Clinical Development

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 - NETTER-P

Statistical Analysis Plan (SAP) – Amendment 2

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
10-Feb-2022	Prior to DB lock	Creation of the final version	N/A - First version	NA
25-May-2023	Prior to DB lock	Incorporate protocol amendment v 2.0.	Updated abbreviations	List of abbreviations
			Minor grammatical updates	Throughout document
			Add language for interim analysis	1 Introduction
			Language added for maximum PPGL population	1.1 Study Design
			Added statement about delivery of safety summaries dependent on available data	2.6 Safety Analyses
			Added additional safety language to support AESIs pulled from eCRS	2.6.1.1 Adverse events of special interest/ grouping of AEs
			[redacted]	
			Added sample size and justification for interim analysis	3 Sample Size
26-mar-2024	Prior to primary DB lock	Incorporate protocol amendment v 3.0.	Added that the primary analyses will be by pooled cohort instead of separate cohorts.	All sections
			Clarified that AESIs and SAEs during the short and long term follow-up will be listed only.	Section 2.6.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Laboratory assessments and vital signs will be performed cumulatively instead of separately by periods	Section 2.6.4 and 2.6.5.2
			[redacted]	[redacted]
			[redacted]	[redacted]

Table of contents

List of tables

List of Figures

List of abbreviations

AA	Amino Acid
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
bpm	beats per minute
BOR	Best Overall Response
cm	Centimeter
CI	Confidence Interval
CL	Clearance
CR	Complete Response
CRO	Clinical Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Common Terminology Criteria
DAS	Dosimetry Analysis Set
DI	Dose intensity
DOR	Duration of Response
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eCRS	Electronic Case Retrieval Sheet
FAS	Full Analysis Set
GBq	Gigabecquerel
GEP-NETs	Gastroenteropancreatic Neuroendocrine Tumors
Gy	Gray
HGLT	High level group terms
HLT	High level terms
IMP	Investigational Medicinal Product
kg	Kilogram
MBq	Megabecquerel
mCi	Millicurie
MedDRA	Medical Dictionary for Regulatory Activities
MIRD	Medical Internal Radiation Dose
MRI	Magnetic Resonance Imaging
NMQ	Novartis MedDRA queries
[redacted]	[redacted]

[redacted]	[redacted]
PDI	Planned Dose Intensity
[redacted]	[redacted]
PK	Pharmacokinetics
PKAS	Pharmacokinetics Analysis Set
PPGL	Pheochromocytoma and Paragangliomas
PR	Partial Response
PRRT	Peptide Receptor Radionuclide Therapy
PT	Preferred Term
RDI	Relative Dose Intensity
[redacted]	[redacted]
ROI	regions Of Interest
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SMQs	Standardized MedDRA queries
SOC	System Organ Class
SPECT	Single Photon Emission Computed Tomography
SRI	Somatostatin Receptor Imaging
SSTR	Somatostatin Receptor
TA	Tumor Assessment
TAC	Time-Activity Curve
TBL	Total Bilirubin
TIAC	Time Integrated Activity Coefficient
UNK	Unknown
ULN	Upper Limit of Normal
VPC	Visual Predictive Check
WBC	White blood cell(s)
WHO-DD	World Health Organization Drug Dictionary

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report(s) (CSR) of study CAAA601A32201, a multicenter open-label phase II study to evaluate safety and dosimetry of Lutathera in adolescent patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NET), pheochromocytoma and paragangliomas (PPGL). This SAP will support the CSRs for all analyses, including any interim, primary, and final analysis.

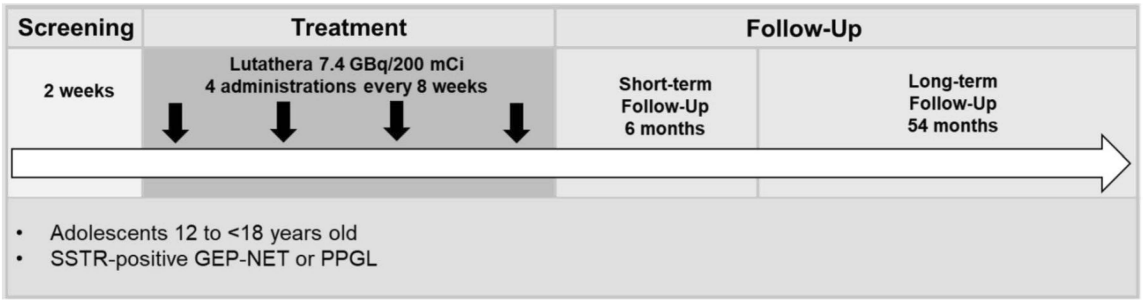
The content of this SAP is based on protocol CAAA601A32201 version 03 dated 14-Dec-2023. All decisions regarding analyses, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

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

The study schedule for each participant consists of the screening period (up to 2 weeks) followed by the treatment period (4 treatment administrations at 8-week (+/- 1 week) intervals), and the follow-up period (5 years).

Figure 1-1 - Study design



During the screening period of up to 2 weeks, participant 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 of the protocol.

Participants 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 participant 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 participant eligibility. Laboratory tests completed before the screening can be used for the assessment of participant eligibility if performed within 2 weeks prior to enrollment.

The treatment period will consist of 4 Lutathera treatments administered at 8 ± 1 week intervals. Lutathera administration will occur on Week 1 Day 1 of each cycle. Each participant 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 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.

For dosimetry assessments, SPECT/CT and whole Body images, urine and blood samples will be collected during the first week of the 1st Lutathera cycle as per Table 8-2 and Table 8-3 of the protocol, i.e. once during the study treatment period for each participant. The calculation of organ absorbed radiation dose, or dosimetry, after the 1st Lutathera administration will allow for estimation of the cumulative absorbed radiation dose from 4 Lutathera doses and for decision making on the next dose levels. In the exceptional circumstances when dosimetry cannot be performed in a particular participant 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. 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, as well as during the follow-up period. A set of safety biomarkers of growth and development, reproductive and endocrine function will be collected and analyzed for each patient.

[redacted]

Participants might need to stay overnight at the hospital or another facility for the day 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 participant's preference.

In order to minimize risk for each participant, an accelerated analysis of dosimetry and safety data will be performed, to enable the Investigator to take a decision for the subsequent Lutathera doses. The results of dosimetry calculations will be provided to the investigators for their evaluation prior to administration of subsequent therapeutic doses in each participant. See Section 6.5.1 of the protocol 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 participant 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 to evaluate long-term safety and efficacy.

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 of the protocol).

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. The interim analyses will be of a descriptive nature, and no statistical hypotheses will be tested.

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 participants. In case the last participant 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 follow-up or have withdrawn from the study.

1.2 Study objectives and endpoints

Table 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]	

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by Novartis/AAA and/or a designated clinical research organization (CRO). SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures and listings unless otherwise specified.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at each center, no center effect will be assessed.
Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.
Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum).

2.1.1 General definitions

Study drug

Study drug will refer to Lutathera® (lutetium Lu 177 dotatate/ lutetium (177Lu) oxodotreotide).

Study treatment

Study treatment will refer to Lutathera® (lutetium Lu 177 dotatate/ lutetium (177Lu) oxodotreotide) plus 2.5% Lys-Arg amino acid solution.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of study treatment was administered as per the Study Drug Administration CRF. The date of first administration of study treatment will also be referred as ***start of study treatment***.

Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a nonzero dose of study treatment was administered as per Dose Administration eCRF.

First cycle

The first cycle is from date of first study treatment administration up to 56 days after date of first administration, the day before the next administration or the day of study discontinuation, whichever comes first.

Study day

The study day describes the day of the event or assessment date relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference date for all assessments (safety, efficacy, dosimetry, etc) is the date of first administration of study treatment as defined above.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of first administration of study treatment is defined as the "baseline" assessment.

If patients have no value as defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

For adverse event reporting, the overall observation period will be divided into three mutually exclusive segments:

1. ***Screening period***: from day of patient's informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 56 days (i.e. 8 weeks) after date of last actual administration of study treatment (including start and stop date).
3. ***short-term follow-up period***: from day 57 after last administration of study treatment to day 183 (6 months) after date of last administration of study treatment
4. ***long-term follow-up period***: starting from day 184 after last administration of study treatment

Safety summaries (tables, figures) include data from either on-treatment, short-term and long-term follow-up periods cumulatively with the exception of selection period data or baseline data which will also be summarized where appropriate. 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) and specific listings of related SAEs and adverse events of special interest (AESI) will be provided for the short-term and long-term follow-up periods.

However, all safety data (including those from the short-term and long-term follow-up periods) will be listed and those collected during the short-term and long-term follow-up periods will be flagged.

Unscheduled visits

In general, by-visit summaries will be presented by the scheduled visits (visit number and corresponding visit name of planned clinical encounter). Visit windowing will not be used for handling unscheduled visits. Instead, all unscheduled visits will be assigned a visit name of "Unscheduled". Such visits will be included in data listings and will contribute to the derivation of best- or worst-case values where required. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

2.2 Analysis sets

Withdrawal of Informed Consent

Any data collected in the clinical database after a participant withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a participant withdraws full consent is recorded in the eCRF.

Full Analysis Set

The full analysis set (FAS) includes all participants who received at least one dose of Lutathera.

Safety Set

The safety set in this case is identical to the full analysis set.

Dosimetry analysis set

The dosimetry analysis set (DAS) consists of all patients who have at least one valid (i.e. not flagged for exclusion by the dosimetrist) dosimetry measurement. The DAS will be used for summaries (tables and figures) and listings of dosimetry data and modeling.

PK analysis set

The PK analysis set (PKAS) consists of all patients who have at least one valid (i.e. not flagged for exclusion) PK measurement. The PKAS will be used for summaries (tables and figures) and listings of PK data and modeling.

2.3 Patient disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by cancer type (i.e. separately for GEP-NET and PPGL patients) and all patients together. No inferential statistics will be provided.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by cancer type. Categorical data (e.g. gender, ethnicity and race) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height and body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum).

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following (when applicable for a specific cancer type): type of PPGL cancer (pheochromocytoma or paraganglioma), primary site of cancer, histological grade of GEP-NET (according to Ki-67 index), disease stage, tumor status for GEP-NET (functional vs non-functional), TNM criteria, presence of metastases, metastatic sites, primary origin, catecholamine secretion, chromaffin tissue, 123I-MIBG uptake, tumor category (non-hereditary, hereditary, unknown), time since initial diagnosis of primary disease, time since most recent relapse/progression, type of somastotatin receptor imaging and tumor uptake score.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF will be summarized and listed by cancer type. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities

(MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

Other

All data collected at baseline will be listed.

2.3.1 Patient disposition

The number (%) of participants included in the FAS will be presented overall and by cancer type. The number (%) of screened and not-treated participants and the reasons for screening failure will also be displayed. The number (%) of participants who discontinued the study phases and the reason for discontinuation will also be presented.

Protocol deviations

The number (%) of participants in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan) overall and by cancer type.

All protocol deviations will be listed.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized by cancer type.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The Safety Set will be used for all treatment summaries and listings unless otherwise specified. Summaries will be reported by cancer type (i.e. separately for GEP-NET and PPGL patients) and all patients together. No inferential statistics will be provided.

2.4.1 Study treatment / compliance

Cumulative dose

Cumulative dose of study treatment is defined as the total dose given during the study treatment exposure and will be summarized by cancer type.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the Dose Administration eCRF.

Duration of exposure

The duration of exposure in weeks is defined as (date of last administration of study treatment – date of first administration of study treatment + 8*7) / 7.

Dose intensity and relative dose intensity

Dose intensity (DI) for participants with non-zero duration of exposure is defined as follows:

DI (MBq / week) = Actual Cumulative dose (MBq) / Duration of exposure to study treatment (weeks).

Planned dose intensity (PDI) is defined as follows:

PDI (MBq / week) = Planned Cumulative dose (MBq) / Duration of exposure (weeks).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (MBq / week) / PDI (MBq / week).

Dose reductions, interruptions or permanent discontinuations

The number of subjects who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

Prior anti-cancer therapies are those therapies that started before the study treatment irrespective of when it ended. A therapy starting prior to the start of study treatment and continuing after the start of study treatment will be considered as both prior and concomitant.

The number and percentage of participants who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized by cancer type. Prior anti-neoplastic medications will be summarized by setting (e.g. adjuvant, metastatic, etc.) and also by lowest Anatomical Therapeutic Chemical (ATC) class and preferred term (PT).

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.

Anti-neoplastic medications will be coded using the World Health Organization Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class, preferred term by means of frequency counts and percentages using FAS.

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after

the date of first administration of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the WHO-DD and summarized by lowest ATC class and PT using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by System Organ Class (SOC) and PT. These summaries will include:

1. Medications starting on or after the date of first administration of study treatment but no later than 56 days after the date of last administration of study treatment and
2. Medications starting prior to the date of first administration of study treatment and continuing after the date of first administration of study treatment.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the date of first administration of study treatment or starting more than 56 days after the the date of last administration of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

2.5 Analysis of the primary objective

The primary objectives 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 PPGLs as a pooled cohort. Summaries will be reported by cancer type (i.e. separately for GEP-NET and PPGL patients) and all patients together.

2.5.1 Primary endpoint

Dosimetry

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

Safety

Adverse events and laboratory toxicities occurring during the first cycle of the GEP-NET and PPGLs as a pooled cohort are also considered as primary endpoints.

2.5.2 Statistical hypothesis, model, and method of analysis

No statistical hypothesis will be tested in the context of this descriptive study.

Dosimetry

The analysis of dosimetry primary endpoint will consist of descriptive summaries and graphical presentations of the absorbed radiation doses in the target organs (e.g. kidney, bone marrow).

Whole body planar, SPECT/CT imaging, blood and urine radioactivity data (measured by gamma-counter) will be used by the dosimetry vendor to calculate the absorbed radiation dose in the target organs.

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

Safety

Adverse events and laboratory toxicities occurring during the first cycle will be summarized descriptively to evaluate the acute toxicities induced by a single full-dose Lutathera infusion (7.4 GBq).

The following AE summaries will be produced based on the safety set for the first cycle of treatment:

- AEs regardless of study drug relationship by SOC, PT, and severity.
- AEs suspected to be study drug related by SOC, PT, and severity;
- SAEs regardless of study drug relationship by SOC, PT, and severity.
- SAEs suspected to be study drug related by SOC, PT, and severity;

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter):

- Worst post-baseline CTC grade (regardless of the baseline status). Each participant will be counted only for the worst grade observed during the first cycle post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value observed during the first cycle.
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value observed during the first cycle.

2.5.3 Handling of missing values/censoring/discontinuations

Missing data will not be replaced.

2.6 Safety analyses supporting secondary objectives

Safety evaluations on the safety analysis set will be based on the incidence, type, severity and consequences (e.g. study discontinuation) of an adverse event (AE) as well as on clinically significant changes in the patient's ECGs, vital signs, and clinical laboratory results. Summaries will be reported by cancer type [redacted] all patients together. Some summaries below may not be created for the short-term follow-up and long-term follow-up in either the interim or primary analysis if there is little safety data available.

2.6.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on-treatment period. Specific listings will also be presented for the SAEs and AESIs occurring during short-term and long-term follow-up. All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug (separately for AEs related to any study drug, related to Lutathera and related to amino acid solution), AE outcome etc. The starting period of

the AEs (screening period, on-treatment , short-term and long-term follow-up periods) will be flagged in the listings.

AEs will be summarized by number and percentage of participants having at least one AE, having at least one AE in each primary SOC and for each PT. AEs will be coded using the MedDRA and assessed according to the CTCAE version 5.0. A participant with multiple occurrences of an AE will be counted only once in the respective AE category. A participant with multiple CTCAE grades for the same PT will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables. In AE summaries, the primary SOC will be presented alphabetically, and the PTs will be sorted within primary SOC in descending frequency. The sort order for the PT will be based on their frequency in the total column.

The following AE summaries will be produced based on the FAS:

- Overview of adverse events and deaths (number and % of patients who died, with any AE, any SAE, any dose reductions/interruptions, any fatal SAEs, etc.);
- AEs regardless of study drug relationship by SOC, PT, and severity;
- AEs suspected to be study drug related by SOC, PT, and severity;
- AEs leading to discontinuation regardless of study drug relationship by SOC, PT, and severity;
- SAEs regardless of study drug relationship by SOC, PT, and severity;
- AEs leading to dose interruption/adjustment by SOC, PT, and severity;
- SAEs suspected to be study drug related by SOC, PT, and severity;

In addition, all AEs and SAEs with a start date in the short term and long-term follow-up will be listed separately.

2.6.1.1 Adverse events of special interest / grouping of AEs

During the treatment period, all AESIs are to be reported to the Sponsor irrespective of causality. During the follow-up period, AESIs are to be reported only if considered related to the study treatment except for all secondary malignancies which need to be reported as AESIs irrespective of causality. The AESIs represent main risks of Lutathera and amino acid treatment reported in adults, as well as potential risks in pediatric population.

The selection of the AESIs will be initially based on the classification of the AEs as reported in the Adverse Event eCRF page.

Additional groupings of AESIs above and beyond those flagged in the eCRF may also be examined in this study. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) or PTs. Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad.

The grouping of AEs in AESI according to project standards will be specified in the electronic Case Retrieval Strategy (eCRS) or separate listing in case of the AESI category is not included in the eCRS, and may be regularly updated.

All AESI categories will be summarized for those events occurring on-treatment. Events starting during the short-term and long-term follow-up periods will be listed.

2.6.2 Deaths

Separate summaries for on-treatment and all deaths (including short-term and long-term follow-up deaths) will be produced by the cause of death.

All deaths will be listed, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened participants.

2.6.3 EudraCT and clinicaltrials.gov requirements for AEs and Death summaries

For the legal requirements of clinicaltrials.gov and EudraCT, two on-treatment tables are required.

- On-treatment deaths resulting from SAEs suspected to be study drug related and SAEs regardless of study drug relationship by SOC and PT;
- Non-serious AEs regardless of study drug relationship, with an incidence rate greater than 5% in the respective cancer type by SOC and PT.

These summaries will include any events starting or worsening in the on-treatment period.

If for the same participant, several consecutive AEs (irrespectively of study treatment causality, seriousness, and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE;
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

The presence of at least one SAE / SAE suspected to be study drug related / non SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

2.6.4 Laboratory data

The routine laboratory tests are assessed locally at each investigational site. The summaries will include all on-treatment assessments available for the lab parameter collected no later than 56 days after the last study treatment administration date (see Section 2.1.1) as well as including all short-term and long-term assessments cumulatively in separate summaries.

The following summaries will be produced for hematology, biochemistry and urinalysis laboratory data as well as for safety biomarkers (by laboratory parameter):

- Worst on-treatment CTC grade (regardless of the baseline status). Each participant will be counted only for the worst grade observed on-treatment.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value.
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

These summaries will be repeated including the short-term and long-term follow-up periods, respectively.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the short-term and long-term follow-up periods will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) and alkaline phosphatase (ALP). The number (%) of participants with worst post-baseline values will be summarized:

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
  - TBL > 2xULN
  - ALT or AST > 3xULN & TBL > 2xULN
  - ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN

Of note, combined elevations (i.e. last 2 categories) are based on the peak values at any post-baseline time for a participant and thus do not need to be concurrent.

Liver function parameters will be listed, and periods of assessment (screening, on-treatment, short term and long term follow-up) will be flagged.

2.6.5 Other safety data

2.6.5.1 ECG and cardiac imaging data

12-lead ECGs including PR, QRS, QT, QTcF, and RR intervals will be obtained for each participant during the study. ECGs are reviewed locally by each investigative site and assessed centrally.

The summaries will include all on-treatment assessments available no later than 56 days after the last study treatment administration date (see Section 2.1.1).

The following summaries will be presented:

- Change from baseline for ECG parameters by timepoint.
- Number and percentage of patients with on-treatment notable ECG values.
  - QT or QTcF
    - New value of > 450 and ≤ 480 ms
    - New value of > 480 and ≤ 500 ms
    - New value of > 500 ms
    - Increase from baseline of > 30 ms to ≤ 60 ms
    - Increase from baseline of > 60 ms
  - HR (=60/RR in seconds)
    - Increase from baseline >25% and to a new HR > 100 bpm
    - Decrease from baseline >25% and to a new HR < 50 bpm
  - PR
    - Increase from baseline >25% and to a new PR > 200 ms
    - New PR > 200 ms
  - QRS
    - Increase from baseline >25% and to a new QRS > 120 ms
    - New QRS > 120 ms

ECG parameters will be listed, and periods of assessment will be flagged.

2.6.5.2 Vital signs

Vital signs assessments are performed in order to characterize basic body function. The following parameters will be collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg).

The summaries will include all on-treatment assessments available no later than 56 days after the last study treatment administration date (see Section 2.1.1) as well as including all short-term and long-term assessments cumulatively in separate summaries.

The number and percentage of participants with on-treatment notable vital sign values (high/low) will be presented.

Vital signs parameters will be listed, and periods of assessment (screening, on-treatment, short term and long term follow-up) will be flagged.

For analysis of vital signs, the clinically notable vital sign criteria are provided in Table 2-1 below.

Table 2-1 - Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase ≥20% from baseline	decrease ≥10% from baseline
Systolic blood pressure (mmHg)	≥180 with increase from baseline of ≥20	≤90 with decrease from baseline of ≥20
Diastolic blood pressure (mmHg)	≥105 with increase from baseline of ≥15	≤50 with decrease from baseline of ≥15
Pulse rate (bpm)	≥100 with increase from baseline of >25%	≤50 with decrease from baseline of > 25%

2.7 Pharmacokinetics and dosimetry analysis supporting secondary objectives

As part of the secondary objectives, PK and dosimetry data will be analysed in the context of the modeling and extrapolation performed using adult data (as detailed in the modeling report). The adult PK (radiolabel plasma concentrations) data was fitted to a two compartment model with a zero-order input and first-order elimination. The adult kidney and bone marrow dosimetry data were described by [redacted]

Plots of observed PK and dosimetry data from adolescent participants overlaid with predictions using the adult model will be first generated to evaluate if the pediatric population is adequately characterized by the model from the adult population. Adolescent PK parameters (e.g., CL, Cmax) will also be compared to those parameters derived from the adult population, to ensure that adolescent values lie within those estimates determined from the adult population. Other methods may also be applied if deemed valuable in the assessment of the adolescent data. These analyses will be based on the DAS and PKAS.

Then, pooled analyses using all adolescent and adult participants for dosimetry data will be performed. For that, parameters from the models will be re-estimated based on population-based non-linear mixed effects modeling using appropriate software. Covariates from the adult model (i.e., dose and creatinine clearance for dosimetry modeling) as well as other covariates such as age, weight and body surface area will be re-evaluated and inter-relationships re-assessed. Model qualification will use graphical methods, such as visual inspection of different diagnostic plots, precision of any parameter estimates (estimated +/- standard error), Visual Predictive Check (VPC) plots (stratified by adult and adolescent populations) as well as decreases in both between-subject variability and residual variability.

Further details on the PK and dosimetry modeling will be given in a separate modeling plan.

Finally, the following model-based PK parameters will be reported for each adolescent participant:

- AUCinf: area under the concentration time curve from 1st administration to infinity
- AUClast: Area under the concentration time curve from 1st administration to the last observed concentration
- Cmax: maximum blood concentration
- tmax: sampling time at which Cmax is reached
- CL: systemic clearance
- V1: Volume of distribution of the central compartment
- V2: Volume of distribution of the peripheral compartment
- Q2: Inter-compartmental clearance.

Other parameter estimates may be determined as deemed appropriate.

[redacted]

[redacted]

[redacted]

3 Sample size calculation

No formal sample size or power calculations were made in the context of this safety study.

For the interim analysis, the sample size is proposed to be a minimum of five patients across the GEP-NET and PPGL indications, including a minimum of 2 GEP-NET patients. Simulations from adult kidney and bone marrow dosimetry models suggested that a clinical trial that has enrolled between 5 and 10 subjects should have the ability to define the median dosimetry values without significant risk of exceeding pre-defined thresholds. Thus, 5 patients across indication should be acceptable.

Dosimetry at the organs of interest is the key measure in this study and is not expected to differ between PPGL and GEP-NET patients (confirmed by the preliminary data). Therefore, the data on PPGL patients will be included in the interim analysis both separately from GEP-NET and combined with GEP-NET to support the overall comparison between pediatric and adult patients. Safety data, to which PPGL patients will also contribute, will be supplemented with literature that provides further justification for the acceptability of this proposal.

For the primary analysis, the overall sample size of 8 participants is deemed sufficient to confirm similar organ dosimetry results in the adolescent population compared to the ones in adults.

Modeling 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. 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 3-1). 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 3-1 - Likelihood of observing at least one patient with acute toxicity for a sample size of 8 patients and incidence of acute toxicities

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

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 AE, ConMeds and safety assessment date imputation

Table 5-1 - Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  o Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

day	• If available month and year = month and year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  o Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 - Imputation of end dates (AE, CM)

Missing Element	**Rule** (*=last treatment date plus 56 days not > (death date, cut-off date, withdrawal of consent date))[1]
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*
1. if start date is > 56 last treatment date plus 56 days then use the same rules but the end date of the on-treatment period is defined as (death date, cut-off date, withdrawal of consent date)	

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

The above imputations are only used for analyses of duration of AEs and concomitant medications.

5.1.1.1 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date , then the evaluation is considered post-cut-off date and will be excluded from analysis.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The latest available version of the document based on the underlying CTCAE version 5.0 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE v5.0, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading

5.4 Statistical models

Kaplan-Meier estimates

An estimate of the survival function in each treatment group will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival for each treatment group will be obtained along with 80% confidence intervals calculated from PROC LIFETEST output using the method of (Brookmeyer and Crowley 1982). Kaplan-Meier estimates of the survival function with 80% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula (Collet 1994).

Special statistical methods

Confidence interval for response rate

Responses will be summarized in terms of percentage rates with $100(1-\alpha)\%$ confidence interval using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table (Clopper and Pearson 1934).

6 Reference

1. Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 - 41.
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3. Collet D (1994). Modelling survival data in medical research. London, Chapman & Hall.
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5. Klein, J. P. and Moeschberger, M. L. (1997), Survival Analysis: Techniques for Censored and Truncated Data, New York: Springer-Verlag.

6. Siegel JA, Thomas SR, Stubbs JB, et al. MIRD pamphlet no. 16: Techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose estimates. J Nucl Med 1999; 37S-61S.