount or by shortening the time intervals between treatments. Treatments (amount of radioactivity and time of administration) will be monitored during the study and any unallowed treatment modification will be considered a major protocol violation.

6.5.2 Dose discontinuation

The discontinuation of treatment with Lutathera is not a reason for patient's withdrawal from the study (reasons for the patient's withdrawal are discussed in Section 9). In case of a patient's withdrawal from the study treatment (based on either the patient's or the Investigator's decision), patients will undergo all exams scheduled for the End of Treatment (EoT) visit (Table 8-2) and continue into the Follow-up period.

If the treatment discontinuation occurs because of laboratory abnormality, or any evidence of toxicity, the Investigator will collect additional specimens for repeat or additional analyses, at intervals appropriate to the abnormality. The patient will be closely followed until sufficient information is obtained to determine the cause or the value regresses. Appropriate remedial measures should be taken and the response recorded in the eCRF.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Patients will be administered the infusions of Lutathera and amino acid during the clinical trial visit at the site. For each single dose of Lutathera a deviation of ±10% from the scheduled dose is allowed. All study treatment dispensed must be recorded in the Drug Accountability Log.

6.6.2 Recommended treatment of adverse events

For the treatment and prevention of nausea and vomiting with antiemetics see Section 6.1.2.

Crises due to excessive release of hormones or bioactive substances may occur following treatment, therefore, observation of patients by overnight hospitalization should be considered in both GEP-NET and PPGL cohorts.

Recommended treatments of patients with GEP-NET hormonal crises are: i.v. high dose somatostatin analogues, i.v. fluids, corticosteroids, and correction of electrolyte disturbances in patients with diarrhea and vomiting.

In PPGL cohort, the treatment of symptoms related to catecholamine release should be done as per standard local practice and physician judgment (see Section 4.5).

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.7 Preparation and administration of Lutathera and sterile amino acid solution

Further to patient screening and drug ordering by the site staff, Lutathera solution is supplied as a ready-to-use radiopharmaceutical solution for infusion. Each dose is infused over 30 minutes. There is no need for the patient to fast before treatment. For the detailed administration instructions, refer to the Pharmacy Manual.

The total amount of administered radioactivity has to be determined by measuring the radioactivity in the Lutathera vial before and after administration (the procedure is provided in the pharmacy manual).

All patients will receive concomitant sterile 2.5% Lys-Arg solution for kidney protection (see Section 6.1.2). The sterile amino acid solution and Lutathera are administered in parallel by peripheral vein infusion at a constant infusion rate through pumps or any other infusion system. The infusion with amino acids starts 30 minutes before the start of Lutathera infusion and continues for a total of 4 h (extension up to 6 h is allowed in case of adverse reactions that require interruption of infusion or slowing the infusion rate). During amino acid infusion patient is allowed to void.

Infusion rates are listed in Table 6-5.

Table 6-5 Administration procedure of antiemetic, amino acid solution and Lutathera

Administered agents	Start time (min)	Infusion rate (mL/h)	Duration
Antiemetic: E.g. granisetron 3 mg (or alternative)	with sufficient lead time prior to amino acid solution	As per local prescribing information	As per local prescribing information
Sterile 2.5% Lys-Arg amino acid solution (1L)	0	250	4 hours
Lutathera with sodium chloride 9 mg/mL (0.9%) solution for injection	30	Up to 400	30 ± 10 minutes

In PPGL cohort, an adequate alpha- and beta-blockade should be maintained to avoid acute symptoms of catecholamine release.

Following administration of Lutathera, patients should remain at the clinical site for an additional 4 to 5 hours in an area with suitable radiation shielding to protect others from unnecessary exposure (Appendix 2) time of release, patients are given written instructions which outline the precautions the patient must take to minimize radiation exposure to people around them.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Lutathera and amino acids must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Lutathera must be prepared in accordance with pharmaceutical quality requirements, and radiation safety regulations. Lutathera and amino acids must be administered at the investigational site and only in accordance with the protocol. Technical complaints are to be reported to the Sponsor.

The amino acids used/unused medications will be returned to the proper local depot for destruction at the study completion or upon expiration or destroyed at site according to Sponsor decision and approval.

Lutathera will be locally discarded according to all disposal requirements for radioactive materials.

The Investigator/Pharmacist must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

It must be possible to reconcile delivery records with those of used and unused medication. Any discrepancies must be accounted for and explained. Appropriate forms of deliveries and returns must be signed and dated by the responsible person at the clinical site and maintained as records. The return or disposal of all study medication will be documented appropriately.For more details about the handling of Lutathera and amino acids refer to the pharmacy manual.

7 Informed consent procedures

Eligible adolescents may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved assent and parent(s)/guardian informed consent.

If applicable, in cases where the adolescent's representative(s) gives consent (if allowed according to local requirements), the adolescent must be informed about the study to the extent possible given his/her understanding. If the adolescent is capable of doing so, he/she must indicate agreement by personally signing and dating the written assent.

Assent and parent(s)/guardian informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining adolescent assent and parent(s)/guardian informed consent must be documented in the participant source documents.

Sponsor will provide to investigators in a separate document a proposed assent and parent(s)/guardian informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed assent/consent form suggested by the investigator must be agreed by the Sponsor before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the adolescent assent and parent(s)/guardian informed consent and should be discussed with the adolescent and his/her parent/guardian during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety report. New information might require an update to the assent/informed consent and then must be discussed with the participant and his/her parent(s)/guardian.

The following informed consents are included in this study and should be used as determined by local regulations:

- Assent for adolescent
- Parent(s)/legal guardian Informed consent form
- Informed consent for adolescents who turn 18 years old during the study
- As applicable, Pregnancy Outcomes Reporting Consent for female subjects or the female partners of any male subjects who took study treatment

Female patients of child-bearing potential must be informed that taking the study treatment can cause fetal harm when administered to a pregnant woman and agree that in order to participate in the study they must adhere to the contraception requirements.

Male patients must also adhere to contraception requirements and be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

Female and male patients must be informed that the study treatment may potentially have temporary toxic effects on female and male gonads. Genetic consultation is recommended if the patient wishes to have children after treatment. Cryopreservation of sperm or eggs can be discussed as an option to patients before the treatment.

A copy of the approved version of all consent forms must be provided to Advanced Accelerator Applications after IRB/IEC approval.

After signing an ICF for participation in the study, each patient is given a patient card, which indicates the contact details of the Investigator (e.g. stamp with telephone number), the patient's Subject ID, as well as the study medication name. The patient shall carry this card with him/her during participation in the study so that the Investigator may be contacted in case of emergency.

Each patient also receives written instructions which outline the precautions that he/she must take to minimize radiation exposure to people around them.

8 Visit schedule and assessments

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-2). All data obtained from these assessments must be supported in the participant's source documentation. Missed or rescheduled visits will not lead to automatic discontinuation.

The screening period must be shortened as much as possible in order to enroll and treat the patients shortly after the informed consent signature. As Lutathera production and shipment will take approximately 12 days, Lutathera first dose must be ordered immediately after confirming patient eligibility and enrollment. There will be no study visits after screening and before the 1st Lutathera administration.

The treatment period consists of 4 treatment cycles, with Lutathera administration on Week 1 Day 1 of each cycle. The dosimetry assessments will be performed during the first week after the 1st Lutathera dose as per Table 8-2 and Table 8-3. In the exceptional circumstances when dosimetry cannot be done in a particular patient after the first dose, it should be done as soon as feasible upon a later dose. Patients might need to stay overnight at the hospital or another facility for the days with intensive assessments (e.g. for Lutathera administration, blood sampling and imaging). The decision on the overnight stay is up to Investigator, as appropriate according to medical judgment, local regulation and patient's preference.

The End of Treatment (EoT) visit should be performed in 8 weeks after the last Lutathera administration for patients who complete all 4 Lutathera doses (end of Cycle 4). Participants who prematurely discontinue the study treatment for any reason should be scheduled for the EoT/Early Termination visit as soon as possible, at which time all of the assessments listed for the EoT visit will be performed (refer to *"EoT or early termination"* column in Table 8-2). At this EoT visit, all adverse events and concomitant medications taken during the Treatment period should be reconciled and recorded on the eCRF.

During the short-term follow-up, visits will occur every 6 weeks until 6 months after the last Lutathera dose, and during the long-term follow-up visit will occur every 6 months until 5 years after the last Lutathera dose. The last follow-up visit (5 years after the last dose of Lutathera) will be considered as End of Study (EoS) visit for each patient.

The assessments listed in Table 8-1 will be performed locally and analyzed centrally. Procedures for centralized evaluations will be detailed in the respective manuals provided to each participating site.

For the visits when several types of assessments need to be performed, the recommended sequence is ECG, followed by vital signs and blood samples.

Table 8-1 Central readings and analysis.

Assessment	Central Reading/Analysis	Study Period	Section
Whole body planar and SPECT/CT imaging for dosimetry assessment	Central imaging evaluation and dosimetry analysis by selected vendors (for image analysis and dosimetry calculations)	Treatment Period Cycle 1 Week 1*	8.3
Blood and urine radioactivity measurement for PK and dosimetry assessment	Blood and urine radioactivity data will be used by the dosimetry vendor for dosimetry assessments. Blood radioactivity data will be used for PK assessments.	Treatment Period Cycle 1 Week 1*	8.3
Safety biomarker assessment	Blood will be collected using the sampling tubes provided by the Sponsor and shipped to a central laboratory.	Treatment Period cycle 1, 2, 3, 4, Short-term and Long-term follow-up	8.4.9
*In the exceptional circumstances when dosimetry cannot be done in a particular patient after the first dose, it should be done as soon as feasible upon a later dose.			

If the COVID-19 pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. When possible, phone calls and virtual contacts (e.g. teleconsult) should be implemented for the duration of the pandemic until it is safe for the participant to visit the site again. To follow is a set of general recommendations on the management of patients visits during COVID-19:

- Study patients should be instructed to contact the study investigator (by telephone or email), if there is a change in their health status.
- The study investigator may consider contacting patients more frequently than is required by the study protocol, with frequency selected according to circumstances and including the individual patient's vulnerability to COVID-19 based on their medical condition. When contacting patients, whether by telephone or in writing, the study investigator should record that contact or save written correspondence to the patient medical record or chart so as to assure a proper source documentation for the trial.
- Safety lab testing - The investigator should consider whether it is possible to arrange for the laboratory panels to be performed at a local certified laboratory for those patients who cannot come to the clinical site as scheduled. In exceptional cases, additional safety assessments might be done outside of clinical site if considered necessary to ensure the patient by investigator. The investigator should collect and file all local lab reports and normal ranges in the patient medical record or chart.
- Scheduled or unscheduled patient study visits can be performed once feasible and considered safe for patients to attend the clinical appointments.

Table 8-2 Assessment Schedule

Visit Name	Screening	Treatment Period[1]										End of Treatment (EoT) or early termination[2]	Follow-up (FU) Period				EoS *
Cycles / Weeks / Days	Day -14 – Day -1	Cycle 1			Cycle 2		Cycle 3			Cycle 4				Short-term Follow-up			Long-term Follow-up	
		Week 1		Week 3, 5, 7	Week 1	Week 3, 5, 7	Week 1	Week 3	Week 5, 7	Week 1	Week 3	Week 5, 7		Week 13 after last dose	Week 19 after last dose	Week 25 after last dose	Every 6 months until 5 years after last dose	
		Day 1	Day 2, 3, 4, 8															
Parent consent and patient assent	X																	
Demography	X																	
Inclusion/exclusion criteria	X																	
Diagnosis and Extent of Cancer	X																	
Medical History and Prior Tx	X																	
Physical Exam [S]	X	X			X		X			X			X	X	X	X	X	X
Body Height	X									X			X			X	X	X
Body Weight	X	X		X	X	X	X		X	X		X	X	X	X	X	X	X
Vital signs[3]	X	X[3a]			X[3a]		X[3a]			X[3a]			X	X	X	X	X	X
ECG	X	X			X		X			X			X					
Karnofsky or Lansky performance score	X	X			X		X			X			X	X	X	X	X	X

Visit Name	Screening	Treatment Period[1]											End of Treatment (EoT) or early termination[2]	Follow-up (FU) Period				EoS *
Cycles / Weeks / Days	Day -14 – Day -1	Cycle 1			Cycle 2		Cycle 3			Cycle 4				Short-term Follow-up			Long-term Follow-up	
		Week 1		Week 3, 5, 7	Week 1	Week 3, 5, 7	Week 1	Week 3	Week 5, 7	Week 1	Week 3	Week 5, 7		Week 13 after last dose	Week 19 after last dose	Week 25 after last dose	Every 6 months until 5 years after last dose	
		Day 1	Day 2, 3, 4, 8															
Blood chemistry	X			X		X			X			X	X	X	X	X	X	X
Hematology	X			X		X			X			X	X	X	X	X	X	X
Urinalysis[4]	X [4a]	X[4b]		X [4a,4c]	X[4b]	X [4a,4c]	X[4b]	X[4b]	X [4a]	X[4b]	X[4b]	X [4a]	X [4a]					
Serum Pregnancy test [5,S]	X			X [5]		X[5]			X[5]			X[5]	X					
Urine Pregnancy test[5,S]							Week 3							Monthly[5]				
SRI[6]	X																	
[redacted]																		
Lutathera/Amino Acid administration		X			X		X			X								
AE[7] and ConMeds[8]	X	X	X	X	X	X	X		X	X			X	X	X	X	X	X
Whole body planar imaging[9]		X (1-3 h)	X															
SPECT/CT			X (2															

Visit Name	**Screening**	**Treatment Period[1]**											**End of Treatment (EoT) or early termination[2]**	**Follow-up (FU) Period**				**EoS ***
Cycles / Weeks / Days	**Day -14 – Day -1**	**Cycle 1**			**Cycle 2**		**Cycle 3**			**Cycle 4**				**Short-term Follow-up**			**Long-term Follow-up**	
		Week 1		**Week 3, 5, 7**	**Week 1**	**Week 3, 5, 7**	**Week 1**	**Week 3**	**Week 5, 7**	**Week 1**	**Week 3**	**Week 5, 7**		**Week 13 after last dose**	**Week 19 after last dose**	**Week 25 after last dose**	**Every 6 months until 5 years after last dose**	
		Day 1	**Day 2, 3, 4, 8**															
imaging[9, 10]			4 h)															
Urine collection for dosimetry[9,11]		X																
Blood sampling for dosimetry[9,12]		X	X (Day 2, 4)															
Biomarkers of Endocrine and Gonadal Function		X[13]		X[14]								X[15]				X	X	X
Biomarkers of Growth and Bone Development		X[13]		X[14]								X[15]				X	X	X

1. Lutathera treatment will be administered every 8 ±1 weeks.
2. The EoT visit should be performed 8 weeks after the last Lutathera administration for patients who complete all 4 Lutathera doses (End of Cycle 4). In patients, who prematurely discontinue the study treatment for any reason, EoT/early termination visit should be scheduled as soon as possible. All AEs should be collected for 8 weeks + 30 days after last Lutathera dose.
3. Blood pressure, pulse rate and body temperature will be assessed for vital signs.
   3a. Monitoring of blood pressure and pulse rate during Lutathera and amino acid infusion is recommended.

Visit Name	Screening	Treatment Period[1]										End of Treatment (EoT) or early termination[2]	Follow-up (FU) Period				EoS *
Cycles / Weeks / Days	Day -14 – Day -1	Cycle 1			Cycle 2		Cycle 3			Cycle 4			Short-term Follow-up			Long-term Follow-up	
		Week 1		Week 3, 5, 7	Week 1	Week 3, 5, 7	Week 1	Week 3	Week 5, 7	Week 1	Week 3	Week 5, 7	Week 13 after last dose	Week 19 after last dose	Week 25 after last dose	Every 6 months until 5 years after last dose	
		Day 1	Day 2, 3, 4, 8														

4. Urine sample will be collected during the treatment period. The urinalysis should include:
   4a: dipstick analysis
   4b: both dipstick analysis and urine protein creatinine ratio (UPCR). Urine sample must be collected before Lutathera infusion and at Week 3 of each cycle.
   4c: urine protein creatinine ratio (UPCR) which is only applied to Week 3 of each cycle.
5. Serum pregnancy testing should be done:
   - at screening,
   - during treatment:
     - at week 3 and 7 for cycle 1 and 2
     - at week 7 for cycle 3 and 4
   - End of treatment

   Urine pregnancy tests will be done:
   - During treatment period:
     - On week 3 at cycle 3 and 4
     - Monthly for 7 months after last dose
   - During Follow-up period: monthly for 7 months after last dose.
6. SRI performed within 3 months prior to enrollment can be used for patient eligibility assessment.
7. For more details about data collection related to AEs, SAEs and AESI please refer to Section 8.4.1 and Section 10.1.
8. During Follow-up Phase and at the EoS visit, recording of medications use will be limited only to the medications administered for related SAEs/AESIs and/or for secondary hematological malignancies. In addition, all new anticancer therapies administered must be collected till EOS.
9. For details and allowed windows for dosimetry assessments see Table 8-3.
10. SPECT/CT to be done on Day 2 (24 h after Lutathera infusion)
11. Urine collection from the start of Lutathera infusion to the 1st whole body planar imaging. If no urine is excreted from the start of Lutathera infusion until the first whole body planar imaging, no urine dosimetry is necessary.

Visit Name	Screening	Treatment Period[1]										End of Treatment (EoT) or early termination[2]	Follow-up (FU) Period				EoS *
Cycles / Weeks / Days	Day -14 – Day -1	Cycle 1			Cycle 2		Cycle 3			Cycle 4			Short-term Follow-up			Long-term Follow-up	
		Week 1		Week 3, 5, 7	Week 1	Week 3, 5, 7	Week 1	Week 3	Week 5, 7	Week 1	Week 3	Week 5, 7	Week 13 after last dose	Week 19 after last dose	Week 25 after last dose	Every 6 months until 5 years after last dose	
		Day 1	Day 2, 3, 4, 8														

12. Blood collection for dosimetry includes 6 radioactive blood samples at the following time points: before the start of Lutathera infusion, at the end of Lutathera infusion, then at 2h, 6h, 24h and 72h after the end of Lutathera infusion.
13. On Day 1 of Cycle 1, safety biomarkers are assessed pre-dose.
14. Safety biomarkers are taken either at Week 7 of cycle 1 or pre-dose of cycle 2.
15. Safety Biomarkers are taken either at Week 7 of cycle 4 or at the EoT visit.

S = assessment to be recorded in the source documentation only and not recorded in CRF page.

* The last FU visit would be the EOS visit for patients who completed the long-term FU period; and a separate EOS visit should be planned for patients who discontinued from the study prior to completion of the long-term FU period.

Variations of ± 1 week are allowed for the visits during the Treatment period (including the window for Lutathera administration visits that should occur in 8 weeks from the previous dose ± 1 week), and during the Short-term Follow-up. The exception is the week when dosimetry assessments are performed – during the dosimetry week, all visits must occur on the Days specified in the Table 8-2.

During the Long-term Follow-up, a visit window of ± 1 month is allowed.

8.1 Screening

8.1.1 Screening

As described in Section 7, informed consent must be obtained before conducting any study-specific procedures and all inclusion and exclusion criteria met before enrolment into the study (see Table 8-2 for list of assessments to be performed).

The screening period occurs between patient screening visit (at which informed consent signature occurs) and patient enrolment (when patient eligibility is confirmed as per inclusion/exclusion criteria). Screening period must be shortened as much as possible.

Somatostatin receptor imaging (SRI) performed before the screening (within 3 months prior to enrollment) can be used for the assessment of patient eligibility. Laboratory tests completed before the screening can be used for the assessment of patient eligibility if performed within 2 weeks prior to enrollment.

Laboratory parameters and any other applicable assessments can be re-evaluated within the initial screening period if the corresponding selection criteria were not met with the initial results. This is not considered a re-screening. If the patient is not enrolled after 2 weeks of screening, the patient should be screen-failed.

It is permissible to re-screen a patient if they fail the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis. Rescreening should only occur after a subject has failed screening. In this case a new subject number will be generated and a specific re-screen form will be added in the eCRF, to collect the original subject number.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening period (see Section 10.1.6 for reporting details).

Participants who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition Case Report Form.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

The data that will be collected on patient characteristics at screening include:

- Demography (age, sex, race, ethnicity), if local regulations allow for the collection of such information
- Diagnosis and extent of cancer: patient's cancer history, including documented primary location of cancer, date of diagnosis, presence of metastases with specification of the metastatic site(s) and tumor grading at study entry.

- Somatostatin receptor imaging (SRI) data obtained within 3 months prior to screening visit date will be collected to confirm the diagnosis and somatostatin uptake.
- A CT/MRI assessment will be performed during the screening period to assess the status of the disease.
- Prior antineoplastic medications/radiotherapy/surgery: information pertaining to any chemotherapy, hormonal therapy, immunotherapy, radiation, or surgery the patient has previously received.
- Other medical history (e.g. important medical, surgical, and allergic conditions from the subject's medical history which could have an impact on the subject's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent).
- Data from the following baseline assessments:
  - Physical examination (only abnormalities resulting from physical exam will be recorded in eCRF)
  - Vital signs
  - ECG
  - Height and weight measurement
  - Laboratory assessments (biochemistry, hematology, urinalysis, safety biomarkers for endocrine and gonadal function, growth and bone development)

8.3 Dosimetry

Patients will have whole body and organ radiation dosimetry (including the critical organs, i.e. bone marrow and kidney) determined following the first Lutathera treatment using planar imaging and blood radioactivity data. In the exceptional circumstances when dosimetry cannot be done in a particular patient after the first dose, it should be done as soon as feasible upon a later dose. For each patient, dosimetry will be performed only once throughout the study.

Dosimetry assessments will be performed as follows:

- Whole body planar image will be acquired on Day 1 (1 to 3 hours after end of Lutathera infusion), 2, 3, 4 and 8 of Week 1
- SPECT/CT scan will be acquired in 24 hours after the end of Lutathera infusion (on Day 2)
- Blood samples for radioactivity measurement will be collected before the start of Lutathera infusion, at the end of Lutathera infusion, then at 2h, 6h, 24h and 72h after the end of Lutathera infusion
- All excreted urine from the start of Lutathera infusion until the first whole body planar imaging will be collected, its volume measured and the radioactivity concentration (kBq/mL) determined in order to calculate the total radioactivity excreted from the body from the start of Lutathera infusion to the time of the first scan. Patients should be asked to void before starting the infusion, so that the chances of voiding after the start of Lutathera before the first whole body planar imaging are minimized. If no urine is excreted from the start of Lutathera infusion until the first whole body planar imaging, no urine dosimetry is necessary.

[redacted]

8.3.1 Whole body planar and SPECT/CT Images

Whole body planar and SPECT/CT images will be obtained at the investigational sites and then provided to a selected vendor for evaluation as DICOM files, which will be made available through a web-exchange system or other suitable IT support (e.g. compact disks). For more details about the images transfer and analysis refer to the dosimetry manual provided to the sites.

8.3.2 Methods used to estimate absorbed radiation doses

According to the Medical Internal Radiation Dose scheme (Bolch 2009, Loevinger 1988, ICRU 1979, NCRP 1985), the radiation dose to a target organ is the sum of the self-dose from this organ and the cross doses from all other target organs. In order to calculate the radiation dose to the various target organs the amount of radioactivity present in the source organs must be measured. The radioactivity uptake in each organ is determined at various time points. This uptake defines the kinetics of the radiopharmaceutical. By integrating such time-activity curve, the number of decays from each source organ per injected activity dose is obtained, and this is the so-called time Integrated Activity Coefficient (TIAC). The TIACs from each organ will be processed by Olinda/EXM software for the calculation of the organ absorbed radiation doses.

8.3.3 Biological samples for PK and dosimetry analysis

Radioactivity in blood and urine will be measured at the investigational sites with a properly calibrated gamma counting system.

The results of the activity concentration in the blood and urine samples (if measured locally) and the volume of the urine excreted before the first scan will be used for PK and dosimetry calculations.

a. Blood sample counting

Whole blood samples (1 mL in heparinized tubes) will be collected from each patient at pre-defined time points and counted in a properly calibrated gamma-counter.

The acquired blood radioactivity data will be used for both dosimetry and PK assessments.

b. Urine sample counting

The majority of the infused Luthatera is excreted via the kidneys into the urine.

The total radioactivity excreted in urine before the first image acquisition will be determined, as this information is needed for dosimetry evaluation. The total cumulative volume of urine eliminated in that interval (from the administration to the first whole body planar imaging) will be measured. A urine sample (1 mL) will be taken from the total volume eliminated in that period for radioactivity measurement by gamma-counter. If no urine is excreted from the start of Lutathera infusion until the first whole body planar imaging, no urine dosimetry is necessary.

8.3.4 Dosimetry equipment and timepoints

The following equipment is necessary for the data acquisition:

1. A gamma-camera with medium energy collimator.
2. Well counter with multichannel analyser or gamma counter to determine 177Lu radioactivity in blood and urine samples.
3. A dose calibrator (activimeter) to measure the radioactivity in the reference source and the injected radioactivity.
4. SPECT/CT equipment

A detailed schedule of the dosimetry assessments is shown in the Table 8-3 below.

Table 8-3 Dosimetry assessments timepoints

<table>
<tr><td></td><td colspan="10">Cycle 1 / Week 1</td></tr>
<tr><td></td><td colspan="8">Day 1</td><td>Day 2</td><td>Day 3</td><td>Day 4</td><td>Day 8</td></tr>
<tr><td>Lutathera administration</td><td></td><td colspan="2">X (30-min ±10 min infusion)</td><td colspan="5"></td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td></tr>
<tr><td>Amino acid administration</td><td colspan="6">X
(4-h infusion (max 6 h))</td><td colspan="2"></td></tr>
<tr><td>Hours from end of Lutathera infusion</td><td>Pre-dose</td><td></td><td>0h</td><td>1h</td><td>2h ±30 min</td><td>3h</td><td>6h ± 1h</td><td>24h ± 4h</td><td>48h ± 6h</td><td>72h ± 6h</td><td>168h ±6h</td></tr>
<tr><td>Blood sampling for dosimetry</td><td>X
(Any time before Lutathera infusion)</td><td></td><td>X</td><td></td><td>X</td><td></td><td>X</td><td>X</td><td></td><td>X</td><td></td></tr>
<tr><td>Whole body planar imaging</td><td colspan="3"></td><td colspan="3">X
(any time 1-3 h)</td><td></td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Urine collection for dosimetry</td><td></td><td colspan="2">X
(from start of Lutathera infusion to 1st whole body planar imaging)</td><td colspan="7"></td></tr>
<tr><td>SPECT/CT imaging</td><td colspan="7"></td><td>X</td><td colspan="3"></td></tr>
</table>

The intervals for dosimetry sampling and imaging in Table 8-3 are recommended and acceptable variations. However, if an assessment cannot be done within specified windows, it can be done at the closest feasible time, even if outside of the window.

Blood sampling times for dosimetry and PK assessments have been optimized based on a population PK model developed in adults to provide robust estimates of individual patient pharmacokinetic parameter values.

8.3.5 Dosimetry and PK parameters

Lutathera bio-distribution, dosimetry and absorbed dose in critical organs will be determined from Time activity Curves (TACs) derived from radioactivity measured in blood and urine samples and in Regions of interest (ROI) for organs and tumor lesions drawn using the acquired planar images. Dosimetry calculations will be performed from the analyses of organs having significant uptake, identified visually. ROI delimiting these organs are used to determine relative radiotracer uptake calculated as a percentage of the injected dose. TACs are derived from mono-, bi-, or tri-exponential functions with best fit to time course data. By integrating the TACs, the Time Integrated Activity Coefficients (TIACs) are obtained. TIACs, also called Number of Decays, will be used to calculate the absorbed radiation dose values (Gy) in target organs.

The absorbed radiation dose in organs is the ultimate output dosimetry parameter that will be provided to Investigators for each patient, and to DSMB, if necessary (see Section 6.5.1.2).

Pharmacokinetic parameters such as the maximum blood concentrations (Cmax), the sampling time at which Cmax is reached (tmax), in addition to the area under the curve ($AUC_{0-\infty}$), systemic clearance (Cl), volume of distribution (V_1 and V_2) will be determined using model based methods. Other parameter estimates may be determined as deemed appropriate.

8.4 Safety assessments

8.4.1 Adverse Event Monitoring

All adverse events (AEs), whether or not spontaneously reported by the patient, will be recorded starting from the signing of the ICF until the end of the Treatment Period. During the Follow-up Period only related serious adverse events (SAE) and adverse events of special interest (AESI) will be recorded, except for all secondary malignancies which need to be recorded as AESI irrespective of causality. For details on AE definitions, collection and reporting refer to Section 10.

In the case where patient on-site study visits are limited due to COVID-19 pandemic, regular phone or virtual calls will occur for safety monitoring and discussion of the participant´s health status until the participant can again visit the site.

8.4.2 Physical examination

A complete physical examination should be performed at screening and EoT, including an evaluation of the head, eyes, ears, nose, throat, neck and lymph nodes, and the cardiovascular, dermatological, musculo-skeletal, respiratory, GI and neurological systems.

Before each Lutathera administration and at each visit during short and long-term follow-up (and at other visits if clinically indicated), a limited, symptom-directed physical examination should be performed at the discretion of the Investigator (see Table 8-2).

Documentation of all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

8.4.3 Vital signs

Vital signs include blood pressure, pulse rate and body temperature.

Blood pressure, pulse rate and body temperature will be assessed at screening, before each Lutathera administration, at EoT and at each visit during short and long-term follow-up (see Table 8-2). Blood pressure and pulse rate should be obtained in a quiet room at a comfortable temperature, with the patient's arm unconstrained by clothing or other material. Blood pressure and pulse rate measurements will be obtained after the patient has been in a sitting or supine position for at least 3 minutes, from the same arm (where possible), in the same position, with the same cuff size, using the same type of an automatic instrument with a digital readout, throughout the study. In addition, monitoring of vital signs (blood pressure and pulse rate) during the Lutathera and amino acid infusion is recommended.

Body temperature measurement can be either oral or tympanic; the method should be maintained throughout the study.

Significant findings that are present prior to baseline will be recorded in the medical history page, while changes during the study (including significant changes of the symptoms due to the underlying disease vs baseline) will be recorded on the Adverse Event page of the eCRF.

For patients enrolled in PPGL cohort, additional measurements of blood pressure can be performed at Investigator discretion for the monitoring of hormone release symptoms (see Section 4.5). Such measurements will be recorded in eCRF as unscheduled visits.

8.4.4 Height and Weight

Height will be taken at screening, week 1 of cycle 4 treatment, EoT, last visit of short-term FUP, and every six months during long-term FUP.

Weight will be taken at screening, before each Lutathera administration, at the EoT, and every six months during long-term FUP. In addition, weight should be measured for each CrCl calculation (i.e. on the days when chemistry tests are taken).

Height will be obtained in centimeters (cm) and body weight in kilograms (kg) and rounded to the nearest 0.1 kg. Weight will be obtained in indoor clothing, without shoes.

8.4.5 ECG

Standard 12-lead ECGs will be performed at screening (baseline), immediately after each Lutathera/amino acid treatment procedure (following the completion of the amino acids infusion), and at the EoT visit (Table 8-2) to measure the ECG intervals (RR, PR, QRS, QT and QTcF).

ECGs will be performed in triplicate (at least 5 minutes apart) after the patient has been in a sitting or supine position for at least 10 minutes, and not immediately after a meal. The parameters will be measured as a mean value of minimally 3 beats; the mean of each parameter has to be used for CRF completion. The preferred sequence of cardiovascular data collection at the timepoints with multiple assessments is ECG collection first, followed by vital signs, and blood sampling.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate.

The Investigator will note in the source documents (and in the eCRF) whether the ECG is normal or abnormal, as well as the clinical relevance of abnormal ECGs results and the different ECG intervals measurements, calculated using the mean value of 3 measurements for each parameter. Relevant ECG abnormalities at screening will be recorded in the medical history page, while changes during the study will be recorded on the Adverse Event page of the eCRF.

The original ECGs on non-heat-sensitive paper or a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site. Each ECG tracing should be labeled with the study number, subject initials (where regulations permit), subject number, subject date of birth, ECG date, and kept in the source documents at the study site.

8.4.6 Laboratory evaluations

The clinical laboratory assessments in this study include blood samples for hematology, blood chemistry, safety biomarkers, a urine sample for urinalysis, and a pregnancy test (Table 8-2, Table 8-4).

Clinically significant abnormalities that are present prior to baseline will be recorded in the medical history page while any clinically relevant change from baseline onwards, will be recorded on the Adverse Event page of the e-CRF, possibly with a single diagnosis encompassing all changes possibly supporting to the single diagnosis.

In the event of a significant laboratory abnormality, or if clinical or laboratory evidence of toxicity occurs, the Investigator will collect additional specimens for repeat or additional analyses, at intervals appropriate to the abnormality. The patient will be closely followed until sufficient information is obtained to determine the cause or the value regresses. Appropriate remedial measures should be taken and the response recorded.

All previous safety laboratory results must be evaluated by the Investigator before each administration of Lutathera.

The list of laboratory parameters described in Table 8-4 will be evaluated at the local laboratory of each site. Laboratory assessments will be performed according to the schedule in Table 8-2.

The laboratory assessments after Lutathera doses (hematology, biochemistry and urinalysis, i.e. at Weeks 3, 5 and 7 of cycle 1 and 2 and at Weeks 5 and 7 of cycle 3 and 4) can be performed at another local laboratory outside of the Investigator site if considered necessary and convenient for the patient and investigator. In this case, the results and normal ranges should be provided for these tests and entered in eCRF as soon as possible to enable ongoing safety monitoring.

During the COVID-19 pandemic, the investigator should consider whether it is possible to arrange for the laboratory tests to be performed at a local laboratory for those patients who cannot come to the clinical site as scheduled. The investigator should collect and file all local lab reports in the patient medical record or chart.

Table 8-4 Laboratory assessments

Test Category	Test Name
Hematology	• WBC with differentials • Platelets • Hb • MCV • Haematocrit
Blood Chemistry	• BUN or urea • Serum creatinine • Creatinine Clearance1 • Uric acid • Albumin • Total bilirubin • AP • AST/ASAT • ALT/ALAT • Gamma-GT • Sodium • Potassium • Magnesium • LDH • Calcium
Urinalysis	• Protein • Blood • Glucose • Leucocytes • pH • UPCR
Pregnancy Test	Serum / Urine pregnancy test

[1] Creatinine clearance must be calculated using the Cockcroft-Gault formula:
*Est. Creatinine Clearance = [[140 - age (yr)]*weight (kg)]/[72*serum Cr(**mg/dL**)]*
(multiply by 0.85 for women)
Or
*Est. Creatinine Clearance = [[140-age(yr)]*weight (kg)]/[0.814* serum Cr(**µmol/L**)]*
(multiply by 0.85 for women)

8.4.7 Urinalysis

A midstream, clean-catch urine specimen will be collected for dipstick analysis of protein, blood, glucose, leucocytes and pH, according to the schedule in Table 8-2. If the dipstick result is 2+ or greater for blood, protein or leukocytes, microscopy needs to be performed. If there is an explanation for the positive dipstick result, e.g., menses, it should be recorded, and there is no need to perform microscopy. A spot urine sample should also be collected before each Lutathera infusion and also 3 weeks after each Lutathera infusion for UPCR test (Table 8-2).

8.4.8 Pregnancy Test

All menarchal girls and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study. It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual activity, pregnancy and contraception is influenced by age, as well as factors such as precocity, socio(educational) economic and familial background. These discussions with the patient and her parents/caregivers are therefore best performed by investigators familiar with the pediatric subject and her family and should be guided by requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the adolescent participant and her family. The investigator should also discuss the management of the pregnancy test results with the patient and her parents/caregivers. The privacy of the patient should be considered in accordance with the local law and ethics.

All female patients should not procreate until seven months after the last Lutathera dose (see Appendix 1 for contraception measures).

A pregnancy test must be performed at screening and prior to each Lutathera treatment (within 2 weeks) for every female patient of childbearing potential. This should be continued during treatment and for 7 months after ending treatment. The pregnancy test must be performed as per schedule described in Table 8-2. During this period, monthly pregnancy serum tests can be changed to urine tests if there is no personal visits. The urine pregnancy testing should use a laboratory-based urine assay or a commercially available kit.

If preferred by the patient, the urine pregnancy tests can be done at the clinical site. In case the urine pregnancy test is positive, the patient must contact the investigator immediately. A positive urine test needs to be confirmed with blood test. If the confirmatory blood pregnancy test is positive during treatment period, the participant must be discontinued from study treatment.

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female pediatric patients who are menarchal or who become menarchal during the study.

Additional pregnancy tests may be performed at the investigator's discretion during the study.

Patients becoming pregnant must be discontinued from study drug. For requirements on pregnancy reporting see Section 10.1.7.

8.4.9 Safety biomarkers

The endocrine (pituitary) function, gonadal function, growth and development, and bone development function of each patient will be evaluated using the safety biomarker tests described in the Table 8-5.

Samples will be collected at the time points defined in the Assessment Schedule (Table 8-2).

A central laboratory will be used for analysis of all safety biomarker specimens. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the central laboratory manual.

Table 8-5 Safety biomarker assessments

Test Category	Test Name
Endocrine (Pituitary) function	• TSH (and free Thyroxine (fT4) if TSH is abnormal) • Luteinizing hormone (LH) • Follicle-stimulating hormone (FSH)
Gonadal function	• Inhibin B in men • Estradiol in women • Testosterone in men
Growth and development	• IGF-1
Bone development	• BALP • N-terminal or C-terminal cross-linked telopeptide of type I collagen (NTX or CTX)

8.4.10 Performance score assessment

Karnofsky performance score (KPS) evaluation must be completed by a medical professional at the time points defined in the Assessment Schedule (Table 8-2). If applicable and preferred by Investigator, KPS can be replaced by Lansky Play-Performance Scale assessment.

8.4.11 Tumor response assessment

[redacted]

CT/MRI imaging will be done at screening [redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Any situation in which study participation might result in a safety risk to the participant including unacceptable adverse event.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2 'Withdrawal of Informed Consent' section).

Where possible, all patients who discontinue study treatment should return for the EoT/Early Termination Visit assessments, and continue into the full Follow-up period as indicated in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified for lost to follow-up (Section 9.1.3). This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, if the patient is unwilling to perform all scheduled assessments, then at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- Survival status
- New / concomitant treatments, including all antineoplastic therapies
- Adverse Events / Serious Adverse Events

During the COVID-19 pandemic, for patients who are unable to come to the study site for their scheduled visit, conducting patient study visits on schedule through phone calls and virtual contacts (e.g. teleconsult) may be possible. As patient safety is the number one concern, patients may need to discontinue treatment based on the investigator's clinical judgment or patient's own decision. The investigator should document in the source notes as clearly as possible the decisions made around continuing or discontinuing study treatment for a patient and the risk-benefit for each case as it may arise. The investigator should consider if alternative therapeutic options exist and may be warranted based on the individual benefit-risk for the patient.

In extraordinary situations due to the very short half-life of radionuclides, e.g. a sudden temporary supply disruption and/or a quality finding after release of the product, the investigator may immediately be:

1. advised on how to manage participants in screening or on treatment;
2. informed to withhold doses from impacted batch and not administer them to the participant;

and/or

3. asked to closely monitor participants who have received a dose from an impacted batch for adverse events.

9.1.1.1 Replacement policy

In general, no treated patients will be replaced, and all patients who received at least one Lutathera dose will be used for the primary safety analysis. However, more than 8 patients may be enrolled if deemed necessary, e.g. in case that a patient is not evaluable for the primary dosimetry analysis.

9.1.2 Withdrawal of informed consent

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of his/her data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts).

This request should be as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent/exercise data privacy rights and record this information. The Investigator should clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant for the study purpose are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in the assessment table.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding consent form.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw consent (or exercise other participants' data privacy rights), the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by the Sponsor at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from DSMB after review of safety data
- Practical reasons (including slow enrollment)
- Discontinuation of study drug development

In taking the decision to terminate, Sponsor will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last patient finishes their last follow-up visit and any assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

Following the end of treatment or early treatment discontinuation, patients will enter in the Follow-up Period unless unfeasible (e.g. consent withdrawal, patient lost to follow-up). Patient visits and assessments will be performed during the follow-up period as per the study schedule of assessments (Table 8-2) and Section 9.1.1.

The last follow-up visit (5 years after the last dose of Lutathera) will be considered as End of Study (EoS) visit for each patient.

When the study planned enrollment is met, study subjects currently on study treatment or in the follow-up period will continue the study as per the study schedule of assessment (Table 8-2).

Study Treatment will not be provided to the enrolled patients after completion of the study as Lutathera is administered as 4 doses and this is a full regimen. No provision of Lutathera post-trial is considered necessary.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events (AE)

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

Adverse events that begin or worsen after informed consent must be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent must be recorded in the Medical History page of the subject's eCRF. Adverse events (including lab abnormalities that constitute AEs) must be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom must be reported as a separate Adverse Event.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2; if the event is adverse event with special interest (AESI) refer to Section 10.1.5):

1. The Severity grade OR the Common Toxicity Criteria (CTC) AE grade (Appendix 3).
   a. If "severity grade" is selected, include the following:
      i. mild: usually transient in nature and generally not interfering with normal activities
      ii. moderate: sufficiently discomforting to interfere with normal activities
      iii. severe: prevents normal activities
   b. If "CTCAE grade" is selected, include the following:
      i. Adverse events will be assessed and graded between 1 to 5.
2. The investigator is obligated to assess the relationship between any treatment used in the study (study treatment, AxMPs) and each occurrence of each AE. The investigator will use clinical judgment to determine the relationship. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. For causality assessment, the investigator will also consult the IB and/or product information, for marketed products. The causality assessment is one of the criteria used when determining regulatory reporting requirements.
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a Serious Adverse Event (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding study treatment
   - Dose not changed
   - Dose reduced

- Drug interrupted/withdrawn

6. Treatment for adverse events. All adverse events must be treated appropriately.
7. Its outcome i.e., its recovery status or whether it was fatal

If the event worsens, it should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Once an adverse event is detected, it must be followed until its resolution (or until it is judged to be permanent) or until 30 days after end of study visit. Assessments must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

For the investigational product and for non-authorized AxMPs (when applicable), information about adverse drug reactions and how to manage them can be found in the Investigator's Brochure (IB) or equivalent documentation. Information about adverse drug reactions can also be found in the product information for marketed products.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

Reporting of AEs related to AxMP(s):

All AEs related to any authorized auxiliary medicinal product used in this study must be reported to Advanced Accelerator Applications. In assessing causality, the investigators will use the points above.

If a suspicion that medical occurrence could be related to study treatment (and/or interaction with study treatment cannot be ruled out), the reporting rules for study treatment apply.

AxMP safety reporting requirements will only apply once the trial has been transitioned under EU Clinical Trial Regulation 536/2014.

10.1.2 Serious adverse events (SAE)

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal

- life-threatening. Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (refer to the ICH-E2D Guidelines).
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

Treatment-emergent elevations in AST or ALT (> 3 × ULN) in combination with total bilirubin > 2 × ULN or jaundice in the absence of cholestasis (defined as ALP < 2 × ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law). The Hy's Law criteria may be changed to increases of transaminases 2-fold above baseline values for subjects with elevated baseline values. For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious unexpected adverse event

(assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

10.1.3 Adverse Drug Reactions (ADR)

An ADR is any noxious and unintended response to an IMP related to any dose with at least a reasonably possible causal relationship with the IMP. Briefly, an ADR is an AE which is suspected to be possibly related to IMP by either the investigator or the study sponsor.

10.1.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

An ADR will be assessed to be “unexpected” if the nature, severity or frequency of the event is not consistent with the applicable product information available for the IMP. An ADR will be assessed to be “expected” if it is listed in the Investigator’s Brochure.

A SUSAR is an adverse event regarded as serious with at least possible causal relationship to the drug, the nature, severity or frequency of which is not consistent with the applicable information available in the reference documents available for the IMP.

10.1.5 Adverse Events of Special Interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the Sponsor’s product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

These potential risks deserve special attention even if they do not fulfill any of the seriousness criteria. These non-serious adverse events of special interest (AESI) should be reported to the Sponsor using reporting procedures for SAEs. During screening, only AESI meeting seriousness criteria should be reported to the Sponsor. During the treatment period, all AESI need to be reported to the Sponsor irrespective of causality. During the follow-up period, AESI need to be reported only if considered related to the study treatment except for all secondary malignancies which need to be reported as AESI irrespective of causality. The AESI represent main risks of Lutathera and amino acid treatment reported in adults, as well as potential risks in pediatric population (Table 10-1).

Table 10-1 Adverse events of special interest

AESI categories
Secondary malignancies
Hematotoxicities
Nephrotoxicities
Endocrine disorders
Bone development disorders
Cardiovascular and electrolyte disorders

Secondary malignancies: any secondary malignancies, including MDS and acute myeloid leukemia, should be reported in every case irrespective of causality, as AESI/SAE, until the end of long-term follow up period.

Hematotoxicity: The main critical organ of Lutathera treatment is the bone marrow. Significant hematotoxicity, defined as Grade 2 or higher thrombocytopenia, or Grade 3 or 4 of any other hematotoxicity (anaemia, leuko-/lympho-/neutropenia) are considered dose-modifying toxicities in the study and must be reported as AESI when not strictly fulfilling the criteria of serious adverse events. Haematological toxicities regardless of severity must be reported as AESI if accompanied by clinical consequences, i.e., infections in the presence of leuko-/neutro-/lymphopenia, hemorrhages / purpuric lesions under thrombocytopenia that is not explained by another coagulation disorder, dyspnea / fatigue in the presence of anaemia not otherwise explained by the underlying carcinoid syndrome or other co-morbidity.

Nephrotoxicity: Since Lutathera is cleared through the kidneys and reabsorbed by the kidneys, the kidneys have always been considered the "critical organs". An infusion of amino acid is used for kidneys protection by inhibition of tubular reabsorption of Lutathera. Pursuant to these risk minimization efforts and in addition to the criteria of dose-modifying toxicities and criteria of inclusion (at baseline and before subsequent treatments) pertinent to renal function measurements, renal and urinary tract toxicities are considered AESI. Investigators must report as AESI renal toxicities including renal failure (ranging from significantly reduced measured or estimated creatinine clearance to clinically overt renal failure other than that of obvious non-IMP-induced origin), suspected radiation nephropathy of any type, such as radiation-induced thrombotic microangiopathy (manifested with, e.g., proteinuria, hypertension, edema, anaemia, decrease serum haptoglobin), or general symptoms and signs of acute radiation toxicity (e.g., increased frequency and urgency of urination, nocturia, dysuria, bladder spasm, bladder obstruction, genitourinary ulceration or necrosis).

Endocrine (hypothalamic-pituitary and growth) disorders: Since the potential effect of the Lutathera treatment on the pituitary-gonadal and pituitary-thyroid axes is not well described in the adolescent population, the endocrine effects will be closely monitored via specific biomarkers. Any suspected endocrine toxicity should be considered AESI regardless of severity.

Effects on bone development: Radiation exposure has a potential effect on the overall quantity and quality of bone by interfering with the trabecular architecture through increased osteoclast activity and decreased osteoblast activity. Biomarkers of bone metabolism help to detect the metabolic imbalance and identify bone toxicities. Any suspected bone toxicity should be considered AESI regardless of severity.

Cardiovascular and electrolyte disorders:

All clinically significant changes in blood pressure, heart rate, electrocardiogram and electrolyte parameters must be reported as AESI if they occur within reasonable propinquity of Lutathera or sterile amino acid solution administration in the judgment of the Investigator. Likewise, clinically manifest consequences of hypo-/hypertension, arrhythmias, cardiac conduction disturbances, electrolyte disorders and other cardiac pathologies evidenced by objective findings / changes on electrocardiogram or echocardiography should also be considered for AESI reporting.

10.1.6 SAE and AESI reporting

SAE reporting:

To ensure subject safety, after the patient signed the informed consent and before the patient received a study drug, only SAE potentially related to any study procedure must be reported. After the first dose of study drug(s), all SAEs regardless of suspected causality and until 30 days after the EoT visit must be reported to the Sponsor within 24 hours of learning of its occurrence. Afterwards, any SAEs experienced during the Follow-up period should only be reported to the Sponsor if the investigator suspects a causal relationship to study treatment.

Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the SAE Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to the Sponsor.

Follow-up information is submitted in the same way as the original SAE Report. Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, the Sponsor may urgently require further information from the investigator for health authority reporting. The Sponsor may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 and EU Clinical Trial Regulation 536/2014 (once transitioned under EU CTR) or as per national regulatory requirements in participating countries.

All SAEs related to any authorized auxiliary medicinal product (whether authorized or not) used in this study must be reported to Advanced Accelerator Applications within 24 hours of the site becoming aware of it. In assessing causality, the investigators will use the points above. If a suspicion that medical occurrence could be related to study treatment (and/or interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply. AxMP safety reporting requirements will only apply once the trial has been transitioned under EU Clinical Trial Regulation 536/2014.

AESI reporting:

During screening, only AESI meeting seriousness criteria should be reported. During the treatment period, all AESI need to be reported to the Sponsor irrespective of causality within 24 hours. During the follow-up period, AESI need to be reported only if considered related to the study treatment except for all secondary malignancies which need to be reported as AESI irrespective of causality.

For all reportable AESI irrespective of their seriousness, SAE form will be completed and submitted to the sponsor within 24 hours.

10.1.7 Pregnancy reporting

For the requirements on pregnancy tests see Section 8.4.8, and for the requirements on contraception see Appendix 1.

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Sponsor using a pregnancy reporting form within 24 hours of learning of its occurrence until the end of follow-up period. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The newborn should be followed-up until one year after he/she was due to be born. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Lutathera treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should also be collected for the female partners of any males who received Lutathera in this study until the end of follow-up period. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

10.1.8 Reporting of study treatment errors including misuse/abuse

Neither overdose nor drug abuse/misuse are expected to be a concern with Lutathera, because it is administered by a trained clinician with appropriate prior training and provided as a single-dose, ready-to-use product containing a predefined amount of radioactivity.

Any AE/SAE/AESI in connection with radiation overdose must be reported as per the general reporting rules.

10.1.9 Reporting rules: summary

The below table summarize all reporting rules and timeframes for safety data reporting (SAE form) to sponsor global safety database described in the above sections:

Table 10-2 Reporting rules and timeframe

Event	During Screening	During Treatment period	During Follow-up period	Reporting timeframe
Non-serious AEs	Not reported	Not reported	Not reported	Not applicable
SAEs	Only SAEs potentially related to any study procedure	All SAEs, regardless of causality, until 8 weeks + 30 days after last dose	SAEs to be reported only if the investigator suspects a causal relationship to study treatment	Within 24 hours of awareness
AESI	Only if SAE, see above	All AESI irrespective of causality	AESI to be reported only if considered related to the study treatment except for all secondary malignancies which need to be reported as AESI irrespective of causality	Within 24 hours of awareness
Pregnancy	To be reported	To be reported	To be reported	within 24 hours of awareness

10.2 Additional Safety Monitoring

10.2.1 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be commissioned by the Sponsor to evaluate accumulating safety and dosimetry data in patients enrolled in the study, to ensure the safety of the patients in the study, and to provide recommendations to investigators and to the clinical teams in charge of conducting the study.

The DSMB will comprise one or several experts in the field of oncology, pediatrics and nuclear medicine. All DSMB members will disclose their financial interests to the sponsor. The DSMB will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DSMB will assess at defined intervals the progress of the clinical trial, including safety and dosimetry data for individual patients if applicable, and recommend to the sponsor whether to continue, modify, or terminate a trial. In addition, the DSMB might take decisions for treatment continuation of individual patients.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DSMB reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DSMB.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Sponsor personnel (and/or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by the Sponsor.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Sponsor representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Sponsor employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

Continuous remote monitoring of each site's data may be performed by the Sponsor or a delegated CRO. Additionally, a central analytics organization may analyze data & identify

risks & trends for site operational parameters and provide reports to Sponsor clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Sponsor monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

The data will be analyzed by the Sponsor and/or designated CRO.

All statistical analyses will be descriptive in nature and will include summaries and graphical presentations of data. No statistical hypothesis will be tested.

Missing data will not be replaced in this study.

Interim analyses will be performed to evaluate dosimetry and safety when at least five patients (including at least two GEP-NET patients) have completed at least one cycle. The data from all completed treatment cycles will be presented. Analysis will be presented across both indications, as well as for GEP-NET and PPGL separately.

The primary analysis will be conducted after at least 8 patients (including at least 3 GEP-NET patients) have completed the first cycle (cut-off before the second dose of Lutathera), at which time both dosimetry and safety assessments of the first cycle will be complete for the assessment of the primary objective. Should the dosimetry assessments be done at a further cycle instead of first cycle, the primary analysis will be done after the dosimetry assessments are performed. All data available at the time of primary analysis will be used for the assessment of the primary and secondary objectives, including analysis of the GEP-NETs and PPGLs as a pooled cohort [redacted]

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

Any data analysis carried out independently by the investigator should be submitted to Sponsor before publication or presentation.

12.1 Analysis sets

The full analysis set (FAS) will include all participants that received at least one dose of Lutathera and will thus be equivalent to the safety analysis set (SAF).

The Dosimetry and PK analysis set will include all participants with at least one available valid (i.e. not flagged for exclusion) dosimetry measurement, who received at least one dose of Lutathera and have no protocol deviations that have an impact on dosimetry data.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for all participants for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term for all participants.

12.3 Treatments

The FAS will be used for the analyses below.

The cumulative dose (MBq) will be summarized by means of descriptive statistics. The number of subjects who have dose reductions, permanent discontinuations or interruptions, and the reasons will also be summarized.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system for all participants.

12.4 Analysis of the primary endpoints

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

12.4.1 Definition of primary endpoints

Dosimetry

The analysis of dosimetry primary endpoint will consist of descriptive summaries and graphical presentations of the derived parameters. The Lutathera dosimetry and absorbed dose in critical organs (e.g. kidney, bone marrow) will be determined from Time activity Curves (TACs). Regions of interest (ROI) will be drawn around the organs of interest in the acquired images and relative radiotracer uptake will be calculated as a percentage (or fraction) of the injected dose per gram of tissue at each timepoint. Blood data will be also collected by measuring (by gamma-counter) the radioactivity of the blood samples withdrawn at the different time points. Tissue activity curves (ACs) will be generated by fitting mono or multi- exponential equations to the organ uptake and blood data.

By integrating such time-activity curve, the Time Integrated Activity Coefficients (TIACs) will be obtained. The TIACs from each organ will be processed by Olinda/EXM software for the calculation of the organ absorbed radiation doses.

Safety

Adverse events and laboratory toxicities occurring during the first cycle of treatment are also considered primary endpoints and the results for GEP-NETs and PPGLs as pooled cohort will be summarized descriptively as defined in Section 12.5.2 to evaluate the acute toxicities induced by a single full-dose Lutathera infusion (7.4 GBq).

12.4.2 Statistical model, hypothesis, and method of analysis

All analyses will be reported descriptively. No statistical hypothesis testing will be performed.

12.4.3 Handling of missing values

Missing data will not be replaced.

The censoring rules will be described in the Statistical Analysis Plan (SAP).

12.5 Analysis of secondary endpoints

12.5.1 Comparative assessment of Dosimetry/PK in adolescents and adults

Pharmacokinetic and the dosimetry data will be collected from the adolescent population and assessed in the context of previously derived adult data. Adolescent pharmacokinetic parameters including (Cmax and AUC_{0-24}) will be compared to those parameters derived from the adult population, to ensure that adolescent values lie within those estimates determined from the adult population. In a similar manner the individual derived dosimetry data from the adolescent patients will be compared to the adult values to ensure that estimates lie within the intervals derived from the adult population. Other methods may also be applied if deemed valuable in the assessment of the adolescent data.

Model based assessments of the individual dosimetry values in light of the individual adolescent creatinine clearance and dose may also be undertaken for comparative purposes.

All adolescent dosimetry and pharmacokinetic data will be pooled and analyzed collectively to ensure covariate effects including age and weight are of limited value in dosimetry prediction. In this way it can be ensured that the pediatric population is adequately characterised by the adult population.

A difference in biodistribution between patients with GEP-NET and PPGL is generally not anticipated, as disease normally does not affect the uptake in organs and normal tissues and thus estimates of absorbed dose. The review of the preliminary dosimetry and safety data already obtained from this study shows a good concordance between adolescent and adult dosimetry patients in line with this hypothesis.

12.5.2 Safety endpoints

For all safety analyses, the FAS will be used. All listings and tables will be presented for all GEP-NET and PPGL participants as a pooled cohort.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries) and long-term safety assessments which will be summarized separately. In addition, a separate summary for death including on treatment and post treatment deaths will

be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to 56 days after the date of the last actual administration of Lutathera.

Adverse events

All information obtained on adverse events will be displayed by participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by primary system organ class and preferred term.
- by primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment.

The number (and proportion) of participants with adverse events of special interest as defined in Section 10.1.5 will also be summarized.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by participant, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by visit/time.

12-lead ECG

1. PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted locally.
2. Categorical Analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these participants will be produced.

All ECG data will be listed by treatment group, participant and visit/time, abnormalities will be flagged. Summary statistics will be provided by visit/time.

Clinical laboratory evaluations

All laboratory data including safety biomarkers will be listed by participant, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

[redacted]

12.7 Interim analyses

For the interim analysis, population pharmacokinetics (PK) and dosimetry models developed based on adult patients will be used to support justification of adolescent population dose by pooling both GEP-NET and PPGL cohort data. Population PK model will be used to derive adolescent PK metrics (i.e. AUC, Caverage), and assess the similarity of exposure in adolescent population as compared to adult PK. Influence of patient baseline characteristics [redacted] on the PK will also be explored. Adult [redacted] and bone marrow will be used to assess the similarity of E-R relationship between dose and dosimetry for adolescent as compared to that for adults. Dosimetry data pooling from GEP-NET and PPGL cohorts, in relation to the adolescent specific creatinine clearance values and other baseline characteristics [redacted] will be explored to confirm that a dose of 7.4 GBq over four cycles would give a median dosimetry value for kidney less than 29 Gy and a median dosimetry value for bone marrow less than 2 Gy.

12.8 Sample size calculation

No formal sample size or power calculations were made in the context of this safety study. The overall sample size of 8 patients (with a minimum of 3 GEP-NET patients) is deemed sufficient to confirm similar organ dosimetry results in the adolescent population compared to the ones in adults.

Modelling and simulation analysis shows that a mean (standard deviation) of the absorbed dose in the kidney of approximately 18 Gy (SD 8) is expected in the adolescent population (Section 4.2). Assuming a standard deviation of 8, a sample size of 8 patients will produce a two-sided 95% confidence interval with a distance from the mean to the limits that is equal to 6.688.

Additionally, a sample size of 8 patients produces an adequate probability of observing acute toxicities (See Table 12-1). Indeed, in the phase III NETTER-1 study grade 3/4 adverse drug reactions related to Lutathera treatment were observed in 30% of patients. The probability to detect similar events assuming a true incidence rate of 30% in this study population is 94.2% with 8 patients.

Table 12-1 Likelihood of observing at least one patient with acute toxicity for a sample size of 8 patients and incidence of acute toxicities

Sample size	Acute toxicities true incidence rate, %				
	10%	20%	30%	40%	50%
8	57.0	83.2	94.2	98.3	99.6

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Sponsor monitors, auditors, Sponsor Quality Assurance representatives, designated agents of The Sponsor, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform The Sponsor immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT or CTIS public website. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Sponsor clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT, CTIS public website etc).

The Sponsor follows the ICMJE authorship guidelines (www.icmje.org). Authors (including Sponsor associates who may qualify for authorship), must therefore satisfy all of the following ICMJE authorship criteria:

1. Substantial contributions to conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The key principles that will be followed for Advanced Accelerator Applications-sponsored, research-related publications are:

- Advanced Accelerator Applications supports the publication of study results for its innovative medicines in a timely manner, whatever their outcome. Advanced Accelerator Applications policy is not to withhold, veto or suppress data. However, due consideration must be given to the rights of Advanced Accelerator Applications to protect confidential and/or patentable information, and to the protection of personal information, in particular patient privacy.
- Review by Advanced Accelerator Applications of draft publications by clinical investigators in advance of submission/presentation of publication is designed to:
    - Confirm the accuracy of the data
    - Verify that proprietary information is not being inadvertently disclosed
    - Secure intellectual property rights, as needed
    - Provide any relevant supplementary information
- Publication of partial data (unless planned in the protocol) is discouraged. As a matter of scientific rigor and fairness to all investigators involved in a clinical study, and in accordance with the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature, issued by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), European Federation of Pharmaceutical Industries and Associations (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA), and Pharmaceutical Research and Manufacturers of America (PhRMA), it is Advanced Accelerator Applications policy for multicenter clinical studies that:
- The first publication in a journal, or a presentation at a congress, be based on consolidated data from all centers, analyzed as stipulated by the protocol and agreed upon by investigators before trial initiation.
- Multicenter trials are designed to take full account of data accumulated from all centers (sample sized, powered with appropriate error rates), and Advanced Accelerator Applications discourages presenting or publishing data gathered from a single, or small group of centers, unless agreed to by study investigators (e.g., Study Steering Committee) and Advanced Accelerator Applications. Center specific analyses have greater variability and lead to exaggerated observed-treatment effects that are inherently less reliable. Valid conclusions regarding the primary endpoint of a clinical trial can only be based on the analyses predefined by the protocol.
- Study results should be published according to the contracted protocol agreements.

13.4 Quality Control and Quality Assurance

The Sponsor maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and The Sponsor systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk-based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Sponsor processes.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

13.5 Data Protection

Participants will be assigned a unique identifier by Sponsor. Any participant records or datasets that are transferred to Sponsor will contain the identifier only: participant's name or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his/her data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Sponsor has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Sponsor and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Sponsor and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

Due to the ongoing COVID-19 pandemic during the conduction of this study, protocol deviations related to COVID-19 in the given time period will be documented as applicable and an explanation will be provided in the clinical study report (CSR) that this was attributed to the coronavirus outbreak.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Sponsor, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Sponsor should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1 – Requirements for contraception

Based on its mechanism of action, Lutathera can cause fetal harm when administered to a pregnant woman. Female patients of child-bearing potential, defined as all female patients physiologically capable of becoming pregnant (i.e. female adolescent patients who are menarchal or who become menarchal during the study), cannot participate in this study, unless they are using highly effective methods of contraception during treatment and for 7 months after the last dose of Lutathera according to Lutathera Investigator's Brochure version 17. If local regulations deviate from the listed contraception methods to prevent pregnancy, local regulations apply and will be described in the ICF.

Female patients of child-bearing potential, who are or might become sexually active, must be informed of the need to prevent pregnancy during the study.

According to CTFG guidance, highly effective contraception methods those methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
- Total sexual abstinence. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

In case of use of oral contraception female patients should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Female patients are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks

ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child-bearing potential.

Sexually active male patients must agree with following requirements:

- remain abstinent (refrain from heterosexual intercourse) or be willing to use condoms and highly effective methods of contraception with female partners of childbearing potential, and to use condoms with pregnant female partners (see above) during the treatment period and for at least 4 months after the last dose of Lutathera.
- refrain from donating sperm during this same period.

The decision on the contraceptive method should be reviewed with each patient at least every 3 months to evaluate the individual need and compatibility of the method chosen.

For requirements on pregnancy tests in the study see Section 8.4.8, and for requirements on pregnancy reporting see Section 10.1.7.

16.2 Appendix 2 – Radioprotection Precautions for Treated with Lutathera lutetium Lu 177 dotatate/ lutetium (^{177}Lu) oxodotreotide

Based on radiation exposure calculations employing whole body clearance data (Wehrmann C et al, 2007) and exposure rates at one meter at 24 h (7.5 ± 3.6 µSv/h, Dpt. of Nucl. Med. Erasmus MC Rotterdam), patients may be treated on an outpatient basis for an administration of 7.4 GBq of Lutathera. As a precaution, it is recommended that patients be kept in radiation isolation for a period of 4 – 5 hours following administration, and be allowed to urinate during that time, and before release. This precaution is deemed prudent because this is the route of Lutathera elimination (approximately 50% of Lutathera eliminated by urination within the first 6 hours; Kwekkeboom et al, 2001). At the time of release, the patient is given written instructions which summarize the precautions to take, in order to keep the exposure to others below regulatory limits.

16.3 Appendix 3 – National Cancer Institute Common Terminology Criteria for Adverse Events

National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) will be used for assessing the severity of adverse events and laboratory toxicities in this study. For the actual CTCAE guide, please refer to the following website: [*://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf]*