Advanced Accelerator Applications

Research and Development

LYSAKARE®

Clinical Trial Protocol CAAA001A12401/ NCT04524442

A multicenter, open-label post authorization safety study to evaluate the effect of LysaKare® infusion on serum potassium levels in GEP-NET patients eligible for Lutathera® treatment

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List of abbreviations

^{90}Y	Yttrium-90
^{111}In	Indium-111
^{177}Lu	Lutetium-177
AAA	Advanced Accelerator Applications
AE	Adverse event
ALAT/ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ASAT/AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DOTA	1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraaacetic Acid
DTPA	Diethylene Triamine Pentaacetic Acid
EC	Ethics Committee
ECG	Electrocardiogram
E-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
GCP	Good Clinical Practice
GEP	Gastro-Entero-Pancreatic
Gy	Gray (unit of radiation exposure; equal to 100 rad)
h	Hours
Hb	Haemoglobin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethic Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
I.V.	Intravenous
LDH	Lactate Dehydrogenase
Lys-Arg	Lysine – Arginine
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter(s)
mmol	Millimole
NCI	National Cancer Institute (USA)
NET	Neuroendocrine Tumor

NYHA	New York Heart Association
PASS	Post-Authorization Safety Study
PI	Principal Investigator
PRRT	Peptide Receptor Radionuclide Therapy
QC	Quality Control
QMS	Quality Management System
SAE	Serious Adverse Event
SAF	Safety Set (SAF)
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reactions
WBC	White Blood Cells
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
GEP-NET	Gastroenteropancreatic neuroendocrine tumors a rare type of tumor that can form in the pancreas or in other parts of the gastrointestinal tract, including the stomach, small intestine, colon, rectum, and appendix. Neuroendocrine tumors arising in the lung are not considered GEP-NETs.
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study.
Study Phase	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, treatment, follow-up, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later.
Study treatment	Includes any drug or combination of drugs in any study treatment administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.

Withdrawal of consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Protocol synopsis

Protocol number	CAAA001A12401
Full Title	A multicenter, open-label post authorization safety study to evaluate the effect of LysaKare® infusion on serum potassium levels in GEP-NET patients eligible for Lutathera® treatment
Brief title	Post-Authorization Safety Study (PASS) of LysaKare® in adult GEP-NET patients.
Sponsor and Clinical Phase	Sponsored by Advanced Accelerator Applications (AAA), Phase IV PASS Study.
Purpose and rationale	This is a category 3 Post-Authorization Safety Study (PASS) following the European Medicines Agency (EMA) marketing authorization of LysaKare® 25g / 25g solution for infusion. LysaKare® is indicated for reduction of renal radiation exposure during peptide-receptor radionuclide therapy (PRRT) with lutetium (177Lu) oxodotreotide in adults. The marketing authorization was granted based on literature data from similar solutions, which have been used for >10 years in Europe (well established use application). The purpose of the study is to evaluate the effect of LysaKare® administration on serum potassium levels. A systematic assessment of serum potassium levels will be performed during infusion and up to 24 hours post start of infusion compared to baseline.
Primary Objective(s)	To assess the effect of LysaKare® administration on serum potassium concentration in GEP-NET patients eligible for Lutathera® treatment
Secondary Objectives	To confirm the safety profile of LysaKare® infusion in GEP-NET patients eligible for Lutathera® treatment without co-administration of Lutathera®
Study design	This is a multicenter, open-label post-authorization safety study (PASS). Approximately 45 patients (to have at least 25 patients evaluable for the primary endpoint) with GEP-NET will be enrolled to receive one infusion with LysaKare® to systematically assess the effect of LysaKare® administration on potassium blood level concentration up to 24 h compared to baseline. The study schedule for each patient consists of a screening period followed by an infusion day with an optional overnight in-clinic stay, and a follow up call. **Screening Phase**

	At screening, patient eligibility will be determined according to inclusion and exclusion criteria, with evaluation of patient's vital signs, ECG and laboratory parameters. The duration of screening can be as short as one day but should not exceed 7 days. Patients who show potassium level > 6 mmol/L at screening should have their potassium level corrected and can be re-screened afterwards. For Poland only, patients with potassium level > 5.5 mmol/L at screening should have their potassium level corrected and can be re-screened afterwards. **Treatment Phase** Eligible patients will be admitted to the in-clinic unit to be dosed with LysaKare® solution for infusion of 1,000 mL, which is administered intravenously over a period of 4 hours. Before the infusion (at 0 h time point), a set of baseline tests will be performed. During and after the infusion, patient condition will be monitored for evaluation of any adverse events. Patients will have an option to stay overnight in the clinic or can choose to leave after the 12 h assessment and return to the clinic for the 24 h assessments. All patients will be discharged from the unit after the completion of the 24 h assessments. Only patients with a potassium level of ≤ 6 mmol/L at screening will be allowed to be dosed. For Poland only, only patients with a potassium level of ≤ 5.5 mmol/L at screening will be allowed to be dosed. Potassium testing on the infusion day will be performed at 0 h (before the infusion), and at 2 h, 4 h, 6 h, 8 h, 12 h, and 24 h after the start of infusion. Vital signs and ECGs will be taken as specified in the assessment schedule. All patients will be monitored closely for signs and symptoms of hyperkalemia, e.g. dyspnoea, weakness, numbness, chest pain and cardiac manifestations (conduction abnormalities and cardiac arrhythmias). Patients should be instructed to drink substantial quantities of water (at least 1 glass every hour) on the day of infusion to remain hydrated and facilitate excretion of excess serum potassium. In case of signs and symptoms of hyperkalaemia, LysaKare® infusion must be stopped and appropriate corrective measures must be taken. Other common adverse reactions during LysaKare® administration are nausea and vomiting. Before the start of LysaKare® infusion, an

	intravenous bolus of an antiemetic medication should be given. The choice of the antiemetic drugs is at the discretion of the physician. **Follow-up Phase** All patients will be called for a safety follow-up in 48 hours after dosing. Patients should not be scheduled to receive repeat dosing with LysaKare® as concomitant medication with Lutathera® within 7 days of the LysaKare® infusion in the study.
Population	Male and female patients that are 18 years or older diagnosed with SSTR positive GEP-NET and meet the criteria for treatment with Lutathera®.
Inclusion criteria	1. Male or female patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs), who are eligible for the treatment with Lutathera® as per Lutathera® label indication. 2. Age ≥18 years. 3. Patients who have provided a signed informed consent form to participate in the study, obtained prior to the start of any protocol related procedures.
Exclusion criteria	1. Pre-existing hyperkalemia (>6.0 mmol/L at screening) if not adequately corrected before starting the LysaKare® infusion. For Poland only, pre-existing hyperkalemia (> 5.5 mmol/L at screening) if not adequately corrected before starting the LysaKare® infusion. 2. Instances when Lutathera® is not recommended per the Lutathera® SmPC: a. Uncontrolled congestive heart failure (NYHA III, IV); b. Kidney failure with creatinine clearance < 50 mL/min calculated by the Cockroft Gault method; c. Impaired haematological function with either Hb < 4.9 mmol/L (8 g/dL), platelets < 75 G/L ($75x10^3/mm^3$), or leucocytes < 2 G/L ($2,000/mm^3$) (except lymphopenia); d. Liver impairment with either total bilirubinemia > 3 times the upper limit of normal or albuminemia < 30 g/L and prothrombin ratio decreased < 70%. 3. Pregnancy or lactation, positive pregnancy test at screening or pre-dose based on the contraindication for Lutathera®. 4. Hypersensitivity to the IMP active substances.

	5. Any significant medical or social condition which may interfere with the subject's ability to comply with the study visit schedule or the study assessments. 6. Patients who have received any investigational agent within the last 30 days. 7. Patients that have received a dose of Lutathera® prior to the screening visit or are scheduled for Peptide Receptor Repeat (PRRT) treatment within 7 days of the study infusion of LysaKare®.
Study treatment	In this study, approximately 45 patients (to have at least 25 patients evaluable for the primary endpoint) with GEP-NET will receive an infusion with LysaKare® solution. This is a single-arm open-label safety study and no comparator or randomization will be used. The investigational drug LysaKare® will be provided in infusion bags, with one 1,000 mL bag containing 25 g of L-arginine hydrochloride and 25 g of L-lysine hydrochloride. LysaKare® will be administered over a period of 4 hours, via peripheral vein infusion at a constant infusion rate of 250 mL/h through a pump or any other infusion system. During the infusion patients are allowed to void. Antiemetics or any other supportive medications will not be supplied by the Sponsor.
Key safety assessments	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 follow-up call (48 hours after infusion). Safety laboratory parameters, vital sign measurements and ECG recordings will be taken at pre-defined time points.
Data analysis	The primary endpoint is the change in serum potassium levels after LysaKare® IV administration compared to baseline. In the only published study assessing hourly potassium changes in 11 patients treated with a 2.5 % Lysine – Arginine solution, peak concentration was observed at 2-4 h post-baseline, the mean baseline level was 4.2 mmol/L, mean increase at 2 h was 0.6 mmol/L and at 4 h it was 0.9 mmol/L (SD=0.3) the maximum increase was 1.5 mmol/L (Krenning 2000). The mild increase in potassium levels did not manifest in any safety issues or clinically significant events. The primary endpoint analysis and sample size considerations are based on the information. The current study is descriptive in nature, and no hypothesis will be tested for the study endpoints. The study will describe and analyze various parameters related to potassium concentration, including mean change, maximum change, time to the maximum change, and the overall dynamics of the concentration curve during and after the LysaKare® infusion.

	In order to calculate the sample size for the study, initially a requirement was chosen that the length of the 95% confidence interval of the mean change from baseline to 4h does not exceed 0.2 mmol/L at an observed historical standard deviation of 0.3. With a targeted minimum of 25 subjects evaluable for this endpoint, the length of this confidence interval is maintained with a slight increase to 0.25 mmol/L. The safety data analysis will be presented with special focus on LysaKare® related treatment emergent events and will be applied to the full Safety Set. Changes in Vital Signs and ECG will be summarized by time. Changes in laboratory parameters (Haematology and Blood Chemistry) will be described by time.
Key words	LysaKare®, amino acid, GEP-NET, PRRT, Lutathera®

Version history

Version Number	Description
Global protocol v00 dated 12-Nov-2019	Initial global protocol. Approved in all countries.
Local protocol v00 PL.01 dated 18-May-2021	Local amended protocol from v00. Approved in Poland
Global protocol v01 dated 01-Dec-2022	Amended global protocol from v00 and local protocol v00-PL.01 dated 18-May-2021

Protocol Amendment 01

As of 08 November 2022, 30 patients were enrolled into the study and received an infusion of LysaKare®.

Amendment rationale

The primary purpose of this amendment is to provide clarification on the sampling requirements for laboratory assessments. The Sponsor identified discrepancies in sampling used for electrolytes which were not performed as per protocol requested procedures. This resulted in samples collected with heparinized blood (2 patients) and whole blood (11 patients) instead of serum sampling across 4 sites. Therefore, the Visit Schedule and assessments in Section 8 have been updated to clarify the requirements of laboratory assessments.

Furthermore, as the potassium levels measured in serum differ from those measured in the heparinized blood or whole blood, the discrepant measurements cannot be used for the assessment of the primary endpoint “change in serum potassium levels at specified time points after LysaKare® IV administration compared to baseline.” Therefore, the target enrollment number has been revised from “40” to “approximately 45” to ensure at least 25 patients have valid data to fulfill the study primary objective, which is to assess the effect of LysaKare® administration on serum potassium concentrations in GEP-NET patients eligible for Lutathera® treatment. For those participants with potassium levels not measured in serum, other collected data (e.g. AEs, ECG, other laboratory tests) will still be used to assess the secondary endpoint “to confirm the safety profile of LysaKare® infusion in GEP-NET patients eligible for Lutathera® treatment without co-administration of Lutathera®.”

This protocol amendment also incorporates the changes made in Poland local protocol amendment v00-PL.01 dated 18-May-2021.

Changes to the protocol

- Protocol synopsis, Section 3 Study Design, Section 6 Treatment: revised from 40 patients to approximately 45 patients (to have at least 25 evaluable for the primary endpoint).
- Protocol synopsis, Section 3.1 Screening phase, Section 3.2 Treatment phase, Exclusion criteria #1: For Poland only, added required hyperkalemia level > 5.5mmol/L per local protocol amendment.
- Section 3.2 Treatment phase, Section 4.3 Risks and benefits, Section 6.3.2 Dose discontinuation: Added text "in the occurrence of severe renal insufficiency referral to hemodialysis unit should be considered per investigator discretion."
- Table 8-1: Updated to clarify the requirements for chemistry and electrolyte testing using serum, for venous blood gas and antiemetic administration. Added text: The same sampling methodology should be used at all time points for consistency. **Before "LysaKare® infusion, an intravenous bolus of an antiemetic should be given. The choice of antiemetic drugs is at the discretion of the physician."
- Section 8.4.2 Laboratory Assessments: Added text detailing the tests and time-points where serum sampling is required. Added text "Samples must be processed and analyzed as soon as possible to avoid degradation."
- Table 8-2: Updated to split haematology and chemistry testing and highlight assessments requiring serum sampling.
- Section 9.1.2 Replacement policy: included reference to serum.
- Section 10.1.1 Adverse Events: Deleted duplicate sentence "The investigator has the responsibility for managing the safety of individual subject and identifying adverse events".
- Section 10.1.5 SAE reporting: Based on latest guidance, added text regarding SAE reporting timelines "immediately without undue delay and under no circumstances later than" 24 hours of learning of its occurrence.
- Section 10.1.6 Pregnancy reporting: Based on latest guidance, added text regarding pregnancy reporting timelines "immediately without undue delay and under no circumstances later than" 24 hours of learning of its occurrence "by using the Pregnancy form".
- Section 12.1 Analysis sets: Added reference to evaluable serum potassium levels for the primary endpoint.
- Section 12.4.1 Definition of primary endpoint(s): Updated the language to further define primary estimand.
- Section 12.4.2 Statistical model, hypothesis, and method of analysis: Added clarification about primary endpoint evaluation and handling of non-serum potassium levels.
- Section 12.8 Sample size calculation: Added text regarding required minimum number of evaluable subjects.

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 do NOT affect the Informed Consent.

Sponsor protocol signature page

Signatures on this page denote approval of the study protocol outline by the respective Sponsor Department

Role	Name and contact	Date & Signature
[redacted]	[redacted] MD [redacted] Tel: [redacted]	[redacted] Digitally signed by [redacted] DN: dc=com, dc=novartis, ou=people, ou=GD, serialNumber=868563, cn=[redacted] Reason: I am approving this document Date: 2022.12.01 13:37:45 -05'00'
[redacted]	[redacted] [redacted] Tel: [redacted]	[redacted] Digitally signed by [redacted] DN: dc=com, dc=novartis, ou=people, ou=GD, serialNumber=1442651, cn=[redacted] Reason: I am approving this document Date: 2022.12.02 09:15:47 +01'00'
[redacted]	[redacted] [redacted] Tel: [redacted]	[redacted] Digitally signed by [redacted] DN: dc=com, dc=novartis, ou=[redacted] serialNumber=1028236, cn=[redacted] Reason: I am approving this document Date: 2022.12.06 09:05:27 +01'00'
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[redacted]	[redacted] [redacted] Tel: [redacted]	[redacted] Digitally signed by [redacted] DN: dc=com, dc=novartis, ou=people, ou=GD, serialNumber=2241687, cn=[redacted] Reason: I have reviewed this document Date: 2022.12.02 14:29:47 +01'00'

Investigator approval signatures page

Clinical Trial Protocol CAAA001A12401

Protocol version and release date: Version 01, 01-Dec-2022

Investigator signature

I have read the protocol and agree to conduct this trial in accordance with all stipulations of the protocol, with applicable laws and regulations and in accordance with the ethical principles outlined in the Declaration of Helsinki.

Investigator	Signature	Date

Center name and address:

_____

Center name:

_____

Address:

_____

1 Introduction

1.1 Background

Lutathera® is the first approved peptide receptor radionuclide therapy (PRRT) in the EU. The approved indication, treatment of somatostatin receptor (SSTR)-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults, is based on the results of the NETTER-1 study in midgut NET, and the Erasmus MC study, which included a wide range of SSTR-positive NET patients, and thus supported the broad indication in GEP-NET, an Orphan disease.

Similar to other PRRT drugs, Lutathera® has partial retention in the kidneys, which increases the risk of renal injury and also limits the amount of effective radioactivity that can be administered to patients. The renal toxicity caused by radiation is well known both from external beam radiation data and from early PRRT studies (Bodei 2008, Kwekkeboom 2009, Bodei 2011). High radiation doses to the kidney can result in variable deterioration of the renal function including organ failure. For this reason, and to maximise the potential benefits of Lutathera®, concomitant renal-protection measures using amino acid (AA) solutions are now a routine practice.

Since Lutathera® requires the co-administration of an AA solution, the pharmaceutical development of LysaKare® has been conducted following discussions with regulators in the context of the Lutathera® marketing authorization application, where the Applicant was encouraged to develop a lysine – arginine (Lys-Arg) solution similar to the one used in the Erasmus MC study, which treated 1214 patients. While commercial AA solutions are available (for different indications, mainly for parenteral nutrition), and have been used in the NETTER-1 study (randomized study in SSTR-positive midgut NET patients, and pivotal evidence of the Lutathera MA, with 112 patients treated in the Lutathera arm), the tolerability of the compounded 2.5% Lys-Arg solution used in the Erasmus MC study was found to be markedly better in terms of nausea and vomiting. However, compounding AA solutions in hospitals may be associated with variable quality and/or sterility, thereby confirming the unmet need for a commercial 2.5% Lys-Arg solution to be administered in combination with Lutathera®.

LysaKare® (LysaKare SmPC) an AA solution indicated solely for the use with Lutathera® (Lutathera SmPC) with the goal to protect the kidneys from renal radiation exposure, has been approved in Europe on 25 July 2019.

It has been shown that treatment with amino acid solutions, including LysaKare®, could be associated with a risk of hyperkalemia. Increased serum potassium levels are generally transient and typically return to near baseline within 24 hours (Giovacchini 2011, Lapa 2014a, Lapa 2014b). Data reported on 2.5 % Lys-Arg solution (Krenning 2000) show that serum potassium levels gradually increased after the start of the infusion and reached a maximum between 2 and 4 hours. The increase in potassium levels was mild and did not manifest in any safety issues or clinically significant events. At 5 hours, the potassium levels appear to plateau/decrease and then decline back to baseline values.

No controlled clinical trials have been conducted with LysaKare® to assess its effect on serum potassium level. Therefore, there is a need to systematically assess the impact of LysaKare® on serum potassium levels in the GEP-NET patient population in a dedicated clinical trial.

1.2 Purpose

This is a category 3 Post-Authorization Safety Study (PASS) following the European Medicines Agency (EMA) marketing authorization for LysaKare® 25g / 25 g solution infusion. LysaKare® is indicated for reduction of renal radiation exposure during peptide-receptor radionuclide therapy (PRRT) with lutetium (^{177} Lu) oxodotreotide in adults. The marketing authorization was granted based on literature data from similar solutions which have been used for > 10 years in Europe (well established use application).

The purpose of this study is to evaluate the effect of LysaKare® administration on serum potassium levels. A systematic assessment of serum potassium levels will be performed during infusion and up to 24 hours post start of infusion compared to baseline.

2 Objectives and endpoints

The primary and secondary objectives of the study and endpoints are described in Table 2-1.

Table 2-1. Study objectives and endpoints

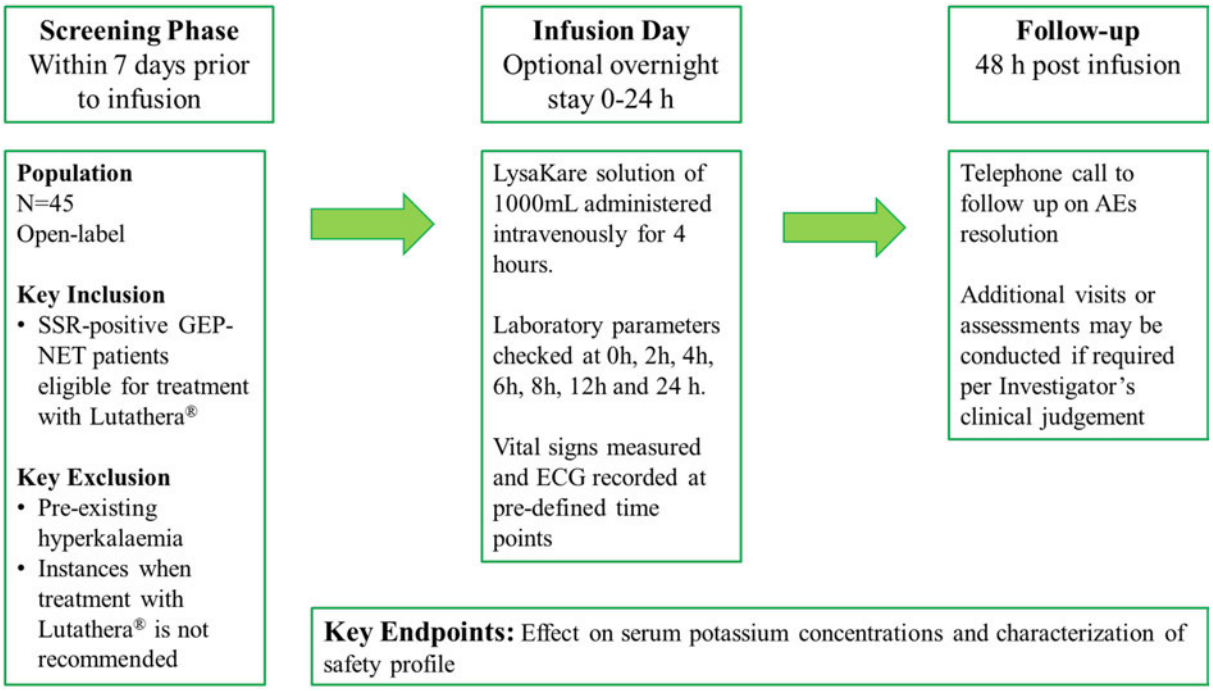
Primary Objective	**Endpoint for primary objective**
To assess the effect of LysaKare® administration on serum potassium concentrations in GEP-NET patients eligible for Lutathera® treatment	Change in serum potassium levels at specified time points after LysaKare® IV administration compared to baseline.
Secondary Objectives	**Endpoints for key secondary objectives**
To characterize the safety profile on LysaKare® infusion in GEP-NET patients eligible for Lutathera® treatment, without co-administration of Lutathera®	• Incidence of LysaKare® related adverse events • Changes in vital signs and ECG parameters • Change in laboratory parameters

3 Study design

This is a multicenter, open-label PASS. Approximately45 patients (to have at least 25 patients evaluable for the primary endpoint) with SSTR-positive GEP-NET will be enrolled to receive an infusion with LysaKare® to determine the effect on serum potassium levels.

The study schedule for each patient consists of a screening period followed by an infusion day with an optional overnight in-clinic stay, and a follow up call 48 h post infusion.

Figure 3-1 Study Design



The primary endpoint of the study is change in the serum potassium levels at specified time points after LysaKare® IV administration compared to baseline. The primary analysis will be performed after the last enrolled patient has completed the follow-up phone contact after LysaKare® infusion.

The study consists of a Screening Phase, a Treatment Period and a Follow-up phone contact.

3.1 Screening Phase

The screening should occur no less than 24 hours and no more than 7 days before the scheduled infusion with LysaKare®.

Patients must not receive a dose of PRRT, including Lutathera® any time before screening visit or any investigational agents within 30 days of the infusion date.

Patients must have known diagnosis with somatostatin receptor positive GEP-NET disease and meet the guidelines for treatment with Lutathera®.

All assessments will be performed locally, including all laboratory assessments and ECG readings.

Laboratory parameters can be re-evaluated within 7 days of the initial screening visit if the laboratory selection criteria were not met. Any patient who fails to receive the study drug infusion within 7 days of the initial screening visit, should be screen failed and can be re-screened afterwards once. Such cases must be discussed and approved by the Sponsor.

In case of pre-existing hyperkalemia, the patient's history of hyperkalemia and concomitant medications should be checked. Patients who show potassium level > 6 mmol/L at screening should have it corrected and can be re-screened one time afterwards to confirm that hyperkalemia has been successfully corrected. For Poland only, patients with potassium level > 5.5 mmol/L at screening should have it corrected and can be re-screened one time afterwards to confirm that hyperkalemia has been successfully corrected.

3.2 Treatment Phase

On the infusion day, patients will be followed according to the assessments schedule in Table 8-1. LysaKare® (1,000 mL solution) will be administered intravenously for 4 hours. Before the infusion (at 0 h time point), a set of baseline tests will be performed. During and after the infusion, the patient's condition will be monitored for evaluation of any adverse events.

Patients will have an option to stay overnight in the clinic or can leave after the 12 h assessment and return to the clinic for the 24 h assessments. All patients will be discharged from the unit after the completion of the 24 h assessments.

Only patients with potassium level of ≤ 6 mmol/L at screening will be allowed to be dosed. For Poland only, only patients with potassium level of ≤ 5.5 mmol/L at screening will be allowed to be dosed. Potassium testing on the infusion day will be performed at 0 h (before the infusion), at 2 h (during the infusion) and 4 h, 6 h, 8 h, 12 h, and 24 h (after the infusion). Vital signs and ECGs will be taken as specified in the assessment schedule.

All patients will be monitored closely for signs and symptoms of hyperkalemia, e.g. dyspnoea, weakness, numbness, chest pain and cardiac manifestations (conduction abnormalities and cardiac arrhythmias).

Patients should be instructed to drink substantial quantities of water (at least 1 glass every hour) on the day of infusion to remain hydrated and facilitate excretion of excess serum potassium. Patients are permitted to void as needed.

In case of signs and symptoms of hyperkalaemia, LysaKare® infusion must be stopped and appropriate corrective measures must be taken. In the occurrence of severe renal insufficiency referral to hemodialysis unit should be considered per investigator discretion.

3.3 Follow-up Phase

After the infusion is complete and the 24-hour sample has been collected the patient will be discharged from the clinic. The investigator will follow-up with the patient via telephone 48-hours after the start of infusion to confirm if the patient experienced any additional adverse events.

If needed, additional visits or assessments (for example, to follow up on adverse events) may be conducted using the Investigator's clinical judgment.

3.4 End of Study

The end of study will occur when the last enrolled patient has completed the follow-up phone contact 48 h after LysaKare® infusion.

4 Rationale

4.1 Rationale for study design

This is a category 3 Post-Authorization Safety Study (PASS) following the European Medicines Agency (EMA) marketing authorization of LysaKare® 25 g/ 15 g solution for infusion. LysaKare® is indicated for reduction of renal radiation exposure during peptide-receptor radionuclide therapy (PRRT) with lutetium (177Lu) oxodotreotide in adults. The marketing authorization was granted based on literature data from similar amino acids solutions (well established use application).

The purpose of the study is to evaluate the effect of LysaKare® administration on serum potassium levels.

The primary endpoint of this study is the change in serum potassium levels after LysaKare® IV administration compared to baseline. The selection of this endpoint is supported by findings of a study, which assessed hourly potassium changes (at 0, 0.5, 1, 2, 4 and 5 hours) measured in 11 patients treated with 2.5% Lys-Arg solution (Krenning 2000). Peak serum potassium levels were observed at 2-4 h post-baseline, the mean baseline level was 4.2 mmol/L, mean increase at 2 h was 0.6 mmol/L and at 4 h it was 0.9 mmol/L (SD=0.3) the maximum increase was 1.5 mmol/L. The mild increase in potassium levels did not manifest in any safety issues or clinically significant events.

The study has a descriptive nature, and no hypothesis will be tested for the study endpoints. The study will describe and analyze various parameters related to potassium concentration, including mean change, maximum change, time to the maximum change, and the overall dynamics of the concentration curve during and after the LysaKare® infusion. In order to calculate the sample size for the study, it was assumed that the mean change in potassium levels over baseline values is less than 1.1 mmol/L (a safety margin of 0.2 mmol/L has been added to the mean increase of 0.9 mmol/L observed in the previous study at 4 h).

AA solutions have fast plasma elimination kinetics with AA levels returning to baseline by 6 hours post-dose (Tangphao 1999, Irving 1986). Serum potassium levels after amino acid administration normally return to near baseline within 24 hours (Giovacchini 2011, Lapa 2014a, Lapa 2014b, Krenning 2000). Therefore, the time points for potassium level assessments in this study extend from 0 h to 24 h, and the follow up is conducted at 48 hours post dose.

The study design and patient population mimic the real-world LysaKare® administration practice in GEP-NET patients who receive amino acid infusion concomitantly with PRRT (Lutathera®). Patient selection thus reflects the indications as well as contraindications and warnings and precautions as outlined in the Lutathera® and LysaKare® labels.

4.2 Rationale for dose/regimen and duration of treatment

A standard approved dose of LysaKare® will be administered to all patients as a 4-hour infusion, as in the real-world practice and according to the EU SmPC. Potassium levels and any clinical manifestations of hyperkalemia will be assessed following the infusion at predefined time points.

The study does not evaluate concomitant administration of LysaKare® with PRRT (Lutathera®) as it is operationally very difficult to collect and analyze radioactive blood samples. From mechanism of action perspective, somatostatin receptor 2 directed PRRT treatment with Lutathera® does not lead to increase of serum potassium levels. The hyperkalaemia observed during PRRT treatment is only related to concomitant administration of AA solution, before and during PRRT treatment. The administration of LysaKare® without PRRT in this study will confirm the safety profile that is related only to LysaKare®, without being confounded by side effects of the treatment with Lutathera®.

4.3 Risks and benefits

Amino acid solutions with similar composition to LysaKare® have been widely used for renal protection during PRRT treatment.

The evaluation of potential risks of LysaKare® for this study is based on the literature data presented in the well-established use application. The LysaKare® IB (Guidance to the Investigator) summarizes potential risks and key risk management activities to consider when administering LysaKare®. The main adverse reactions reported after the amino acid solution administration include nausea, vomiting and hyperkalemia.

- Nausea and vomiting

  The main adverse reactions are nausea (approximately 25%) and vomiting (approximately 10%). Pre-treatment with an antiemetic 30 minutes prior to start of LysaKare® infusion is recommended to reduce the incidence of nausea and vomiting.

- Hyperkalemia

  An increase of serum potassium levels may occur. Serum potassium level increases are generally mild and transient. Vital signs should be monitored during the infusion regardless of baseline serum potassium levels. Patients should be instructed to drink substantial quantities of water (at least 1 glass every hour) on the day of infusion to remain hydrated and facilitate excretion of excess serum potassium. In case hyperkalemia symptoms develop during LysaKare® infusion, appropriate corrective measures must be taken. In the occurrence of severe renal insufficiency referral to hemodialysis unit should be considered per investigator discretion.

Safety effects of LysaKare® will be carefully assessed in this study, and patients will be closely monitored.

As LysaKare® is administered in medical practice with Lutathera® as a kidney radiation protection agent and it does not have a therapeutic effect on GEP-NET itself, there is no direct benefit to the patients participating in the study. However, this study will be essential in better understanding the effect of LysaKare® on serum potassium levels in the GEP-NET patient population for its safe use with Lutathera®.

5 Population

5.1 Inclusion criteria

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

1. Male or female patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumor (GEP-NETs), who are eligible for the treatment with Lutathera® as per Lutathera® label indication.
2. Patients ≥18 years of age at screening.
3. Patients who have provided a signed informed consent form to participate in the study, obtained prior to the start of any protocol related activities.

5.2 Exclusion criteria

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

1. Pre-existing hyperkalemia (>6.0 mmol/L at screening) if not adequately corrected before starting the LysaKare® infusion. For Poland only, pre-existing hyperkalemia (> 5.5 mmol/L at screening) if not adequately corrected before starting the LysaKare® infusion.
2. Instances when Lutathera® is not recommended per the Lutathera® SmPC:
    a. Uncontrolled congestive heart failure (NYHA III, IV);
    b. Kidney failure with creatinine clearance < 50 mL/min calculated by the Cockcroft Gault method;
    c. Impaired haematological function with either Hb < 4.9 mmol/L (8 g/dL), platelets < 75 G/L ($75x10^3/mm^3$), or leucocytes < 2 G/L ($2,000/mm^3$) (except lymphopenia);
    d. Liver impairment with either total bilirubinemia > 3 times the upper limit of normal or albuminemia < 30 g/L and prothrombin ratio decreased < 70%.
3. Pregnancy or lactation, positive pregnancy test at screening or pre-dose based on the contraindication for Lutathera®.
4. Hypersensitivity to the IMP active substances.
5. Any significant medical or social condition which may interfere with the subject's ability to comply with the study visit schedule or the study assessments.
6. Patients who have received any investigational agent within the last 30 days.
7. Patients that have received a dose of Lutathera® prior to the screening visit or are scheduled for Peptide Receptor Repeat (PRRT) treatment within 7 days of the study infusion of LysaKare®.

6 Treatment

In this study, approximately 45 patients (to have at least 25 patients evaluable for the primary endpoint) diagnosed with GEP-NET that meet the criteria for treatment with Lutathera® will be enrolled and receive an infusion with LysaKare®.

The LysaKare® solution will be provided by the Sponsor. Amino acid solutions compounded at the hospital pharmacy are not permitted in this trial.

After the study, treatment with PRRT is only permitted after at least 7 days have elapsed from the LysaKare® infusion. The PRRT will not be provided by the Sponsor.

6.1 Study treatments

6.1.1 Study Drug Product: LysaKare®

The 1000 mL solution of LysaKare® (2.5% Lys-Arg solution for infusion) will be administered intravenously over a 4-hour period (infusion rate: 250 mL/h). Only 1 infusion will be given in the treatment phase of the trial.

The composition of the LysaKare® solution is shown in Table 6-1 below.

Table 6-1 LysaKare® solution composition

Component	Quantity/1000 mL
L-lysine HCl	25g
L-arginine HCl	25g
Water for injection	qs 1000 mL

Appearance: clear, colourless solution, free from visible particles

pH: 5.1 – 6.1

Osmolarity: 420 – 480 mOsm/L

6.1.2 Prohibited medication

Treatment with PRRT is prohibited any time before screening into the study until 7 days after the study treatment with LysaKare® has been completed.

No interaction by LysaKare® with other medicinal products is expected since there is no information that other drugs are re-absorbed by the same kidney re-absorption mechanism.

In case of pre-existing hyperkalemia, concomitant medications should be checked as potential cause of hyperkalemia. Hyperkalemia must be corrected accordingly before starting the LysaKare® infusion.

6.2 Subject numbering

For all patients who have signed the ICF, a screening number will be assigned in chronological order starting with the lowest number available on site. Patients will be identified by a unique

patient identification number (Patient ID No.) composed of the center number and the screening number.

6.3 Dose compliance, modification and discontinuation

6.3.1 Dose compliance

Patients must receive at least 900 mL of the LysaKare® dose to be considered compliant with the study treatment protocol.

6.3.2 Dose discontinuation

If a patient discontinues the LysaKare® infusion prior to receiving at least 900 mL of LysaKare® they should continue with the assessments as outlined in Table 8-1. In case hyperkalemia associated symptoms develop during LysaKare® infusion, appropriate corrective measures must be taken per standard of care and physician judgment. Discontinuation of LysaKare® infusion should be considered in cases of hyperkalemia related safety concerns as judged by the investigator. In case of severe symptomatic hyperkalemia, the LysaKare® infusion should be stopped. In the occurrence of severe renal insufficiency referral to hemodialysis unit should be considered per investigator discretion.

6.4 Preparation and dispensation of LysaKare®

The ready-to-use LysaKare® solution will be provided by the Sponsor and must be administered by peripheral vein infusion at a constant infusion rate through pumps or any other infusion system. The infusion rate should be 250 mL/h and should be completed in a total of 4 hours +/- 20 minutes. During the LysaKare® infusion the patient is allowed to void.

6.4.1 Handling of study treatment and additional treatment

LysaKare® must be stored, handled and administered only by qualified/authorized personnel. Drug inventory and accountability records for the study medication will be kept by the Investigator/Pharmacist and must be documented throughout the study. The Investigator will not supply investigative study medication to any person, except the patients in this study.

The used medications will be locally discarded according to local disposal requirements after the study monitor has completed the drug accountability verification. The unused medication will be returned to the proper local depot for destruction at the study completion or upon expiration, according to IPM/Sponsor instructions. On an ongoing basis the Investigator/Pharmacist agrees to conduct a study medication supply inventory and to record the results of this inventory on the study Medication Accountability Record. 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.

7 Informed consent procedures

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

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

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 informed consent must be documented in the subject source documents.

Advanced Accelerator Applications will provide to investigators in a separate document a proposed 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 consent form suggested by the investigator must be agreed by Advanced Accelerator Applications before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the subject informed consent and should be discussed with the subject 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 finding. New information might require an update to the informed consent and then must be discussed with the subject.

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

It is recommended that the Investigator inform the patient’s general practitioner of his/her participation in the study, provided that the patient has a general practitioner and the patient agrees to disclose this information.

The informed consent form (ICF) signed at the time of the inclusion foresees the patient’s participation in the Study until the end of the Follow-up Phase.

8 Visit schedule and assessments

The assessments listed in Table 8-1 will be performed locally at the sites. The assessment schedule lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Table 8-1. Visit Assessment Schedule

Visit Name	Screening	Treatment Phase (Infusion Day)							Follow-up
	Within 7 days before the infusion day	0 h (pre-dose)	2 h	4 h	6 h	8 h	12 h	24 h	48 h (phone contact)
Informed consent	X								
Demography	X								
Inclusion/exclusion criteria	X								
Cancer diagnosis and grading	X								
Relevant medical history/current medical history	X								
Physical Exam	X	X						X	
Height	X								
Vital Signs	X	X	X	X	X	X	X	X	
ECG	X	X		X		X		X	
Hematology	X	X						X	
Chemistry (**serum**)	X	X						X	
Electrolytes (**serum**)*	X	X	X	X	X	X	X	X	
Venous blood gas*	X	X	X	X	X	X	X	X	
Pregnancy Test	X	X							
LysaKare® infusion		4-HOUR INFUSION							
Antiemetic administration**		X							
Prior and concomitant anti-cancer therapies	X	X							X
Prior and concomitant medications	X	X							X
Adverse Events	X	X							X

*The same sampling methodology should be used at all time points for consistency.
**Before LysaKare® infusion, an intravenous bolus of an antiemetic should be given. The choice of antiemetic drugs is at the discretion of the physician.

8.1 Demographics and Baseline Characteristics

Each patient's age or date of birth, gender, ethnicity, weight, height and relevant baseline characteristics will be recorded in the e-CRF.

8.1.1 Diagnosis and Extent of Cancer

Patient disease history, including documented diagnosis of gastro-entero-pancreatic tumor, date of diagnosis as well as disease status at study entry, will be collected. This includes the date of first diagnosis and current disease grade. Confirmation of the tumors somatostatin receptor positivity will also be collected.

8.1.2 Prior Antineoplastic Medications / Radiotherapy / Surgery

Information pertaining to any chemotherapy, hormonal therapy, immunotherapy, radiation, or surgery the patient has previously received will be documented. Previous treatment with somatostatin analogs will be also documented if applicable.

8.2 Prior/Concomitant Medications

All medications taken at the start of screening until the end of the Follow-Up are to be recorded. This includes prescription and over-the-counter medications taken during this time frame.

8.3 Efficacy Assessment

Efficacy assessment is not applicable in this study.

8.4 Safety and Tolerability

8.4.1 Adverse Events

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 Follow-up. Definitions and reporting procedures are outlined in Section 10.

8.4.2 Laboratory Assessments

The laboratory assessments in this study require blood samples for hematology and blood chemistry, electrolytes and blood gas, as well as a pregnancy test. The full Chemistry assessments are required at Screening and on Infusion day at 0h (pre-infusion) and 24h from the start of the infusion and **must** be performed strictly on **serum** samples. Electrolyte measurements (with or without the full Chemistry assessment) are required at Screening and on Infusion day at 0h (pre-infusion) and, 2h, 4h, 6h, 8h, 12h and at 24h from the start of the infusion and **must** be performed strictly on **serum** samples. Venous blood gas (VBG) samples are required at Screening and on Infusion day at 0h (pre-infusion) and, 2h, 4h, 6h, 8h, 12h and 24h from the start of the infusion and can be performed as per site standards. The same sampling methodology should be used at all time points for consistency. Laboratory assessments will be performed at the investigational site. **Samples must be centrifuged within one hour and analyzed within 3 hours of collection to avoid degradation.** Laboratory normal ranges must be provided for all laboratory assessments.

At Screening: all patients will have screening laboratory assessments per the Table 8-1 no less than 24 hours and no more than 7 days prior to the infusion date.

During the Treatment Phase (infusion day): a time window of +/- 5% (equal to 3 min/h) is permitted for study assessments at 2h, 4h, 6h, 8h, 12h. A time window of +/- 2 hours is accepted for the 24-hour assessments.

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 safety laboratory results must be evaluated by the Investigator before administration of study medication.

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 related clinical changes.

Table 8-2. Hematology and Chemistry Laboratory Assessments

Haematology (for assessment at screening, pre-dose and 24h after start of the infusion)	**Blood Chemistry** (serum) (for assessments at screening, pre-dose and 24h after start of the infusion)	**Electrolytes** (serum) (for assessments at screening, pre dose and, 2h, 4h, 6h, 8h, 12h, 24h after start of the infusion)	**Venous blood gas** (for assessments at screening, pre dose and, 2h, 4h, 6h, 8h, 12h, 24h after start of the infusion)
• WBC with differential • Platelets • Hb • Haematocrit	• BUN or urea • Uric acid • Serum creatinine • Creatinine clearance (calculated using Cockcroft-Gault formula) • Albumin • Total bilirubin • ALP • AST/ASAT • ALT/ALAT • Gamma-GT • Glucose • LDH	• Potassium • sodium • chloride • HCO3	• pH • lactate • pCO2

8.4.3 Pregnancy Test

A pregnancy test (serum or urine) must be performed at screening and prior to the start of the infusion with LysaKare® for every female patient of childbearing potential.

8.4.4 ECG

Standard 12-lead ECGs will be performed. ECGs will be recorded at screening, and the 0 h, 4 h, 8 h and 24 h timepoints to measure the different ECG intervals (RR, PR, QRS, QT and QTcF).

An ECG in triplicate (at least 5 minutes apart) will be taken supine, after 10 minutes rest, 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 eCRF 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.

8.4.5 Physical Examination and Vital Signs

Physical examinations will be performed by the Investigator, or qualified designee. All body systems will be examined, and any relevant findings will be documented in the source documents and eCRF. Physical examinations should include weight measurement (height will only be measured at baseline). Vital signs measurements should include heart rate, blood pressure and respiratory rate, and will be performed after the patient rests for 5 minutes. For each patient, all blood pressure recordings shall be made using the same type of instrument (i.e., manual BP recording vs. automatic digital vital signs monitor) on the same arm.

Significant findings in physical examination and vital signs that are present at screening 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.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject is defined as a situation when study treatment infusion is stopped earlier than the protocol planned duration of 4 h ± 20 minutes.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being or result in a safety risk to the subject.

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

Subjects 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. Where possible, they should complete all assessments indicated in the assessment schedule for the infusion day. If subjects fail to return for these assessments for unknown reasons, every effort should be made to contact the subject.

9.1.2 Replacement policy

Subjects may be replaced if no serum potassium level measurements are performed after LysaKare® infusion. The Sponsor will make decision on replacing a patient based on the patient data provided.

9.1.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore

  and

- Does not want any further visits or assessments

  and

- Does not want any further study related contacts

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

In case of withdrawal of informed consent during the study drug infusion, it must be discontinued. If a patient withdraws informed consent from the follow-up, no further

assessments will be conducted, and the data that would have been subsequently collected will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up. All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed for the 24 h visit.

Advanced Accelerator Applications will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits after the discharge from the clinic (i.e. for the 24 h and 48 h assessments) without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.5 Early study termination by the sponsor

The study can be terminated by Advanced Accelerator Applications at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Advanced Accelerator Applications will always consider the subject welfare and safety. Should early termination be necessary, any subject that has signed ICF but not yet been treated should be notified immediately. 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 subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Telephone Follow-up

Subjects must be contacted 48 hours after the start of LysaKare® infusion per the schedule of assessments to collect any adverse events that may have occurred (refer to Table 8-1).

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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 subject or clinical investigation subject 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 subject and identifying adverse events.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

AAA 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 event monitoring must be continued for at least 48 hours after the infusion until the follow up call. 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 subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject 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):

1. The Severity grade OR the Common Toxicity Criteria (CTC) AE grade.
    - 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

- If "CTCAE grade" is selected, include the following:
    i. Adverse events will be assessed and graded from 1 to 5.

2. Its relationship to the study treatment. The assessment of causality will usually be either 'Suspected' or 'Not suspected.'
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 SAE (see Section (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding with study treatment.
    - Dose not changed
    - Drug interrupted/withdrawn
6. All adverse events must be treated appropriately.
7. Its outcome i.e., its recovery status or whether it was fatal.

If the event worsens the event 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.

Conditions that were already present at the time of informed consent should be recorded in the medical history of the patient.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment 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.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

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 subjects with the underlying disease.

10.1.2 Serious adverse events

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 subject 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 (please 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 information consent
  - social reasons and respite care in the absence of any deterioration in the subject'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 subject 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 subject 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 (please refer to the ICH-E2D Guidelines).

All 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.

10.1.3 Adverse Drug Reaction (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 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 2 days after the patient has stopped study treatment must be reported to AAA pharmacovigilance immediately without undue delay and under no circumstances later than 24 hours of learning of its occurrence. 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 immediately without undue delay and under no circumstances later than 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 AE/SAEs is collected and recorded on the SAE report 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 AE/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 to AAA pharmacovigilance as per timelines defined above.

Follow-up information is submitted in the same way and timelines as the original AE/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, AAA pharmacovigilance associate may urgently require further information from the investigator for health authority reporting. AAA 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 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 2-day period should only be reported to AAA Safety if the investigator suspects a causal relationship to study treatment.

10.1.6 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent form must be reported by the investigator to AAA Pharmacovigilance immediately without undue delay and under no circumstances later than within 24 hours of learning of its occurrence by using the Pregnancy form. 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.

Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported through the SAE report form.

10.1.7 Reporting of study treatment errors including misuse/abuse

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

10.1.8 Annual Safety Report

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

Once per year, the sponsor or PI will supply a report on the safety of trial patients with all available relevant information concerning patient safety during the reference period to the Competent Authorities of all Countries where the trial is being conducted. This report will also be supplied to the responsible ethics committee.

11 Data Collection and Database management

11.1 Data collection

The 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 Principal investigator is responsible for assuring that the data (recorded on eCRFs) 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 subject 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

Advanced Accelerator Applications personnel (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 is 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 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.

Data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked on the study drug accountability logs. An electronic system for the Drug Supply Management might be implemented for this trial. The local monitor will provide training material to order the study drugs during the initiation visit. Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Advanced Accelerator Applications.

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

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, an Advanced Accelerator Applications representative will review the protocol and data capture requirements (eCRFs) with the investigators and their staff. During the study, Advanced Accelerator

Applications 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 subject 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 Advanced Accelerator Applications. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Advanced Accelerator Applications clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject 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 eCRFs must be traceable to these source documents in the Subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Advanced Accelerator Applications 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 eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

12.1 Analysis sets

The Safety Set (SAF) comprises all subjects who received any volume of the LysaKare® infusion in the study.

The Safety Set will be used for the analyses below, whereas the primary endpoint analysis is further restricted to an evaluable subset based on the following specification.

Potassium levels are evaluable for the primary endpoint only if there are at least 2 values measured from serum: one from baseline and one (minimum) from the post-treatment window where the acute serum potassium changes are expected. Therefore, the Primary Analysis Evaluable Set comprises of subjects who received any volume of the LysaKare® infusion and have both pre-dose and at least one post-dose (between 4 and 8 hours) potassium levels measured from serum.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for the Safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical history and current medical conditions at baseline will be summarized separately by system organ class and preferred term.

12.3 Treatments

All subjects will receive an infusion of LysaKare® in the study, without co-administration of Lutathera®.

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

The scientific objective guiding the primary analysis is to assess the effect of LysaKare® administration on serum potassium concentrations in GEP-NET patients eligible for Lutathera® treatment irrespective of treatment interruption or discontinuation. The primary endpoint is the change in serum potassium levels after LysaKare® IV administration compared to baseline.

The primary estimand is described by the following attributes:

1. The **target population** comprises patients diagnosed with SSTR positive GEP-NET and are eligible for treatment with Lutathera®.h
2. The **primary variable** is change in serum potassium concentration from pre-dose to 2, 4, 6, 8, 12, and 24 hours after start of LysaKare® administration.

3. **Treatment of interest** is LysaKare® solution administered intravenously over a period of four hours.
4. **Intercurrent events** of interest in this study are treatment discontinuation for any reason and treatment interruption for any reason, which are ignored.
5. The **summary measure** is the mean of change in serum potassium levels from pre-dose to 2, 4, 6, 8, 12, and 24 hours, after beginning of LysaKare® administration.

12.4.2 Statistical model, hypothesis, and method of analysis

The study is descriptive in nature, and no hypothesis will be tested for study endpoints. The study will analyze and describe various primary variables related to potassium concentration, including mean change, maximum change, time to the maximum change, and the overall dynamics of the concentration curve during and after the LysaKare® infusion.

The primary endpoint analysis will be conducted on the Primary Analysis Evaluable Set.

In particular, maximum change and time to the maximum change will be summarized by descriptive statistics (N, median, minimum, maximum, and interquartile range). The mean (+/- SD) concentration-time profiles for serum potassium will be displayed graphically on the linear view.

12.4.3 Handling of missing values/censoring/discontinuations

There will be no replacement of missing data.

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses

The time course of the percent change as well as actual numerical change at each time point will be tabulated. A Mixed Model Repeated Measures will be fitted to assess the whole-time course.

12.5 Analysis of secondary endpoints

All other safety endpoints will constitute the secondary endpoints, see below.

12.5.1 Safety endpoints

Adverse events

All information obtained on adverse events will be displayed for the Safety set and by subject.

The number (and percentage) of subjects 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.

- by Standardized MedDRA Query (SMQ) and preferred term

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 subjects with adverse events of special interest/related to identified and potential risks (see Section 10.1) will be summarized.

A subject 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 subject, and time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by time.

12-lead ECG

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each subject during the study. ECG data will be read and interpreted locally. The ECG parameters will be summarized by time.

Clinical laboratory evaluations

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

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 or current version. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be categorized as low/normal/high based on laboratory normal ranges.

12.6 Analysis of exploratory endpoints

Not applicable

12.7 Interim analyses

Not applicable

12.8 Sample size calculation

The primary endpoint is the change in serum potassium levels after LysaKare® IV administration compared to baseline. In a previous study, which assessed hourly potassium

changes in 11 patients treated with LysaKare®, peak concentration was observed at 2-4 h post-baseline, the mean baseline level was 4.2 mmol/L, mean increase at 2 h was 0.6 mmol/L and at 4 h it was 0.9 mmol/L (SD=0.3); the maximum increase was 1.5 mmol/L (Krenning 2000). The mild increase in potassium levels did not manifest in any safety issues or clinically significant events. Since the maximum mean increase was observed at 4h, the change from baseline to 4h will be of primary interest.

The current study will describe the expected mean change at 4h by a point estimate and the corresponding 95% confidence interval. In historical data a mean increase from baseline to 4h of 0.9 mmol/L was observed with a standard deviation of 0.3.

The criterion for choice of sample size will be based on length of confidence interval of the mean change at 4h calculated using the t-distribution. A requirement was initially chosen that the confidence interval has a total length not exceeding 0.2 mmol/L assuming the historical standard deviation to be valid, i.e. the distance should be no more than 0.1 mmol/L from the mean to the limit of the confidence interval when the estimated standard deviation is 0.3.

The initially estimated sample size of 38 subjects produces a two-sided 95% confidence interval with a distance from the mean to the limits that is equal to 0.099 when the estimated standard deviation is 0.3. With the required minimum number of 25 evaluable subjects for the primary endpoint analysis, the confidence interval (CI) total length is maintained with a slight increase to 0.25 mmol/L. Additionally, the originally estimated sample size of 38 implies an adequate probability of observing common AEs, see Table 12-1 below. This estimate holds true because the current laboratory sampling issue only impacts the evaluable number for the primary endpoint. Other safety assessments based on AEs remain evaluable for the whole safety set.

Table 12-1 Likelihood of observing at least one case for given sample size and incidence

Sample size	Incidence of Adverse Event	
	5%	10%
10	0.401	0.651
20	0.642	0.878
30	0.785	0.958
38	0.858	0.982
40	0.871	0.985

The table displays the probability of observing at least one case of a certain AE which has the incidence 5% or 10% in this patient population for the sample sizes 10, 20, 30 and 40. Any further increase in total sample size ensures that this probability remains above 87%.

Since the sample size of 38 subjects assumes no drop-out, additional subjects have been added to hedge against drop-out. Given the design of the study, no or very minor drop-out is expected. The additional precaution is taken to ensure at least 25 subjects are evaluable for the primary endpoint analysis as discussed in the amendment rationale. Therefore, the adjusted sample size is approximately 45 subjects.

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, 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, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. 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 Advanced Accelerator Applications monitors, auditors, Advanced Accelerator Applications Quality Assurance representatives, designated agents of Advanced Accelerator Applications, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Advanced Accelerator Applications 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. 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 Advanced Accelerator Applications clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

Advanced Accelerator Applications (AAA) 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 AAA-sponsored, research-related publications are:

- AAA supports the publication of study results for its innovative medicines in a timely manner, whatever their outcome. AAA policy is not to withhold, veto or suppress data. However, due consideration must be given to the rights of AAA to protect confidential and/or patentable information, and to the protection of personal information, in particular patient privacy.
- Review by AAA 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 AAA 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 AAA 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 AAA. 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

Advanced Accelerator Applications 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 Advanced Accelerator Applications 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 Advanced Accelerator Applications processes.

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 subjects 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 Advanced Accelerator Applications and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators agree to 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 Advanced Accelerator Applications and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

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 Advanced Accelerator Applications, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject 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 subject included in this study, even if this action represents a deviation from the protocol. In such cases, Advanced Accelerator Applications 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

Appendix 1 – National Cancer Institute Common Terminology Criteria for Adverse Events

This is an extract of the whole document. For the complete CTCAE guide, version 5.0, please refer to the following website:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf