Post Authorization Safety Study information

Protocol title	An International, Non-Interventional, Post-Authorization Long-Term Safety Study of Lutathera®, in Patients with Unresectable or Metastatic, Well-Differentiated, Somatostatin Receptor Positive, Gastroenteropancreatic Neuroendocrine Tumours (SALUS study).
Protocol N°	A-LUT-T-E02-402
Protocol version	1.1
Protocol version date	15-JUN-2018
PAS register number (Europe)	*Study not yet registered as of 15-JUN-2018*
Active substance	INN: lutetium (^{177}Lu) oxodotreotide USAN: lutetium Lu 177 dotatate ATC code: V10XX04
Medicinal product	Lutathera 370 MBq/mL solution for infusion
Product reference	EU/1/17/1226/001 IND N° 77219
Procedure number	EMEA/H/C/004123/MEA/001
Marketing authorization holder	Advanced Accelerator Applications, a Novartis Company 20 rue Rudolph Diesel 01630 Saint Genis Pouilly Tel: +33 04 50 99 30 70 www.adacap.com / info@adacap.com
Joint PASS (Europe)	No

Research question and objectives	**Research Question:** What is the long-term safety profile of Lutathera according to the label indication (SmPC/USPI)? **Primary research-objective:** To assess the incidence and nature of potential long term second primary malignancies, including solid tumours and haematological neoplasia, occurring over a 7-year follow-up period in patients with unresectable or metastatic, well-differentiated, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours. **Secondary research-objectives:** - To quantify the incidence of other important identified and potential risks specified in the Lutathera Risk Management Plan (RMP) such as: renal dysfunction, myelosuppression/cytopenias, myelodysplastic syndrome, hypogonadism, sexual dysfunction, drug interaction with somatostatin/somatostatin analogues, tumour cell lysis-related hormone release-induced crises, hepatotoxicity, radiotoxicity. - To detect potential new risks overall, and potential risks in patients under-represented in the clinical trial, including elderly patients, patients with renal and liver impairment, reduced bone-marrow reserve, exposure in breast-feeding women, accidental foetal and child exposure. - To describe the patterns of drug utilisation that may add knowledge about the safety of Lutathera
Participating countries	Clinical sites and countries will be selected from the most representative ones in terms of numerical contribution to the European Compassionate Use Program (CUP) and US Expanded Access Program (EAP). An initial set of circa 20 sites from France, United Kingdom, Portugal, US and Finland will be invited to participate in the SALUS study. Additional ones could be incorporated later from the countries where Lutathera has been granted with Marketing Authorization.

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SPONSOR APPROVAL SIGNATURE PAGE

Name	Signature	Date
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Marketing authorization holder

Marketing authorization holder	Advanced Accelerator Applications, a Novartis Company 20 Rue Diesel 01 630 Saint Genis-Pouilly France
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INVESTIGATOR APPROVAL SIGNATURE PAGE
Protocol version 1.1, 15 JUN 2018

I have carefully read this protocol entitled **"An International, Non-Interventional, Post-Authorization Long-Term Safety Study of Lutathera®, in Patients with Unresectable or Metastatic, Well-Differentiated, Somatostatin Receptor Positive, Gastroenteropancreatic Neuroendocrine Tumours (SALUS study)"**, and agree that it contains all the necessary information required to conduct the study. I agree to conduct this study as outlined in the protocol.

1. I understand that this study will not be initiated without approval of the appropriate Institutional Review Committee/Ethics Committee and that all administrative requirements of the governing body of the institution will be complied with fully.
2. I confirm that I will conduct the study in accordance with the principles of International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and Food and Drug Administration (FDA) requirements as specified in Title 21, Code of Federal Regulations, Part 50, 54, 56, 312 and the provisions of the Helsinki Declaration, where appropriate; copies of these documents have been given to me by the Sponsor.
3. I will also ensure that Sub-Investigator(s) and other relevant members of my staff have access to copies of this protocol, the ICH GCP guidelines, and the Helsinki Declaration to enable them to work in accordance with the provisions of these documents.
4. Informed written consent will be obtained from all participating subjects (in case of death next of kin) in accordance with institutional and ICH Guidelines for GCP. Where next of kin consent is not required by local regulation for patients already deceased at time of enrolment, pseudonymised data collection will be performed when the clinical information is available at the centre, by the subject's care team to preserve confidentiality, in order to minimize any selection bias (omission of data from patients who already died) (see Annex 2).
5. I understand that my signature on each completed Case Report Form indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.
6. I understand that the information presented in this study protocol is confidential and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Sponsor unless this requirement is superseded by the Competent Authorities and Ethic Committees.

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Printed Name

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Affiliation

1. Table of contents

List of tables

2. List of abbreviations

Abbreviation	Full words
5-H1AA	5-hydroxyindoleacetic acid
AAA	Advanced Accelerator Applications
ADR	Adverse Drug Reactions
AE	Adverse Event
ALT	Alanine-aminotransferase
AP	Alkaline phosphatase
AST	Aspartate-aminotransferase
ATC	Anatomical Therapeutic Chemical (ATC) Classification System
ATU	‘’Autorisation temporaire d’utilisation’’
BMI	Body Mass Index
CA	Competent Authority
CépiDc	‘’Centre d'épidémiologie sur les causes médicales décès’’
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIMS	Crisis Information Management System
CRA	Clinical Research Assistant
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Computerized Tomography
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
CUP	Compassionate Use Program
DDI	Drug-drug Interaction
DMP	Data Management Plan
DOR	Duration of Response
DVP	Data Validation Plan
EAP	Expanded Access Program
EC	Ethic Committee
ECCG	e-CRF completion guidelines
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EMC	Erasmus Medical Centre
ENETS	European Neuroendocrine Tumor Society
EU PAS	European Post Autorisation Study
FDA	Food and Drug Administration
FU	Follow-up
G1	Grade 1

G2	Grade 2
GBq	Giga Becquerel
GCP	Good Clinical Practice
GDMP	Good Data Management Practices
GDPR	General Data Protection Regulation
GEP-NET	Gastroenteropancreatic neuroendocrine tumours
GGT	Gamma-glutamyl transferase
GP	General Practitioner
Hb	Haemoglobin
HCT	Haematocrit
IARC	International Agency for Research on Cancer
ICF	Informed consent form
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IT	Information Technology
ITMCI	IT Management, Compliance and Integration
LAR	Long Acting Release
LDAP	Lightweight Directory Access Protocol
LDH	Lactate dehydrogenase
MAH	Marketing Authorization Holder
MC	Medical Center
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NEC	Neuroendocrine carcinoma
NPU	Name Patient Use
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall survivalsurvivalOverall Survival
PASS	Post Authorization Safety Study
PFS	Progression-Free Survival
PLT	Platelets
PMS	Post Marketing Study
PRAC	Pharmacovigilance Risk Assessment Committee
PRRT	Peptide Peptide-receptor Radionuclide Therapy
PV	Pharmacovigilance
QA	Quality assuranceassuranceQuality assuranceAssurance

QC	Quality Control
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	Risk management plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPECT-CT	Single-photon emission computed tomography- computed tomography
SRI	Somatostatin Receptor Imaging
SSTR	Somatostatin Receptor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNM	Tumor-Node-Metastasis
UK	United Kingdom
ULN	Upper Limit of Normal
UMC	Uppsala Monitoring Centre
USA	United States of America
USAN	United States Adopted Name
USPI	United States Product Information
WBC	White Blood Cells
WD NET	Well-differentiated neuroendocrine tumours
WHO	World Health Organization

3. Responsible parties

Clinical sites and countries will be selected from the most representative ones in terms of numerical contribution to the European Compassionate Use Program (CUP) and US Expanded Access Program (EAP). An initial set of circa 20 sites from France, United Kingdom, Portugal, US and Finland will be invited to participate in the SALUS study. Additional ones could be incorporated later from the countries where Lutathera has been granted with Marketing Authorization.

4. Abstract

4.1. Title

An international, non-interventional, post-authorization long-term safety study of Lutathera®, in patients with unresectable or metastatic, well-differentiated, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (SALUS study).

4.2. Rationale and background

Gastroenteropancreatic neuroendocrine tumors

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) constitute a heterogeneous group of neoplasms arising from the diffuse neuroendocrine system representing less than 2% of all malignant tumors (Öberg K, 2004). GEP-NETs are derived from cells of the diffuse neuroendocrine cell system and the two major GEP-NET subgroups are carcinoids and islet cell tumors.

By convention, GEP-NETs are divided into foregut, midgut and hindgut tumors based on the embryonic origin of the different tumors; where the foregut primaries are located in the lung, thymus, stomach, duodenum, and pancreas; the midgut with primary tumors in the ileum, caecum and proximal colon; and the hindgut with the primaries in the distal colon and rectum. A more recent World Health Organization classification system (WHO/IARC Classification of Tumors, 2017) has been developed which is considered more clinically relevant. It specifies five subtypes (irrespective of the site of origin) under two main categories (well differentiated and poorly differentiated) and is therefore relevant for all neuroendocrine tumor types:

- Well Differentiated Neuroendocrine Tumors (WD NET)
  - Grade 1 (<3% Ki-67 index)
  - Grade 2 (3%-20% Ki-67 index)
  - Grade 3 (Ki-67 proposed up to 50-55% but other characteristics to be considered)

- Poorly Differentiated Neuroendocrine Carcinoma (NEC)
  - Small cell type
  - Large cell type

The European Neuroendocrine Tumor Society (ENETS) / tumor-node-metastasis (TNM) classification system is also used which complements classification by providing information based on location as it focuses on tumor grading and staging based on the Ki-67 index (Rindi 2006, Kloppel 2011, Crippa 2016).

GEP-NETs may also be divided into functioning and non-functioning tumors. Functioning tumors clinically present with symptoms related to overproduction of biogenic amines and peptide hormones. The

majority of GEP-NETs do not secrete sufficient levels of biologically active substances to induce symptoms and are therefore classified as non-functioning and consequently often present fairly late with symptoms of mass effects, or distant metastases (Garcia-Carbonero 2010). Öberg et al. (2010) state that 70% of carcinoid tumors are diagnosed as non-functioning, and that 45 to 60% of pNETs are non-functioning. Among the functioning tumor types, each of the specific secreted substances causes a clinical syndrome and may serve as a specific marker for diagnosis as for example, urinary 5-hydroxyindoleacetic acid (carcinoid tumors), serum or plasma gastrin (Zollinger-Ellison), insulin (insulinoma), vasoactive intestinal polypeptide (Verner-Morrison) and glucagon (glucagonoma). General markers such as chromogranin A, synaptophysin, pancreatic polypeptide, serum neuron-specific enolase and glycoprotein human alpha subunit, have been used for screening purposes in patients without distinct clinical hormone-related syndromes. The most important general circulating tumor marker is chromogranin A, expressed in 80-90% of all patients with GEP-NETs. Chromogranin A determination is also useful for staging, prognosis and follow up, since the serum concentration correlates to the tumor mass (Garcia-Carbonero 2010, Diez 2013). Delayed diagnosis is typical (5-7 years) in patients with non-functioning GEP-NETs, resulting in greater morbidity, increased probability of metastatic disease, and increased mortality (Garcia-Carbonero 2010).

PRRT with Lutathera®

Tumor-targeted peptide receptor radionuclide therapy (PRRT) has been under clinical evaluation since 1992 for GEP-NETs expressing somatostatin receptors (De Jong 2002; Valkema 2002, 2006; Waldherr 2001; Paganelli 2001; Bodei 2008, 2009, 2010, 2011; Kwekkeboom 2003, 2005, 2008; Forrer 2007, 2009; Menda 2010; Sansovini 2013; Ezziddin 2014; Paganelli 2014; Sabet 2015, Strosberg 2017).

Lutathera® (USAN: lutetium Lu 177 dotatate/INN: lutetium (^{177}Lu) oxodotreotide) consists of a somatostatin peptide analogue, coupled to a metal-ion complexing moiety (DOTA). It can be labeled with beta-emitters, for example, Lutetium-177 (^{177}Lu). By targeting somatostatin receptor positive tumors, a tumoricidal radiation dose is delivered. ^{177}Lu is a medium-energy beta-emitter with a maximum tissue penetration of 2 mm and a physical half-life of 6.7 days. It also emits medium and low-energy gamma radiation, which can be used for imaging and dosimetry. DOTA^{0}-Tyr^{3}-Octreotate binds with high-affinity to somatostatin receptors (especially SSTR2) and retains its binding properties and physiological function when complexed with ^{177}Lu (Reubi 2000).

Clinical studies have shown that Lutathera is an effective treatment option for functioning and non-functioning subtypes, resulting in high response rate and survival outcome (Kwekkeboom 2008; Ezziddin 2014, Sansovini 2017; Brabander et al, 2017).

In September 2017 and January 2018 Lutathera was approved in Europe and US respectively for the treatment of unresectable or metastatic, progressive, well differentiated, somatostatin-receptor positive GEP-NETs in adult.

Lutathera safety and efficacy

The marketing authorization for Lutathera was based on the results of the pivotal phase III NETTER-1 study and the Erasmus MC Phase I-II study. Several patients have been also treated with Lutathera as part of the Compassionate Use Program (Europe) and Expanded Access Program (US) (approved in ten European countries since March 2012 and in the US since January 2016).

The NETTER-1 Phase III study

The multicentre, randomized, comparator controlled, parallel-group NETTER-1 study sponsored by Advanced Accelerator Application (EudraCT number 2011-005049-11) was conducted in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumors treated with Lutahera® (4 administrations of 7.4 GBq every 8 weeks) plus supportive care with 30 mg Sandostatin® LAR compared to treatment with Sandostatin® LAR alone (60 mg, every 4-weeks) (Strosberg 2017).

Lutathera was shown to be superior to Octreotide 60 mg in terms of progression-free survival (PFS) which at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the Lutathera group and 10.8% (95% CI, 3.5 to 23.0) in the control group. At the time of analysis, the median PFS had not yet been reached in the Lutathera group and was 8.4 months (95% CI, 5.8 to 9.1) in the control group (hazard ratio for disease progression or death with Lutathera vs. control, 0.21; 95% CI, 0.13 to 0.33; P<0.001), representing a 79% lower risk of disease progression or death in the Lutathera group than in the control group.

In terms of overall survival (OS), at interim analysis, a total of 14 deaths versus 26 deaths were observed in the Lutathera versus the control group, which represented an estimated risk of death that was 60% lower in the Lutathera group than in the control group (hazard ratio for death with Lutathera group versus control, 0.40; P=0.004). The O'Brien–Fleming threshold for significance at the first interim analysis was 0.000085.

The most common adverse events (AEs) among patients in the Lutathera group included, nausea (65 patients [59%]) and vomiting (52 patients [47%]). A majority of these cases (in 42 of the 65 patients [65%] and in 38 of the 52 patients [73%], respectively) were attributable to amino acid infusions that were performed concurrently with administration of Lutathera and the events resolved once the infusions were completed. Other common adverse events in the Lutathera group included fatigue or asthenia, abdominal pain, and diarrhea; however, a majority of the patients in whom these events were reported (≥97%) had events of grade 1 or 2.

Regarding myelodysplastic syndrome (MDS), one patient in the Lutathera group (0.9%) underwent a bone marrow biopsy that revealed histologic changes consistent with the myelodysplastic syndrome that were considered by the Investigator to be possibly related to the investigational therapy. The patient had a history of monoclonal gammopathy of unknown clinical significance with cytopenias.

The Erasmus Phase I-II study

An Investigator-sponsored Phase I/II study with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Lutathera) was activated in 2000 at the Erasmus Medical Centre (Rotterdam, the Netherlands) (Brabander 2017). The study enrolled 1,214 patients with GEP-NETs, who were treated with 4 intravenous administrations of ^{177}Lu-DOTA^{0}-

Tyr^3-Octreotate (200 mCi/ 7.4 GBq at 6-13 week intervals). In 2011/2012, with the aim of pursuing the Marketing Authorization of Lutathera, Advanced Accelerator Applications has conducted a retrospective independent verification of the Erasmus MC study data. The study concluded that treatment with ^{177}Lu-$DOTA^0$-Tyr^3-Octreotate was safe, efficacious and well tolerated. More specifically, the median PFS as assessed by the Investigator for the GEP-NET Dutch (national) FAS group (N: 360) according to RECIST criteria was 28.5 months with a 95% CI of 24.8-31.4 months, the ORR was 45, the median duration of response (DOR) (N: 162 responders) was 22.9 months and the median OS was 61.2 months with a 95% CI of 54.8-67.4 months. In terms of safety, in the Phase I/II study 626 patients (51.6%) experienced at least one treatment emergent serious adverse event (SAE) and 16.8% of those experienced at least one SAE that was assessed as possibly or probably related to study drug. SAEs with the highest frequencies were; pancytopenia (8.0%), diarrhoea (4.7%), death (4.5%), abdominal pain (4.4%), anaemia (4.0%), vomiting (3.8%), pyrexia (3.3%), nausea (3.2%) and thrombocytopenia (3.0%). Overall out of the 1,214 subjects, MDS was reported for 17 (1.4%) and acute leukaemia and acute myeloid leukaemia were reported for 2 (0.2%) and 3 (0.2%), respectively. These observed incidences of MDS and acute leukaemia were within the reported ranges of current chemotherapy practise in oncology and haematology and use of radioiodine for treatment of thyroid cancer. Out of a total of 44 cases of renal failure or impairment only 4 were reported as related to the ^{177}Lu-$DOTA^0$-Tyr^3-Octreotate treatment. Of note co-infusion of amino acids was found to reduce the kidney absorbed dose by a mean of 47%.

The Lutathera compassionate and expanded programs

Compassionate Use and Named Patient Use programs with Lutathera have been activated by Advanced Accelerator Applications in Europe since March 2012 and involved 10 European countries (Austria, France, Estonia, Finland, Greece, Spain, Portugal, Denmark, Switzerland and UK) and 76 European centres up to January 2018. The US Expanded Access program was activated in January 2016 with 30 US participating centers as of January 2018.

More than 2000 patients have been treated under these programs since the programs activation up to January 2018.

Justification for the SALUS study

The review of the marketing authorization application for Luthatera® conducted by the CHMP and the FDA concluded that the safety data provided was limited owing to the lack of routine safety recording in the Erasmus trial (Brabander 2017) and the limited long-term follow-up data from the NETTER-1 trial (Strosberg 2017). To this purpose, a post-authorization safety study (so called PAS registry in Europe and Post Marketing Study, PMS, in US) was recommended to assess the long-term safety of Lutathera. This was in line with the Applicant's proposed Pharmacovigilance Plan.

4.3. Research question and objectives

Research Question:

What is the long-term safety profile of Lutathera when used according to the label indication (SmPC/USPI)?

Primary research-objective:

To assess the incidence and nature of potential long term second primary malignancies, including solid tumours and haematological neoplasia in patients with unresectable or metastatic, well-differentiated, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours.

Secondary research-objectives:

- To quantify the incidence of other important identified and potential risks specified in the Lutathera Risk Management Plan (RMP) such as: renal dysfunction, myelosuppression/cytopenias, myelodysplastic syndrome, hypogonadism, sexual dysfunction, drug interaction with somatostatin/somatostatin analogues, tumour cell lysis-related hormone release-induced crises, hepatotoxicity, radiotoxicity.
- To detect potential new risks overall, and potential risks in patients under-represented in the clinical trial, including elderly patients, patients with renal and liver impairment, reduced bone-marrow reserve, exposure in breast-feeding women, accidental foetal and child exposure.
- To describe the patterns of drug utilisation that may add knowledge about the safety of Lutathera.

4.4. Study design

This is a multinational, multicentre, non-interventional, retrospective and prospective study of patients with GEP-NET receiving treatment with Lutathera.

The recruitment and data collection processes are summarized below:

- **Potential subject selection:** A list of all the patients treated with Lutathera in the CUP/EAP or upon its availability on the market will be prepared by the Investigators at the selected centers.
  Participation in this study will be proposed to all the patients treated at the identified centers to avoid selection bias. All the available data from the NETTER-1 study (from patients treated in the Lutathera arm) will be utilized and automatically merged in this long-term safety study database, after patients re-consent according to local regulation (see Annex 2).
- **Protocol submission and approval**: The Sponsor and designated Clinical Research Organization (CRO) will prepare and submit the Protocol and the required accompanying documentation to the relevant Competent Authorities and Ethics Committees.
  Approach for consent: Once approval for the study has been granted, the Investigators or designated personnel will approach potential subjects to obtain consent for the study. In the case the subject has died at the time of the registry activation, consent will be requested from their next of kin where this is required according to local regulations (see Annex 2 or contact your local monitor for

additional information). Where next of kin consent is not required, pseudonymized data collection will be performed when the clinical information is available at the center, by the subject's care team to preserve confidentiality, in order to minimize any selection bias (omission of data from patients who already died).

Data Collection: Data will be collected either by an external researcher or a member of the patient's care team, as required according to local regulations (to be agreed in each country before data collection commences). Pre-specified information will be collected in the study-specific electronic Case Report Form (eCRF). All adverse events will be collected and documented via the eCRF (AE/ADR) and the SAE form (serious AE/ADR).

- **Data Analysis:** All data collected will be analyzed according to the Statistical Analysis Plan (SAP).

4.5. Population

Clinical sites and countries will be selected from the most representative ones in terms of numerical contribution to the Compassionate Use and Expanded Access programs. An initial set of circa 20 sites from France, United Kingdom, Portugal, US and Finland will be invited to participate in the SALUS study. Additional ones could be incorporated later from the countries where Lutathera has been granted with Marketing Authorization.

Patients are eligible if they are adult patients, with unresectable or metastatic, well-differentiated, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours treated with Lutathera.

Patients are not eligible in case of hypersensitivity to Lutathera (active substance or any of the excipients), in presence of established or suspected pregnancy or when pregnancy has not been excluded, in presence of kidney failure with creatinine clearance < 30 mL/min.

Patients who fulfil these criteria among those who participated in the Lutathera Compassionate Use and Expanded Access programs or among the newly treated patients with Lutathera upon its availability on the market, will be considered for enrolment in this non-interventional safety study. All the patients will be contacted by the Investigator to explain the study purpose and to obtain the signature of the informed consent. In the case a subject has died, consent will be approached as described in the section 4.4. All patients in this study who participated in the CUP/EAP or were treated with Lutathera upon its availability on the market, will be assessed as part of the standard institutional care practice by means of routine clinical follow up to document long-term safety events and living status.

All the available data, including long term safety follow up data, from the patients who previously consented to the NETTER-1 study and who were treated in the Lutathera arm will be utilized and automatically merged in this long-term safety study database, after patients re-consent according to local regulation.

4.6. Variables

The primary objective is incidence and type of second primary cancer. Data to collect will include patient demographics, information needed to characterize patient eligibility (including medical history, past and current disease characteristics, and tumour SSTR status), Lutathera exposure (including starting dose, full-treatment administered, and dose adjustments or discontinuations if applicable), existing comorbidities at the time of treatment initiation (including renal, hepatic, others), social and family environment to characterize potential radiation exposure (including working status, family environment, which will be assessed for alive patients via a dedicated questionnaire), survival status, and safety events occurring during the treatment period or during the long-term follow-up (including serious adverse events, adverse events leading to dose modification, and adverse events of special interest [including kidney function, bone-marrow function, emergence of malignancies]).

4.7. Data sources

Data will be retrospectively and prospectively gathered from medical charts for patients treated during commercialization of the drug, or from data already collected during the NETTER-1 trial, or during the CUP/EAP. All participants treated with Lutathera in the CUP/EAP or upon its availability on the market will be invited to give their consent to participate in this long-term follow-up safety study.
As the NETTER-1 study duration for each patient is close to 7 years (18 months of treatment/assessments phase monthly visits, followed by 5 years of follow-up visits every 6 months), no additional data will be collected from the NETTER-1 study patients.

4.8. Study size

Assuming a cumulative incidence of second primary cancer of between 1-2% over 5 years of follow-up, ~900 patients would be required to achieve a precision of ±1% around the observed incidence rate with an acceptable confidence level i.e. with 900 patients the Jeffrey's interval would lie within the range of the observed incidence +/- 1% (see section 9.5 for further details). If the observed incidence of second primary cancer will be >2%, with 900 patients we will ensure a similar relative level of precision for these higher incidences. i.e. the Jeffrey's interval around the incidence would lie well within the range of the observed incidence +/- 0.5*observed incidence (i.e. 3% +/- 1.5%, or 4% +/- 2%). To account for any possible lost to follow up patients (assumed to be a maximum rate of 10%), ~1000 patients will be recruited to the study.

4.9. Data analysis

All data will be presented for the overall full analysis set, and by potential risk factors including gender, age, bone metastasis, prior therapies, prior external-bean radiation therapy, radiolabeled-SST analogue tumour uptake, tumour load, type and grade of toxicity during treatment, baseline blood counts and renal function. Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be

summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of Lutathera.

4.10. Planned Milestones

- PRAC/FDA submission of protocol: Q4 2017
- PRAC/FDA final opinion on protocol: Q3 2018
- Competent authority and Ethics Committee submissions, notifications and approvals: Q3 2018
- Site identification, selection, recruitment, set-up: Q3 2018
- Start of data collection: Q3-Q4 2018
- Registration in the EU PAS register and in the US clinicaltrials.gov website: Q3 2018
- Last patient treated: Q3 2020
- End of data collection: Q4 2024
- Final report of study results: Q4 2025

Note: The final study report should be submitted within 12 months of the end of data collection (see section 6). Progress reports will be also produced during the study on a yearly basis.

5. Amendments and updates

Number	**Date**	**Section of protocol**	**Amendment**	**Reason**
1.0	9-JAN-2018	-	NA (first version)	-
1.1	15-JUN-2018	Data collection methods.	-	Changes requested by PRAC (before submission to local EC/CA)

6. Planned Milestones

Milestone	**Planned date**
Registration in the EU PAS register and in the US clinicaltrials.gov website	Q3 2018
Start of data collection	Q3-Q4 2018
End of data collection	Q4 2024
Descriptive interim report 1	Q3 2021
Final report of study results	Q4 2025

Progress reports will be also produced during the study on a yearly basis.

7. Rationale and background

Advanced Accelerator Applications submitted in April 2016 an application for marketing authorization to the European Medicines Agency (EMA) for Lutathera, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. Application was made for the following indication: treatment of unresectable or metastatic, somatostatin receptor positive gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs) including foregut, midgut and hindgut in adults. Positive opinion by consensus was issued by the CHMP in July 2017.

The final application for marketing authorization was submitted to the US Food and Drug Administration Agency (FDA) in July 2017. Approval in the US was obtained on 26 January 2018 for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors, in adults.

To support the marketing authorization application both in Europe and US, the applicant submitted results from 2 clinical trials: The Erasmus Medical Centre (EMC) phase I/II study and the multicentre randomized phase III NETTER-1 trial (EudraCT number 2011-005049-11; IND number 77219).

The review conducted by the CHMP and the FDA concluded that the safety data provided was limited owing to the lack of routine safety recording in the Erasmus study and the limited long-term follow-up data from the NETTER-1 study. To this purpose, a post-authorization safety study was recommended to assess the long-term safety of Lutathera. This was in line with the Applicant's proposed Pharmacovigilance Plan.

The SALUS post-authorization safety study, will be conducted with the aim to assess the safety profile of Lutathera, and to characterize further the potential safety hazards described in the Risk Management Plan (RMP). It is part of the MAH-proposed safety management to monitor the long-term safety follow-up of Lutathera in the post-authorization setting.

The SALUS study will be implemented with the objective to address the important identified risks, important potential risks, and relevant missing information from the controlled clinical trials conducted to obtain the marketing authorization of Lutathera.

Important Identified risks: renal dysfunction, acute myelosuppression, acute cytopenias, long-term myelodysplastic syndrome (MDS), leukaemia, hypogonadism, sexual dysfunction, drug-drug-interaction with somatostatin and somatostatin analogues.

Important Potential risks: hormone release-induced crises, hepatotoxicity, radiotoxicity.

Missing information: radiation exposure during breast feeding, renal impairment, severe hepatic impairment, secondary non-hematologic malignancies, and long-term safety data.

8. Research question and objectives

Research Question:

What is the long-term safety profile of Lutathera when used according to the label indication (SmPC/USPI)?

Primary research-objective:

To assess the incidence and nature of potential long-term second primary malignancies, including solid tumours and haematological neoplasia in patients with unresectable or metastatic, well-differentiated, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours.

Secondary research-objectives:

- To quantify the incidence of other important identified and other potential risks specified in the Lutathera Risk Management Plan (RMP) such as: renal dysfunction, myelosuppression/cytopenias, myelodysplastic syndrome, hypogonadism, sexual dysfunction, drug interaction with somatostatin/somatostatin analogues, tumour cell lysis-related hormone release-induced crises, hepatotoxicity, radiotoxicity.
- To detect potential new risks overall, and potential risks in patients under-represented in the clinical trial, including elderly patients, patients with renal and liver impairment, reduced bone-marrow reserve, exposure in breast-feeding women, accidental foetal and child exposure.
- To describe the patterns of drug utilisation that may add knowledge about the safety of Lutathera.

9. Research methods

9.1. Study design

This is a Phase IV non-interventional post authorization safety study, using primary and secondary collection of data.

The objective is to assess the incidence of second primary malignancies over a follow-up period ranging from 4 to 7 years in patients with GEP-NETs treated with Lutathera. The design of choice is an observational longitudinal safety follow-up study, designed as a cohort study of exposed patients. There is no formal comparison group. The incidence rate observed in the study will be compared with the expected incidence rate of 1 to 2 % (Strosberg 2017; Brabander 2017). The follow-up of patients will occur up to 7 years after the start of the study, up to patient withdrawal from the study (by patient or physician decision or patient-related motive), or end of participation of Investigator(s), or loss to follow up, or patient death or end of study, whichever comes first. Note that follow-up will continue even if progression occurs.

9.2. Setting

9.2.1. Study Population

Adult patients with unresectable or metastatic, well-differentiated (G1 and G2), somatostatin receptor positive GEP-NETs, treated with Lutathera.

The study population will be identified among:
- patients randomized in the Lutathera arm of the NETTER-1 trial, who are patients with unresectable or metastatic, well-differentiated (G1 and G2), somatostatin receptor positive neuroendocrine tumours of the small bowel (midgut carcinoid tumours);
- patients treated with Lutathera in the CUP/EAP for unresectable or metastatic, well-differentiated (G1 and G2), somatostatin receptor positive GEP-NETs;
- Patients who will be newly treated, for unresectable or metastatic, well-differentiated (G1 and G2), somatostatin receptor positive GEP-NETs, after the marketing authorization of Lutathera.

Inclusion criteria are:
- adult patients (fulfilling the definition of "age of majority" per local regulations),
- with unresectable or metastatic, well-differentiated, somatostatin receptor positive GEP-NETs
- and who were treated with Lutathera (regardless of the quantity and number of doses administered and whatever the reasons for ending).

Exclusion criteria are:
- Hypersensitivity to Lutathera (active substance or any of the excipients),
- presence of established or suspected pregnancy or pregnancy not excluded,
- presence of kidney failure with creatinine clearance < 30 mL/min.

The study population will be representative of the overall source population (i.e the population targeted by the product indication) as few exclusion criterion are applied. We expect to include all GEP-NETs subpopulations (fulfilling the tumour characteristics as per indication), however the midgut-NETs will likely be over-represented in the study population sample since the NETTER-1 study will provide only patients with this tumour type. If subpopulations allows for analysis, incidence of second primary malignancies will be estimated and described for each of these. Of note, patients from the NETTER-1 trial were selected according to the eligibility criteria applied in the trial, especially excluding severe renal failure, uncontrolled congestive heart failure (NYHA II, III, IV), uncontrolled diabetes mellitus as defined by a fasting blood glucose >2 ULN etc. We expect that the selection at inclusion applied in the NETTER-1 study (134 cases, including non-randomized patients enrolled in the NETTER-1 pk/dosimetry sub-study) will be balanced by patients who will be included prospectively in the SALUS registry. Sensitivity analyses will be conducted excluding patients from the NETTER-1 trial to verify the robustness of the study findings. In addition, sensitivity analyses restricted to patients with follow-up longer than or equal to 5 years will be conducted.

9.2.2. Follow-up

All patients from this study will be documented for their second primary tumour and living status during follow-up period ranging from 4 to 7 years. This will be done by Investigators (chart reviews) and/or by contact with the patients or their proxy respondent by site staff (more details are provided in section 9.4).

A list of eligible but not included patients will be maintained at the recruiting centres, including the reason for exclusion, to be able to assess potential selection bias.

9.2.3. Study sites

Sites will be selected based on the high number of patients enrolled during the CUP/EAP. An initial set of circa 20 sites will be invited to participate in the SALUS study. Additional ones could be incorporated later on from the countries where Lutathera will be granted with Market Access.

9.2.4. Study time period

Accrual of the 1000 patients to include in the SALUS study is expected to take place over 18 to 24 months after study set-up.

The data-collection start-date is March 2012 (date of initiation of the EU CUP) and Q3-2018 for prospective new patients.
Date of last, newly treated patient included in the study in: Q3 2020. End of data collection for all patients (retrospective and prospective phase): Q4 2024

Analysis and report will be delivered by Q4 2025.

9.3. Variables

9.3.1. Exposures

Exposure of interest studied in the present study is Lutathera treatment. All study patients will be by definition exposed as this is an inclusion criterion. Exposure is defined as at least one administration of Lutathera regardless of the dose.
However, patients may have received the total planned dose of treatment or less, to a minimum of only one dose. Patients will be further characterized according to the total dose of Lutathera received, and subgroup analysis according to this characterization will be conducted where sample sizes are sufficient.

Use of GEP-NET treatment history such as somatostatin analogs, radiotherapy, chemo-embolization, radio-embolization, surgery, endo-radiotherapy, chemotherapy, kinase/signal-transduction inhibitor, will be expressed in a 2-category variable for each treatment (yes/no). These variables will be described and taken into account (individually or grouped) to adjust for indication bias and allow for a correct interpretation of the results.

9.3.2. Outcomes

Primary Safety Outcomes

The primary safety outcome is incidence and type of a second primary cancer (a solid tumour or an haematological cancer).

This outcome will be systematically asked for, searched for in the patient's chart, and collected in the eCRF during each ''data collection point'' over the follow-up. A second primary cancer will be considered as an outcome when the diagnosis is confirmed with appropriate procedures according to the participating physician (data on diagnosis characteristics and procedures not collected).

Secondary Safety Outcomes

All the outcomes will be systematically documented through patient's chart, and collected during each 'data collection point' over the follow-up.

Specific Safety Outcomes

- AEs and SAEs related to Lutathera
- AEs/SAEs of specific interest related to Lutathera. These are important identified risks and potential risks, as outlined in the RMP:
  - renal dysfunction
  - myelosuppression/cytopenias
  - myelodysplastic syndrome (MDS)
  - hypogonadism,
  - sexual dysfunction
  - drug-drug interaction (DDI) with somatostatin/somatostatin analogues
  - tumour cell lysis-related crisis
  - hormone release-induced crises
  - Hepatotoxicity
  - radiotoxicity.
- mortality (all causes)
- new AEs/SAEs related to Lutathera, in particular those related to the safety concerns classified as "missing information" in the RMP, such as:
  - radiation exposure during breast-feeding,
  - exposure in patients with renal impairment,
  - and exposure in patients with severe hepatic impairment.

Safety outcomes (primary and secondary) will be collected in AE/SAE forms. As defined in Sections §9.6.1 and §9.6.2, they will be coded with MedDRA.

Other Outcomes

- Impact of tumour location at baseline on the safety profile. Safety profile will be described according to initial GEP-NET location.

Other Secondary Outcomes

- Description of Lutathera use patterns: dose per administration, total dose, number of administrations, total duration from 1st to last administration, number of patients with dose modification, number of patients with switches from Lutathera to another drug, in the overall population and according to subgroups: age, type of GEP-NET, baseline renal impairment, baseline hepatic impairment.

9.3.3. Other variables

Covariates will be considered for descriptive analyses and sub-group stratification, as relevant, and include, where available in the dataset: age, type of GEP-NET, anti-cancer treatment used, comorbidities and history of previous malignancies.

The following variables will be considered for descriptive assessments.

Variables to characterize patients at baseline:

- Age and sex
- Race and Ethnicity, where possible
- BMI
- Primary GEP-NET site
- Characteristics of the GEP-NET at the time of Lutathera treatment:
  - Unresectable or metastatic
  - Grade (Ki67 index) ≤ G2
  - Progressive disease
  - SSTR uptake score ≥2

Risk factors

- GEP-NET treatment history: somatostatin analogs, radiotherapy, chemo-embolization, radio-embolization, surgery, endo-radiotherapy, chemotherapy, kinase/signal-transduction inhibitor, other to specify
- Existence of a prior malignancy history
- Patient's comorbidities will be described and grouped by clinically relevant categories such as cardiovascular [cardiac, vascular and diabetes] comorbidities, hematologic comorbidities, hepatic comorbidities or renal comorbidities.
- Patient's chronic treatments (other than Lutathera) will be described and grouped according to the same clinically relevant categories as the diseases above.

Variables to characterize Lutathera treatment administered:

- Time between GEP-NET diagnosis and Lutathera first administration date
- Duration of administration period
- Kidney-protectant measures
- Lutathera total administered dose (see section 'Other Secondary Outcomes' above)

9.3.4. Potential confounding variables and effect modifiers.

As there is no association measurement in this study, confounding and effect modifying are not directly applicable here.

However, age, baseline renal impairment and baseline hepatic impairment can be considered as both types of variables; and for this reason stratified analysis will be held on different age subgroups (depending on the distribution that we will find), no-to-moderate renal impairment vs severe renal impairment, and relevant categories for hepatic impairment.

9.4. Data sources

Source data must be available and retained at the Investigational Site (study center) to document the existence of the study subjects and substantiate the integrity of the study data collected. They must include the original documents relating to the study, as well as the medical treatment and medical history documentation of the subject.

The source medical records may include:

- Subject identification (name, date of birth, gender);
- Documentation of eligibility criteria, i.e. medical and medication history, and confirmation of diagnosis, including pathology assessment report;
- Participation in study (including study number);
- Study discussed, signed and dated informed consent form (ICF);
- Social and family environment (dedicated questionnaire);
- Dates of all visits;
- Pathology, laboratory and Specialist's (e.g., ECG) reports;
- Images/scans (e.g., SPECT-CT, Ga-68 PET, OctreoScan® and CT/MRI) and reports;
- Documentation that protocol-specific procedures were performed;
- Study medication start and end dates;
- Record of AEs and other safety parameters;
- Record of previous and concomitant therapies;
- Date of study completion or reason for early discontinuation (if applicable).

The following documents are also considered as source documents: subject diaries, nurse records, and worksheets.

The author of an entry in the source documents should always be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the eCRF are consistent with the original source data.

9.4.1. Data collection overview

The SALUS study population will consist of:

a. Available data from the NETTER-1 study (Lutathera arm) will be automatically merged in this long-term safety study database, following re-consent process according to local regulation.

b. Patients enrolled in the CUP/EAP at the selected sites:

   i. Identification of patients will be performed thanks to a review of records in the participating centres;

ii. A retrospective data collection from CUP/EAP patients that completed Lutathera treatment, and that are expected to be followed-up at the same institution where the treatment was administered (the EU CUP started in March 2012 and the US EAP in January 2016), will be performed for baseline data and for semi-annual data (or more frequently if the information is available at site) until the moment of the study start;

iii. Then, a prospective data collection will start for these patients for a maximum of 7 years from this long-term safety study activation, or loss-to FU, or death.

c. Newly treated patients with Lutathera upon its availability on the market:

i. Identification of these patients will be performed thanks to a review of records in the participating centres;

ii. A retrospective data collection from patients that completed Lutathera treatment, will be performed for baseline data and for semi-annual data (or more frequently if the information is available at site) until the moment of the study start;

iii. Then, a prospective semi-annual data collection (or more frequently if the information is available at site) will start for these patients for a maximum of 7 years from this long-term safety study activation, or loss-to FU, or death.

Baseline is defined as the period just before the first treatment administration; all available follow up information available at site will be collected until the end of their planned follow-up or death, whether they have received the whole Lutathera regimen or not.

During the recruitment period that will occur over the 18-24 months after study set-up, participating physicians will be instructed to invite all identified eligible patients without exercising any selection, thus the recruitment should be consecutive. Patients previously administered with Lutathera in the CUP/EAP and patients who initiated their treatment with Lutathera after its availability on the market, will all be invited to participate in the SALUS study to collect follow-up information up to a maximum of 7 years from the date the study commences recruitment. All available anonymized/pseudonymized data, including long term follow up, from the patients who previously consented to the NETTER-1 study and who were treated in the Lutathera arm will be utilized and automatically merged in this long-term safety study database.

Patients (in case of death, next of kin when applicable) will be provided with an information sheet about the SALUS study and a patient consent form to participate in the study and will be given sufficient time to read and understand the information given and will have the opportunity to give back a positive or negative answer to this invitation (for more details, see section 10).

By agreeing to participate in the cohort, patients accept their medical data to be collected at baseline (just before the first treatment administration), and during the whole time of follow-up.

A list of eligible but not included patients will be maintained at the recruiting centres, including the reason for exclusion, to be able to assess potential selection bias.

9.4.2. Follow-up of patients

- All patients will be followed in a similar way whatever the group they were originally from (NETTER-1, CUP/EAP or prospective/new). Except for NETTER-1 patients who are followed-up every 6 months as per protocol, the other patients enrolled in this long-term safety study will follow a routine care (no visit imposed) where drug administration, clinical assessments, questionnaires, biological samples, and patient follow-up are performed as part of the standard institutional practice.
- However, a minimisation of attrition rate will be sought through:
  - Recalls of Investigators on time milestones;
  - Contact with patients and/or their proxy respondent by mail and/or telephone and/or SMS (consent will be obtained at entry in the cohort), by site staff;
  - Contact with the patients' usual physicians (consent will be obtained at entry in the cohort), by site staff. Physicians will not be asked to plan visits of patients or apply any specific testing, examination or biopsy solely for the purpose of the study. This is a non-interventional study. Nevertheless, participating physicians will be reminded to register all available follow up data up to the most recent contact.. They will be asked to fill in an e-CRF for each visit, with the record of the medical information and tests results available. If no patient' visit is planned, no CRF will be completed. The CRF will be completed when new medical data are available. Participating physician will also record regularly information on the vital status of patients (alive or dead; if dead – date and causes of death) during the whole follow-up.

9.4.3. Data collection during the study

The SALUS study is observational in nature for patients treated with Lutathera, with unresectable or metastatic, well-differentiated (G1 and G2), somatostatin receptor positive GEP-NETs and who will be managed according to routine clinical care. No visit will be imposed.

All patients who consent to participate will be intended to be followed up to 7 years from this long-term safety study activation or until death, whichever comes first (see Table 1).

For each patient in the cohort, the data collected will start just before the first administration of Lutathera for patients' characteristics at baseline.

Patients will be identified in all study records by a unique study code to preserve patient confidentiality. Data will be collected either by an external researcher or a member of the care team according to local regulations (to be agreed in each country before data collection commences). Data will be uploaded onto a pseudonymized eCRF via a web-based platform. The e-CRF will be designed to register follow up data

every-6-months (or more frequently if the information is available at site). A 6-month frequency follow-up is considered part of a normal follow-up of patients with such condition. However, this 6 month-frequency is an indication: if a patient has a planned visit at 4 months or at 9 months after the previous one, then the data will be collected at the 4- or 9-month visit date. Censoring may occur due to lost to follow-up, interfering event (radical intervention, other major illness interfering with study, patient withdrawal from study, death).
All available data related to the study endpoints from the medical records of eligible subjects will be collected from baseline until the end of the observation period, i.e. for subjects who have died from baseline until their date of death and for subjects who are still alive data will be collected from baseline until the most recent documented contact before the end of data collection.
Efforts will be made to identify causes of loss to follow-up through contacts with the recruiting sites, e.g. asking them to reach patients treating physician or to access to national mortality records where applicable or to use any other available source to document causes of loss to follow-up.

9.4.4. Medical data to collect

All physicians participating in the study will fill in an e-CRF at baseline and at subsequent so-called "point of data collection", reporting the most recent information available since the previous follow-up (the same e-CRF will be used for each follow up):

The Baseline e-CRF visit will record the following data based on availability:

- Day, month and year of birth
- Sex
- Height and weight
- Race and Ethnicity, where possible
- Social and family environment status (dedicated questionnaire)
- Disease and past treatments at baseline:
  - Primary GEP-NET site
  - GEP-NET diagnosis date
  - GEP-NET treatment history and date of administration: somatostatin analogs, radiotherapy, chemo-embolization, radio-embolization, surgery, endo-radiotherapy, chemotherapy, kinase/signal-transduction inhibitor, other to specify
  - Prior malignancy history
  - Lutathera treatments and kidney-protectant measures
  - Characteristics of the GEPNET at the time of Lutathera treatment:
    - Unresectable or metastatic
    - Grade (Ki67 index) ≤ G2
    - Progressive disease

  - SSTR uptake score ≥2
- Any manifestation the patient experienced under Lutathera:
  - Secondary malignancy
  - Renal dysfunction
  - Myelosuppression
  - Hypogonadism
  - Hepatotoxicity
  - Hormone-release crisis
  - Other clinically relevant event
- Patient's current comorbidities and history: cardiac, vascular, metabolic, endocrine, hematologic, hepatic or renal impairment and others to specify.
- Patients current chronic treatments (other than Lutathera)

The follow-up e-CRF visits will record the following data based on availability:

Participating physicians are instructed to complete an adverse event report form for any clinically relevant finding during follow-up, even retrospectively.

- Current patient's vital status: alive, deceased, unknown and last known alive date
- Current treatments: any and anti-cancer
- Any manifestation the patient experienced since last visit: to report if presence or absence of the manifestation; and if yes: to specify the confirmed diagnosis:
  - Second primary malignancy
  - Renal dysfunction
  - Myelosuppression
  - Hypogonadism
  - Hepatotoxicity
  - Hormone-release crisis
  - Other clinically relevant event
- Physical Examination: Normal/abnormal; clinically relevant or not; and if clinically relevant: to specify the finding and to report it in a AE report form:
  - General Appearance
  - Skin
  - Eyes, Ears, Nose & Throat
  - Head, Neck & Thyroid
  - Cardiovascular
  - Respiratory
  - Abdomen

  - Extremities
  - Genitalia
  - Anorectal
  - Lymph Nodes
  - Muscular-Skeletal
  - Neurological
  - Others to specify
- Vital Signs: Blood pressure, pulse, weight
- ECG trace findings
- Hematology: WBC, RBC, Hb, HCT, MCV, MCHC, PLT, neutrophils, lymphocytes, monocytes, eosinophils, basophils, reticulocytes
- Biochemistry: sodium, potassium, chloride, bicarbonate, calcium, urea, creatinine, total protein, total Br, albumin, ALT, AST, AP
- Phone Contact: dates and outcomes
  - Current patient's vital status
  - Current treatments
- End-of Study form:
  - Off-study reason:
    - Study plan completed
    - Withdrawn prior to enrolment: PI's decision/Patient's decision/Lost to FU
    - Withdrawn after enrolment: PI's decision/Patient's decision/Lost to FU
    - Death
    - Other to specify
  - Current patient's vital status
  - Current treatments

All AEs occurred during treatment and follow-up will be collected prospectively and retrospectively.
For each AE, the following information will be collected: description of the AE, start and end date, CTCAE grade, seriousness, actions taken (e.g. concomitant medications and procedures performed), outcome, relationship with the drug, plausibility of the relationship. For more details, see section ' Management and reporting of adverse events (AE) / adverse reactions (ADR)'.

Table 2: Data to be collected from Medical Records if available

Assessment	Baseline[(1)]	LutTx[(2)]	6-monthly FUP PostLutTx[(3)]
Informed consent confirmation	X	-	-
Demography	X	-	-
Diagnosis & past cancer treatment history	X	-	-
PRRT risk factors	X	-	-
Lutathera treatment		X	
Vital signs and physical examination[(4)]	X	X	X
Performance Status (ECOG)[(5)]	X	X	X
Haematology[(6)]	X	X	X
Biochemistry[(7)]	X	X	X
Urinalysis[(8)]	X	X	X
Electrocardiogram (ECG)	X	X	X
Radiological tumor assessment[(9)]	X	X[(10)]	X
Tumor biomarker assessment[(11)]	X	X	X
Clinical progression[(12)]	X	X	X
Metabolic assessment based on SRI[(13)]	X	X	X
Adverse Events	X	X	X
Current/ Concomitant medication	X	X	X
Social and family environmental questionnaire[(14)]	X (at enrolment if possible, otherwise any time after consent)		

[(1)]**Baseline**: Last visit prior to 1st Lutathera treatment
[(2)]**LutTx**: Lutathera treatment visit
[(3)]**PostLutTx**: Post-final Lutathera treatment visit. Follow up data will be tentatively collected on a 6-monthly basis, depending on standard care local practice and source documents available at sites.
[(4)] **Vital signs:** Pulse rate (sitting, if available), Systolic and diastolic blood pressure (sitting, if available). **Physical examination:** General Appearance, Skin, Eyes, Ears, Nose & Throat, Head, Neck & Thyroid, Cardiovascular, Respiratory, Abdomen, Extremities, Genitalia, Anorectal, Lymph Nodes, Muscular-Skeletal, Neurological.
[(5)] **Performance status:** the ECOG scale should be used
[(6)] **Haematology:** Only normal/abnormal status, and clinical relevance as well as values and units for abnormal clinically relevant parameters, will be collected for White Blood Cells (WBC), Red Blood Cells (RBC), Haemoglobin (Hb), Haematocrit (HCT), Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin Concentration (MCHC), Platelets (PLT), Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, Reticulocytes.
[(7)] **Biochemistry:** Only normal/abnormal status, and clinical relevance as well as values and units for abnormal clinically relevant parameters, will be collected for Sodium, Potassium, Chloride, Bicarbonate, Calcium, Urea, Creatinine, Total protein, Total bilirubin (Tot. Br), Albumin, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (AP), Gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH).
[(8)]**Urinalysis**: Only normal/abnormal status and clinical relevance as well as values and units for abnormal clinically relevant parameters will be collected for Protein, Glucose, Red Blood Cells and Leukocytes, pH.[(9)]**Radiological assessment**: as measured using Magnetic Resonance Imaging (MRI) or Computerized Tomography (CT) and according to RECIST Version 1.1 (see Annex 1. RECIST Criteria Version 1.1)
[(10)]Only after the 2nd and 4th Lutathera treatment and on a 6 monthly interval thereafter
[(11)]**Biomarker assessment**: Urinary 5-hydroxyindoleacetic acid (5-H1AA) and Chromogranin A, if available and according to routine clinical practice at the site, will be collected
[(12)]**Clinical progression assessment**: as assessed/ recorded by the Investigator at the site
[(13)]**Metabolic assessment based on SRI** (eg Octreoscan, Tektrotyd, Ga-SSA-PET): if available and according to routine clinical practice at the site
[(14)] When possible, alive patients should be asked to compile the study questionnaire to collect data on social and family environment status to characterize potential radiation exposure (at enrolment if possible, otherwise any time after consent).

If needed and taking into account the inherent limitations of a non-interventional and largely retrospective study, an attempt to collect and analyze additional variables on treatment effectiveness may be performed to respond to questions from Health Technology Assessment Agencies or other Agencies.

9.4.5. Operational steps to set up the study

Study set-up activities ('pre-study activities') will include:

- **Ethics Committees submission process**
  - Study agreement/documents preparation for submission to ECs / Local Health Authorities, as applicable
  - Ethics committees' submission fees, as/when applicable
- **Sites selection**
  - Circa 20 sites have been already identified as being the most representative ones in terms of potential recruitment
  - The selected CRO will send invitation letters to all known sites to propose the study participation.
  - After signature of the confidentiality agreement, the CRO will share with the sites the start-up documents package, which includes (but it is not limited to) the synopsis and protocol, the e-CRF template, the study presentation.
  - In case a site will decline participation, the reason will be documented by the CRO.
- **Study activation**
  - The selected sites will initiate the local start-up process with the support of the CRO: local EC submissions (when relevant), contracts negotiation and execution and collection of study documents (e.g. Financial Disclosure forms from the participating Investigators, Protocol signature page, Site staff delegation log, Site staff Study/eCRF/GCP/SAEs-pregnancy notification training logs etc).
  - Before patient's recruitment activation, the CRO will provide a Site File dossier to each site containing all the needed study documentation.

9.4.6. Monitoring during the course of the study

During the course of the study, each participating site will be monitored by CRAs either remotely and on site (frequency of monitoring can be modulated according to identified needs and number of patients enrolled):

- Contact will be done by phone to explain the study and its process, verify acceptance to participate and general study conditions.
- Regular monitoring contacts (whether by visit or phone, as needed) will be done with the sites to ensure the processes adherence to protocol, that data collection was performed in an unbiased

manner, according to study instructions and consistently with the source documents available at site. The site staff will be trained by the assigned CRAs during the initiation visit; re-training sessions will be organized as needed. For patients already treated, the retrospective data collection will start immediately after the activation of the site. Prospective data will be collected as the information becomes available at the site.

- Besides monitoring visits, risk based audits will be conducted by Sponsor (clinical sites/CROs to be audited are targeted at a minimum of 5% where the percentage can increase, if deficiencies are discovered) to ensure that all the patients were consecutively recruited or documented in the Registry of eligible non-included patients, and to verify the accuracy and completeness of the information collected in the CRF for the eligible included patients.

During the entire study, a thorough data cleaning process will be implemented (automatic queries and manual queries from medical review) to minimise and ideally avoid missing and inconsistent data.

9.5. Study size

This study which is mainly descriptive in nature does not implicate hypothesis testing so no formal sample size calculation based on current or historical comparisons has been or will be performed. However, from the accumulated clinical data available to date, it is expected that by early 2018 the average number of patients that should have been exposed to Lutathera will be around 2500, and from the historical series of patients receiving Lutathera (i.e. EMC phase-I/II study) the expected incidence of second primary malignancies may be between 1 - 2%.

Various hypotheses on the confidence level of the precision and of the expected incidence of second malignancies have been made to estimate the adequate size of the population exposed to Lutathera which would be necessary to characterize the events of interest (Table 2). As the expected incidence is small, calculations with precision of 1% were considered appropriate (Table 3). Jeffreys intervals were used as suitable estimates in this situation where the expected incidence levels required to be detected were low.

Table 3. Sample size calculations for various confidence levels and frequency of outcome factor in the population hypotheses.

Hypothesized incidence of 2nd malignancies	Precision*	Confidence Level	Sample Size required
1%	1%	95%	650
1%	1%	80%	300
1.5%	1%	95%	810
1.5%	1%	80%	360
2%	1%	95%	1050
2%	1%	80%	460

*confidence limits to be within the hypothesized incidence +/- 1%.

In the Erasmus Medical Center (Erasmus MC, Rotterdam, the Netherlands) study the maximum required follow up to second primary cancer out of patients with a second primary cancer is about 50 months in the targeted population (Brabander 2017) [55 months for patients developing acute leukemia (AL) (n=4, range 32-125 months) and 28 months for patients developing myelodysplastic syndrome (MDS) (n=9, range 9-41 months)]. Therefore, a seven-year study duration, with a minimum follow up of approximately 4 years for the last patient included, has been chosen to ensure adequate follow up of the patients to characterize the incidence of the events.
Based on Table 3 above, it is considered that ~900 patients would provide suitable precision (+/- 1%) and level of confidence considering the range of incidences that could occur. If the observed incidence of second primary cancer is >2%, with 900 patients we will ensure a similar relative level of precision for these higher incidences. i.e. the Jeffrey's interval around the incidence would lie well within the range of the observed incidence +/- 0.5*observed incidence (i.e. 3% +/- 1.5%, or 4% +/- 2%).

Given the high mortality due to patient's initial primary malignancies over the study time, correcting the required sample size for the competing risk with death was considered. However, as the primary objective of the trial is to estimate the incidence rate of 2nd malignancies in this population of all patients treated with Lutathera, the fact that some patients will die before having chance to develop the 2nd malignancy, was felt to reflect the broader population that this result would be applied to, and so no correcting for this competing risk is proposed. Nevertheless, with 900 patients in the trial it is expected ~450 patients will survive for at least 5 years (median overall survival in the targeted population is about 60 months (Brabander 2017)) and a proportion of the shorter surviving patients will also have had long enough follow-up to develop the 2nd malignancy, and so subgroup analyses of patients with longer follow-up are considered likely to have reasonable power to detect incidence rates with suitable precision.

The impact of patients who may be lost to follow-up was considered on the required sample size. It is expected to be at a maximum rate of ~10%. Therefore approximately 1000 patients will be included in the study to ensure that approximately 900 patients are followed up over 7 years from the start of the study (up to the end of the study or death if before).

9.6. Data management

Data management and handling of data will be conducted according to the study specific Data Management Plan and CRO standard operating procedures (SOPs). Data for this study will be captured using pseudoanonymized eCRFs.

Shortly before the study start, the Study Monitor (the CRO Project Manager/Clinical Research Associate) will meet with the Investigator and Investigational Site Staff involved in the study in order to explain and reviewing all procedures regarding study conduct and recording of data in the eCRF. The site staff will be provided with Data Collection Guidelines to facilitate consistent completion of the eCRF.
Data collection and entry into the eCRF will be the responsibility of the designated Investigators.
The Study Monitor will review the eCRFs and evaluate them for completeness and consistency. The accuracy and quality of data collection will be monitored by source data verification (SDV). SDV will be performed on the complete dataset of 100% of patients from each center. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. SDV will be performed by a member of the care team or other member of the study team (e.g. a researcher based at the study center or an external researcher) who did not collect data for that subject record and using a methodology appropriate to local regulations and requirements for consent. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee (e.g. a member of the care team or an external researcher, as appropriate according to local regulations).

Once the clinical eCRF data have been submitted, corrections of the data fields will be audit trailed, meaning that the reason for change, as well as the name of the person performing the change will be registered together with the change date and time. Roles and rights of the site personnel responsible for entering the data into the eCRF will be determined by the Principal Investigator.

The data will be subjected to validation according to the Data Validation and Medical Review Plans and relevant SOPs in order to ensure that the information in the eCRF is complete, consistent and accurate.
If corrections to an eCRF are needed, the responsible Study Monitor or Data Manager will raise a query in the eCRF application. The Investigator will be responsible for resolving data queries issued by CRAs and Data Management team. A system audit trial will be used to maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of study personnel authorizing entry or change.

Prior to the database lock, the eCRF will be completed and electronically signed by the Principal Investigator or authorized delegate from the clinical study site staff. A complete eCRF package will be transferred to Sponsor and the Investigator will receive a copy at the end of the study.

For any data transfer, measures will be undertaken to protect subject data handed over against disclosure to unauthorized third parties and subject confidentiality will be maintained at all times.

9.6.1. Data collection

This study will be monitored by Sponsor-appointed Study Monitor and may also be audited/ inspected by the CRO, Sponsor or by an independent body and/or authorities. By agreeing to this Protocol, the Investigator

agrees to fully co-operate with compliance checks by allowing access for authorized individuals to all relevant study documents.

It is a prerequisite of the Investigator's participation in this study that the Study Monitor has access to source data for data collection and verification, according to subject consent and local regulations. All information on CRFs must be traceable to these source documents in the subject's file (permission will be sought from the subject/next of kin if required, as part of the consent process). Access to source documents will also be required for representatives of the Sponsor and may be required for regulatory authorities, according to subject consent and local regulations (see Annex 2).

In addition, participation and personal information will be treated as strictly confidential to the extent the applicable law permits and will be not publicly available. In case of an audit or inspection, this may include, for example, a review of all source documents, drug records, original clinical medical notes, some or all of the facilities used in the study.

Data are collected in CIMS V5.1, a fully validated FDA 21 part 11 CFR compliant application. Data processing, handling and cleaning will be conducted in adherence with the GDMP (Good Data Management Practices), and data protection laws, under the guidance of company SOPs and working guidelines. Application and data access are strictly controlled.

During each step of the study lifespan:

- Study start-up: study collection tools/system modules review; Case Report Form (CRF) creation and annotation; database structure and development specification document creation; data entry screen and database validation; creation of the following documents: i) Data Management Plan (DMP) ii) e-CRF completion guidelines (eCCG) iii) Data Validation Plan (DVP).
- Ongoing study process: data review and validation; query management, database updates; generation of study reports; SAE reconciliation; medication & AE coding; study data management documents maintenance (including Data Review Guidelines); periodic database quality controls.
- Coding: medication reported by the participating physician, or from any other source (prescriptions if any) will be encoded by using the WHO drug dictionary. All diseases, comorbidities or adverse events reported will encoded by using the current MedDRA version. The same version of WHO drug Dictionary and MedDRA will be used from the start until the end of the study.
- Study end: final quality control performance per Data Review Guidelines; database finalization check prior to lock; creation of the data management report; database lock process; archiving of study documentation.
- Application and associated database for medical data are hosted on CRO's secure servers with strict access control.

- The physical and environmental policy defines the primary requirements for physical security for information and information technology and is used throughout CRO. It ensures the protection of equipment from security threats and environmental hazard, e.g. fire protection measures. All CRO facilities housing CRO business and information technology equipment provide physical protection from unauthorised access, damage, and interference, offering protection by a defined parameter with appropriate entry controls and security barriers.
- Administration and configuration of security parameters on servers and database systems is limited to information security personnel, and is performed in accordance with best practices as to protect CRO information assets against unauthorised access.
- All computers are accessible through personal secured identifier and password. Initial password is randomly generated, and forced for change at first logon by the user. Passwords follow complexity requirements (minimum 8 characters, alpha numeric, special character construction, lowercase and uppercase). All passwords are changed at the LDAP level on a quarterly basis. All computers are protected using Symantec Endpoint Protection Software.
- The application is accessed via secure UAL (SSL encystation technology or https). User access to CIMS systems is granted strictly based on demonstrated business need, with procedures for request, approval, granting, changing and removal of system access to individuals. Different levels of access are strictly controlled.
- Each user to CIMS is given a unique, non-shared identifier and password for the performance of set tasks, to ensure proper accountability. System generated temporary passwords are granted and changed by the user to a private password of their choice following strong password criteria and complexity requirements upon first logon. Passwords are stored encrypted.
- Data integrity is protected by CRO's user access management process, which allows data and system access to individuals based upon demonstrated business need for such access. All data and operations to the data are stored in audit trail.
- Database Maintenance: To maintain the integrity and availability of IT services, system maintenance and back-up procedures are developed. Such procedures specify appropriate periodic maintenance activities associated with each system depending on classification. Patches and releases are tested based on security requirements prior to development. All patches and releases are applied using proper change control procedures.
- All CRO data exist in at least two physical locations. Back-up requirements include the storage of copies of data either on or offline.

9.6.2. Medical coding

Coding of prior and concomitant medications will be performed using WHO Drug Dictionary. AEs and Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

9.6.3. Anti-Fraud Protection

Compliance with ITMCI (IT Management, Compliance and Integration) network policy ensures anti-fraud protection through the following (but not limited to) means: 1) Continuous checking of the Network systems; 2) Data Encryption; 3) Network perimeter security; 4) Internet security (internal data is protected from the internet through firewall controls); 5) Email usage (email for business use only, the email transmission of CRO critical information strictly forbidden); 6) access to networked systems is logged, where determined critical the logging of transactions is included, the log data is restricted; 7) LAN security is ensured through operating system security, remote LANs are connected through Virtual Private Networks. The communications between LANs encrypted using strong encryption mechanisms. LAN data directories are protected against unauthorized access using operating system access control mechanisms, controlling read/write/delete access rights on a least privilege basis.

9.7. Data analysis

Analyses including procedures for data preparation are performed using SAS software version 9.2 or higher (SAS Institute, Inc. NC, USA).

In addition, other tools could be used to explore the data and prepare some graphs.

Statistical methods will be described in detail in the Statistical Analysis Plan (SAP).

9.7.1. General principles for data analyses

All analyses will be mainly descriptive in nature and no formal hypothesis will be tested.

9.7.1.1. Management of extreme/aberrant and missing values

Prior to any analyses data will be checked for missing and aberrant values.

Extreme or aberrant values will be checked and managed differently whether the value is an outlier (the value is true but out of usual range) or an oversight (non-plausible value). Outliers will be reported using the min and max in Tables. Non-plausible values will be treated as missing values.

Missing data will be reported. No imputation will be made on missing data for descriptive analyses.

9.7.1.2. Analysis population

The primary analysis population will be the population of all eligible patients included in the study.

Patients will be followed up to 7 years from the start of the study, regardless incidence of second malignancy, unless they die or they are lost-to-follow-up.

Stratified or subgroup analysis might be considered if deemed relevant (see 9.7.4).

9.7.1.3. Descriptive analyses methods

All analyses will be performed for all countries and sites together.

Categorical variables will be described by counts n and % on each category.

Continuous variables will be described by mean, standard deviation, median, interquartile and min-max ranges.
No imputation will be performed on missing data. Instead, missing data can be reported as an independent category.
In addition, if relevant, outcomes will be reported through their Incidence in population-time (person years): the number of events, the total number of person-years of the population considered and the incidence rate (/10,000 py) and its 95% confidence interval.

9.7.2. Context of data collection

Prior to the data analysis, the context of data collection will be described. This includes the description of:
The recruiting physicians from which patients' data were collected will be described in terms of:

- Number of patients treated per year.
- The time window covered by the data collection (in years).
- The time elapsed between Lutathera first administration and inclusion in the study (in months). Summary statistics will be provided as well as the full distribution displayed as a histogram. Median times will also be reported per index year.

9.7.3. Analysis

Firstly, descriptive analyses will be performed on the analysis population:

- Sociodemographic: country of inclusion, age (in years), gender, body mass index
- Baseline data, risk factors and variables to characterize Lutathera treatment administered (section 9.3.3).

Secondly, assessment of the long-term safety profile of patients will be performed through the following endpoints:

1. Estimation of the incidence rate of second primary malignancies, further divided on solid tumours and haematological malignancies.
2. Description of the type of second primary malignancies
3. Estimation of the incidence rate of all AEs at least possibly related to Lutathera
4. Estimation of the incidence rate of serious AEs at least possibly related to Lutathera
5. Incidence rate of mortality overall and by cause
6. Incidence of all AEs reported

All collected AEs will be analysed descriptively.
The occurrence of AEs can be described by:

- total number (and by country);
- type of adverse events (by body system);

- severity (CTCAE grade);
- relationship to treatment;
- duration;
- seriousness and seriousness criteria;
- action taken (or no action taken);

Lutathera use patterns will be described: dose per administration, cumulative dose, number of administrations, total duration from 1st to last administration, patients with dose modification, patients with switches from Lutathera to another drug.

If needed and taking into account the inherent limitations of a non-interventional and largely retrospective study, an attempt to collect and analyze additional variables on treatment effectiveness may be performed to respond to questions from Health Technology Assessment Agencies or other Agencies.

9.7.4. Subpopulations and sensitivity analyses

Sub-analyses will be made to further evaluate the long-term safety of Lutathera in the sub-populations of patients, this may include but is not limited to:

- Patients stratified in age groups: to be defined according to the description of baseline patient's characteristics.
- Patients with renal impairment
- Patients with hepatic impairment
- Patients grouped by exposure
- Patients stratified on race/ethnic groups,
- Other ''missing information'' subpopulations if figures allow it.

Sensitivity analyses without patients from the NETTER-1 trial will be performed to check the robustness of the study findings. In addition, sensitivity analyses restricted to patients with follow-up longer than or equal to 5 years will be conducted.

9.8. Quality control

The Sponsor or delegated CRO is implementing and maintaining quality assurance (QA) and quality control (QC) systems with written SOPs to ensure that studies are conducted and data are generated, documented (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor will conduct risk based quality audits of selected clinical sites and CROs using risk based parameters/indicators to rank the sites based on risk. For example, clinical sites will be inspected based on risk based indicators such as: number of patients enrolled (e.g. highest patient enrollment), evaluation of

monitoring reports/monitoring issues, number of patients screened/randomized (e.g. highest screen failures), number of protocol deviations; number of inclusion/exclusion deviations, number of reported adverse events (AEs), sites with noted regulatory deficiencies, or sites with multiple clinical trials, etc.

Clinical sites/CROs to be audited are targeted at a minimum of 5% where the percentage can increase, if deficiencies are discovered. The auditor is independent from the clinical monitoring and project management team at the Sponsor's and CRO site. The audit may include on-site review of regulatory documents, eCRFs and source documents. The auditors will have direct access to these documents.

On a periodic basis (not less than bi-annually), reconciliation between AAA pharmacovigilance safety database and the clinical database will be performed. At minimum, the following items will be reconciled: site and patient ID, gender, age at time of onset of event, AE reported term(s), event onset/end date, outcome, seriousness criteria, date of death (if applicable), treatment start and action taken with the drug, reported causality.

9.9. Limitations of the research methods

- Selection bias: recruitment of patients will be done consecutively to avoid selection bias. Besides monitoring visits, audits will be conducted in randomly selected sites on randomly selected time-period to ensure that all the patients are consecutively recruited or documented in the registry. Reason for exclusion of eligible patients not included in the study will be collected in the eCRFto allow a comparison with enrolled patients and their geographical distribution to be able to assess potential selection bias.
- Informed written consent will be obtained from all participating subjects. Where next of kin consent is not required by local regulation for patients already deceased at time of enrolment, pseudonymized data collection will be performed when the clinical information is available at the centre, by the subject's care team to preserve confidentiality, in order to minimize any selection bias (omission of data from patients who already died) (see Annex 2; or contact your local monitor for further information).
- Censoring may occur due to lost to follow up and patient withdrawal from study. Efforts will be made to identify patients lost to follow-up, and to ensure patient visits and data collection continuity. Sites will be encouraged to access national mortality records where applicable.
- Survival bias may occur if eligible patients who are more likely to develop a second primary malignancy or die during the follow-up would not consent to participate in the study. The way of identifying patients in this study will ensure that patients' recruitment is conducted irrespective of the treatment outcomes.
- Morbidity and mortality are particularly important outcomes in this long term follow-up study. This is why particular efforts will be made to document as much as possible those two outcomes in patients with unknown or uncertain status as the follow-up progresses.
    - Vital status will be informed at each physician data collection. In order to prevent a bias related to a higher rate of loss to follow-up among deceased patients, the vital status of patients with an unknown vital status by the end of their planned follow-up will be thoroughly searched by external methods

available in each country participating to the study (in France for instance through the national CepiDc registry or vital status enquiry through records at the town hall of birth). Participating physicians will be instructed to do so.

  - Vital status will be informed for all patients who will have not been included or who refused to participate in this follow-up study in the participating sites, through the participating Investigator or by external methods available in each country participating to the study.

- A similar bias to survival (depletion of susceptible) would be observed if withdrawal from the study would occur early after the start of treatment, for any reason. Measures will be taken to assess and avoid such bias, particularly by documenting the medical history of patients and their previous treatments.
- Information bias may be observed if there is a difference in frequency of follow-up and completeness of data, among patients with and without second primary malignancies or other serious complications. The protocol will detail the method for the collection, measurement and interpretation of information. Efforts will be made during data collection to ensure all available data is correctly completed in the eCRF. Investigators should be blinded to the exposure and outcomes of interest.
- This study should provide generalizable results as it will be conducted in a representative population of the overall source population (i.e the population targeted by the product indication) if no selection bias occurs during the study. We expect to include all GEP-NETs subpopulations (fulfilling the tumour characteristics as per indication) (see section 9.2.1 where representativeness of the source population is discussed, including an assessment of the population difference compared to NETTER-1).

9.10. Other aspects

None.

10. Protection of human subjects

This study will comply with each country's requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

This is an observational study of usual practice as it occurs in the participating countries. There is no intervention and no attempt will be made to modify usual practice. The Data Controller for this study is Advanced Accelerator Applications International. Rue de la tour de l'Ile 4, 1204 Geneva, Switzerland. The study has been designed to minimize the data collected to that which is required for the planned analyses. Data will be collected in pseudonymized format and no personally identifiable information on any participant will be collected or removed from the participating centers in order to preserve patient confidentiality. Subjects will be assigned a study-specific unique patient identification number which will be referenced in a study log. This subject log will not leave the participating center location and will be the responsibility of the Investigator at that study center. Pseudonymized subject data will be processed for the purposes of the research study described in this protocol in accordance with the recognized EU Model Clause Agreement to safeguard participant anonymity. Subjects' data will be retained for a period of five

years after the end of the study (unless a subject withdraws their consent and requests that their data is deleted).

Ethics approval and data privacy approval will be sought in each country, in line with country-specific regulations, and when applicable, in each site participating in the study.

Patients will be provided with a study information sheet and a consent form to be signed before initiating the data collection procedures. Patients will have the opportunity to provide with a positive or negative answer to this invitation without any impact on their health care. Patients who agree to participate in this study will sign an informed consent form. They will be able to withdraw their consent at any time without any impact on their health care.

By signing this informed consent form, patient will confirm that s/he received the Patient Information Guide and had the opportunity to discuss with physician any questions s/he might have regarding the study.

By agreeing to participate in the study, patient will accept:

- their medical data to be collected at baseline and over the whole follow-up period. No visit will be imposed, and the follow-up of patients will be naturalistic. Participating physicians will be asked to fill in an e-CRF for each visit.
- that the participating physician completes an e-CRF in order to record their medical data to be accessible for the study team.
- and that information on their vital status (alive or dead; if dead – date and causes of death) will be collected via their physician, via linkage to the national mortality records when possible or contacts with the patient directly, patient's GP or proxy.

The collection and processing of patients' data will be done in accordance with local applicable laws and regulations governing the processing of data (see Annex 2). For details of data management and security, see section 9.6 and Annex 2.
Available data, including long term follow up, from the patients who previously consented to the NETTER-1 study and who were treated in the Lutathera arm will be utilized and automatically merged in this long-term safety study database, after re-consent process according to local regulations.

11. Management and reporting of adverse events (AE) / adverse reactions (ADR)

An electronic eCRF will be implemented in the sites to facilitate reporting to pharmacovigilance of all adverse events (AEs) / adverse drug reactions (ADR) occurring in the study patients. At any moment the physician who becomes aware of an AE/ADR, the event must be registered in the eCRF.

This AE/ADR form will include the following variables: clinical description of the AE, AE start and end dates, intensity, seriousness, actions taken, outcome, relationship with the drug, and concomitant medications and procedures.

AEs/ADRs will be collected up to 7 years since the date of activation of this long-term safety study.

All participating physicians will be informed about their safety reporting responsibilities and will receive a training to notify all AEs/ADRs via eCRF.

All serious AEs/ADRs identified from the treatment start until the end of the study as defined by the protocol for each patient must be promptly reported by the participating physicians to the Sponsor's pharmacovigilance department.

Participating physician assessment of the seriousness and causal relationship between the AE and the medication received should be provided at the time of the initial report.

Solicited reports derived from this non-interventional post authorization long-term safety study, will include clinical trials (NETTER -1), EU Compassionate Use Programs (CUP) or Name Patient Use (NPU) reports, Expanded Access programs (EAP) and use of marketed drug.

All solicited reports of suspected ADR, which occur in this long-term safety study, will be recorded in the AAA PV database.

Collected adverse events should be systematically assessed to determine whether they are possibly related to the studied medicinal product.

Causality assessment methods should be applied for assessing the causal role of the studied medicinal products in the occurrence of the solicited adverse events.

Serious AEs suspected to be related to the studied medicinal product by the primary source or the notified organization, should be recorded in the AAA pharmacovigilance database.

Abnormal laboratory results, considered clinically significant by the Investigator, will be reported and treated as AEs/ADRs.

All ***fatal outcomes*** should be considered as serious adverse events and should be collected. Investigators should assess whether notified fatal cases refer to study outcomes (efficacy end points eg. disease with high mortality, or because the fatal outcomes have no relation with the study).

The design of this non-interventional this long-term safety study is based on:

- **Primary data collection** directly from healthcare professionals (events of interest collected as they occur specifically for the study),
  AND
- **Secondary use of data** (retrospective), as events of interest have already occurred and have been collected for another purpose.

Pharmacovigilance Data Collection

Patients enrolled	**Current Study Status**	**(Retrospective) Secondary data collection***	**Primary data collection**
CUP/EAP	ongoing	- Serious & Non-serious cases[b]	- Any new ADR/AE - Any serious and non-serious[b] FU report (including fatal outcome)
Erasmus (Phase I/II)	closed	- Serious AE (SUSAR & SAR)	- Any new serious & non-serious ADR/AE
NETTER-1 (Phase III)	FU ongoing	- Serious AE (SUSAR & SAR, regardless the causality assessment) - AESI[a]	- Any new serious & non-serious ADR/AE - Any FU report (including fatal outcome)
SALUS new patients (Phase IV)	planned	Not applicable	- All new serious & non-serious ADR/AE - Any FU report (including fatal outcome)

* *For some retrospective cases, it can be not feasible to make a causality assessment at individual case level.*

[a] *As per NETTER-1 protocol, AEs of special interest: hepatotoxicity, secondary hematological malignancies, nephrotoxicity, cardiovascular events*

[b] *According to national pharmacovigilance regulation applied to Compassionate Use Program (CUP) or Expanded Access Program (EAP)*

11.1. Definitions

In the context of a post-authorization safety study, individual cases of suspected adverse reactions (ADR) are managed in accordance with the provisions of Good Pharmacovigilance Practices (GVP).

Adverse reaction is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
An adverse reaction, in contrast to an adverse event (AE), is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.
Adverse reactions may arise from use of the product **within or outside** the terms of the marketing authorization or from occupational exposure. Use outside the marketing authorization includes *off-label use, overdose, misuse, abuse and medication errors*.
Therefore, all spontaneous reports notified by healthcare professionals or consumers are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the primary source specifically state that they believe the event to be unrelated or that a causal relationship can be excluded.

Occupational exposure. This refers to the exposure to a medicinal product as a result of one's professional or non-professional occupation.

Off-label use. This relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorization.

Overdose. This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.

Misuse. This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorization

Abuse. This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Medication errors. This is an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the patient.

Causality. The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event1.

An **Adverse event** (AE) is defined as any untoward medical occurrence in a patient or clinical investigation patient who have been administered a pharmaceutical product; this untoward occurrence does not necessarily have to have a causal relationship with the treatment.

Serious ADR/AE. A serious adverse reaction corresponds to any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Note: the term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical and scientific judgment should be implemented when deciding whether expedited reporting is required in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require medical or surgical intervention (i.e., specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

11.2. Physician obligations regarding safety reporting

For the prospective portion of the study, all AEs/ADRs identified from the treatment start until the end of the collection period as defined by the protocol for each patient, are to be recorded

- Immediately (within **24 hours** of awareness)
  All serious AE/ADR and/or special situations associated with serious AE/ADR (occupational exposure, off-label use, overdose, misuse, abuse and medication errors) as well as pregnancy reports

- within **30 days** of awareness
  For non-serious AE/ADR and/or special situations associated with non-serious AE/ADR (occupational exposure, off-label use, overdose, misuse, abuse and medication errors)

- within **30 days** of awareness
  For cases of special situations NOT associated with an AE/ADR (occupational exposure, off-label use, overdose, misuse, abuse and medication errors)
  Note: Reports with no associated suspected adverse reaction should be recorded when becoming aware of them and considered in the periodic reports as applicable.

11.2.1 Reporting to the Sponsor's pharmacovigilance department:

Serious and Non-serious AE/ADR:

Enter the information related to the AEs/ADRs in the relevant section of the eCRF (within timelines specified in the section 11.2)
If any AE/ADR is marked as serious by the Investigator/physician in the eCRF, the system will automatically send a notification to the Sponsor. In case of serious adverse events, the SAE form will have to be completed within 24 hours from awareness by the Investigator (training will be provided at the initiation visit).
The SAE form will be sent to Sponsor by fax or e-mail:

Email: [redacted]
or
Fax: [redacted]

The Sponsor pharmacovigilance department may contact the Investigator/physician to ask for further information about the case. Sponsor queries should be responded promptly.

Care should be taken to ensure that the patient's identity is protected and that the patient's identifiers in the study are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
Any further SAE follow up information must be notified to Sponsor within the same timelines as for the initial report. In addition, any effort should be made to further document each SAE that is fatal or life threatening within the week (7 days) following initial notification.

11.3. Safety observations

The physician should take all appropriate measures to ensure the safety of the patients as per normal clinical practice. In case of any serious AE/ADR, the patient must be followed up until clinical recovery is complete and the laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study.

11.4 Causality Assessment Methods

Analysis of causality assessment for the adverse events can be done by the following methods:

- Global Introspection: clinical medical judgment (assessments: related or unrelated)
- WHO-UMC Causality Categories
- Begaud Method (Mandatory for case reports submitted to the French Agency)

WHO-UMC Causality Categories

Causality term Assessment criteria

Certain

- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)
- Rechallenge satisfactory, if necessary

Probable/Likely

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable

- Rechallenge not required

Possible

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal may be lacking or unclear

Unlikely

- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
- Disease or other drugs provide plausible explanations

Conditional/Unclassified

- Event or laboratory test abnormality
- More data for proper assessment needed, or
- Additional data under examination

Unassessable/Unclassifiable

- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

11.5 Study governance

A study governance committee composed of the principal participating physicians and of MAH's representative will be called on a regular basis to review and validate the protocol and data collection tools. The committee will meet at least every 12 months to review all the available safety data. Additional meetings may be called at any time in case of the emergence of events requiring special attention.

12. Plans for disseminating and communicating study results

All information regarding the investigational product under study in the outlined protocol and Sponsor's operations, such as patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by the Sponsor and not previously published, are considered confidential by the Sponsor and shall remain the sole property of the Sponsor. The Investigator agrees to use this information only to perform this study and will not use it for other purposes including publications and presentations without the Sponsor's written consent.

It is understood by the Investigator that the information developed during the conduct of this study is considered confidential and will be used by the Sponsor for the development of the specified investigational medication. This information may be disclosed as deemed necessary by the Sponsor to other Investigators, scientific/medical community, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this study and to ensure complete and thorough analysis, the Investigator is obligated to provide the Sponsor with complete test results and all data developed in this study, and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

Any publication or public presentation of the results of this study must be according to the Sponsor's standards. The first publication is multicenter and coordinated by the Sponsor. The Investigator agrees that before he/she publishes any results of this study, he/she shall send the draft manuscripts and copies of the information to be presented to the Sponsor at least 30 working days before submission to a publisher or presentation. The Sponsor reserves the right to review these materials before submission for publication or presentation. This is not intended to restrict or hinder publication or presentation but instead to allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the investigator(s).

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Directive 2001/83/EC Art 107 m-q, and Regulation (EC) No 726/2004 [REG], as regards the collection, data management and reporting of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in the European Union (EU);

Good Pharmacovigilance Practice (GVP), Module VIII and Module VIII, Addendum I (Rev 1);

Guidelines ICH, E2B(R3) Electronic Transmission of Individual Case Safety Reports Implementation Guide.

Annex 1. RECIST Criteria Version 1.1

The complete criteria are included in the published RECIST 1.1 document (Eisenhauer et al, 2009). A summary is provided below.

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable: Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by CT-scan (CT-scan slice thickness no greater than 5 mm).

10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be P15 mm in short axis when assessed by CT-scan (CT-scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable: Non-measurable are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with P10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Specifications by methods of measurements

Measurement of lesions: All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment: The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT-scan based on the assumption that CT slice thickness is 5 mm or less. When CT-scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).
In addition to the planned measurement of one-dimensional changes in tumor size, an assessment of changes to the tumor volume may be applied. The three-dimensional size (X, Y and Z dimensions) of the tumor would be evaluated by applying a dedicated software on the tumor contours delineated in multiple slices from already available CT/MRI imaging scans. This would be an exploratory evaluation of already available information that may provide additional knowledge by reflecting changes in the three-dimensional size of the tumor as compared with changes reflected in one-dimension only.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only subjects with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether subjects having non-measurable disease only are also eligible.

Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have

only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of P15 mm by CT-scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT-scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm·30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis P10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

1. **Evaluation of target lesions**

   Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

   Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

   Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

   Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2. **Evaluation of non-target lesions**

   Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

   Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

Confirmatory measurement/duration of response

1. Confirmation

In non-randomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies. However, in all other circumstances, i.e. in randomized studies (Phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2. Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

3. Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of subjects achieving stable disease for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

Progression-free survival/proportion progression-free

This guideline is focused primarily on the use of objective response endpoints for Phase II studies. In some circumstances, 'response rate' may not be the optimal method to assess the potential anticancer activity of

new agents/regimens. In such cases ‘progression-free survival’ (PFS) or the ‘proportion progression-free’ at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled study, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as subject selection and not the impact of the intervention. Thus, Phase II screening studies utilizing these endpoints are best designed with a randomized control. Exceptions may exist where the behavior patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomized study is justifiable. However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progression-free in the absence of a treatment effect.

Annex 2. International and EU applicable law acts and guidelines

Country	Applicable Law/Guidelines
United Kingdom	Health Research Authority Guidelines https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/what-law-says/consent-research/ Common Law Duty of Confidentiality https://www.health-ni.gov.uk/articles/common-law-duty-confidentiality NHS Code of Practice https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/200146/Confidentiality_-_NHS_Code_of_Practice.pdf UK Data Protection Act https://www.legislation.gov.uk/ukpga/1998/29/contents GDPR
France	Research involving human subjects *Law n°2012-300 of 5th March 2012* *Ordinance n° 2016-800 of 16th June 2016* *French Public Health Code* https://www.legifrance.gouv.fr/affichTexte.do;jsessionid=1A9B9FF6D07805F41F1740E3F94174FD.tplgfr24s_2?cidTexte=JORFTEXT000032719520&dateTexte=20180516 Data protection https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000000886460 https://www.legifrance.gouv.fr/affichTexte.do;jsessionid=1A9B9FF6D07805F41F1740E3F94174FD.tplgfr24s_2?cidTexte=LEGITEXT000006068624&dateTexte=20180525 GDPR https://eur-lex.europa.eu/legal-content/FR/ALL/?uri=CELEX%3A32016R0679
Spain	Local regulation for conduct post-authorization studies: Orden SAS/3470/2009, 16th December – This is the local regulation that provides guidance on the non-interventional studies in Spain. See link (local language only): https://www.aemps.gob.es/legislacion/espana/medicamentosUsoHumano/docs/farmacovigilancia/rcl_2009_2577.pdf *121/000013 Proyecto de Ley Orgánica de Protección de Datos de Carácter Personal* (comes into force on May, 25th2018). This is the official explanation by the Spanish government (in local language only), which can be found on the link http://www.lamoncloa.gob.es/consejodeministros/Paginas/enlaces/101117enlacedatos.aspx
Portugal	Portuguese Clinical Research Law Law 21/2014 – Portuguese Clinical research law: Lei n.º 21_2014_Investigação Clinica.pdf http://www.infarmed.pt/documents/15786/1068535/036-B1_Lei_21_2014_1alt.pdf Portuguese Data Protection Authority law: Law 67/1998 Lei n.º 67_1998_Lei da Protecção de Dados Pessoais https://www.cnpd.pt/bin/legis/nacional/lei_6798.htm
United States	Health Insurance Portability and Accountability Act of 1996 https://www.hhs.gov/hipaa/for-professionals/security/laws-regulations/index.html https://www.hhs.gov/sites/default/files/ocr/privacy/hipaa/administrative/combined/hipaa-simplification-201303.pdf Code of Federal regulations https://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR&searchPath=Title+45%2FSubtitle+A%2FSubchapter+C%2FPart+164&oldPath=Title+45%2FSubtitle+A%2FSubchapter+C%2FPart+164%2FSubpart+E&isCollapsed=false&selectedYearFrom=2017&ycord=1980
Finland	Law 785/1992: Act on the Status and Rights of Patients (No. 785/1992) http://www.hus.fi/en/patients/patients-rights/Pages/default.aspx National Committee on Medical Research Ethics –TUKIJA http://tukija.fi/en/publications1 General data protection: Data Protection Ombudsman http://www.tietosuoja.fi/en/ Committee to approach for data from deceased patients: National Advisory Board on Social Welfare and Health Care Ethics – ETENE http://etene.fi/en/frontpage

*if updated during the course of the study, the new regulation becomes the new reference (your local monitor will provide appropriate training).