Title Page

A prospective, randomised, **C**ontrolled, **O**pen-label, **M**ulticentre phase III study to evaluate efficacy and safety of **Pe**ptide Receptor Radionuclide **T**herapy (PRRT) with ^{177}Lu-Edotreotide compared to targeted molecular therapy with **E**verolimus in patients with inoperable, progressive, somatostatin receptor-positive (SSTR+), neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET).

^{177}Lu-edotreotide vs. Everolimus in GEP-NET – COMPETE

Study purpose:	Confirmation of efficacy and safety of ^{177}Lu-edotreotide PRRT in GEP-NET		
Clinical study phase:	III	**Date:**	29-Sep-2022
EudraCT No.:	2016-001897-13	**Version No.:**	8.5, Amendment 11
IND No.:	136823		
Authors:	Dr. [redacted] Prof. Dr. [redacted] [redacted]		

Document History:

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05-Oct-2016	Initial Protocol Version 2.2	NA	Global
25-Jul-2017	Amendment 01	Substantial	Global
20-Mar-2018	Amendment 02	Substantial	Global
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08-Jun-2020	Version 3.0, Amendment 04	Substantial	Global
02-Dec-2020	Version 4.0, Amendment 05	Substantial	European Union and United Kingdom
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18-Aug-2021	Version 7.0, Amendment 08	Substantial	United States
20-Oct-2021	Version 8.3, Amendment 09	Substantial	Australia, South Africa, Switzerland, United States, United Kingdom
01-Aug-2022	Version 8.4, Amendment 10	Non-substantial	Australia, South Africa, Switzerland, United States, United Kingdom

29-Sep-2022	Version 8.5, Amendment 11	Non-substantial	Australia, South Africa, Switzerland, United States, United Kingdom

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Sponsor Approval Signature Page

I agree to conduct this trial in accordance with this Clinical Trial Protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- Good Clinical Practice / International Conference on Harmonisation (CPMP/ICH/135/95)
- All applicable laws and regulations

Study Title: A prospective, randomised, controlled, open-label, multicentre phase III study to evaluate efficacy and safety of Peptide Receptor Radionuclide Therapy (PRRT) with ^{177}Lu-edotreotide (^{177}Lu-DOTATOC) compared to targeted molecular therapy with everolimus in patients with inoperable, progressive, somatostatin receptor-positive (SSTR+), neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET).

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29. SEP. 2022
Date

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29. SEP. 2022
Date

Principal Investigator Agreement Page

Study Title: A prospective, randomised, controlled, open-label, multicentre phase III study to evaluate efficacy and safety of Peptide Receptor Radionuclide Therapy (PRRT) with ^{177}Lu-edotreotide (^{177}Lu-DOTATOC) compared to targeted molecular therapy with everolimus in patients with inoperable, progressive, somatostatin receptor-positive (SSTR+), neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET).

Version: 8.5
Date: 29-Sep-2022
Amended: Amendment 11

Principal Investigator Signature:

I confirm that I have read and that I understand this Protocol, the Investigator's Brochure, and any other Product Information provided by the sponsor.

I agree to conduct this study in accordance with the requirements of this protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

I will also appropriately direct and assist the personnel at the trial site who will be involved in the conduct of the study.

(Name and Function) **(Signature)**	**Date**

Serious Adverse Event Reporting

Notification in case of Serious Adverse Events
All serious adverse events (SAEs) should be reported via paper form using the following email address: Email: SAE-reporting@itm-radiopharma.com Only in situations when email cannot be used, SAEs should be reported via paper form using the following Fax number: Fax: +49 89 329 8986 6068

Synopsis

Study title	A prospective, randomised, **C**ontrolled, **O**pen-label, **M**ulticentre phase III study to evaluate efficacy and safety of **Pe**ptide Receptor Radionuclide **T**herapy (PRRT) with ^{177}Lu-Edotreotide compared to targeted molecular therapy with **E**verolimus in patients with inoperable, progressive, somatostatin receptor-positive (SSTR+), neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET).
Short title	^{177}Lu-edotreotide vs. everolimus in GEP-NET – COMPETE
Clinical study phase	III
Study objective(s)	**Primary objective** To demonstrate the efficacy of PRRT with ^{177}Lu-edotreotide to prolong progression-free survival (PFS) in patients with inoperable, progressive, SSTR+ GEP-NET, compared to everolimus **Key secondary objectives** 1. To assess objective response rates (ORR), defined as the proportion of patients achieving partial response (PR) or complete response (CR) as best outcome, after treatment with ^{177}Lu-edotreotide compared to everolimus 2. To assess overall survival (OS), defined as the time from the date of randomisation until death **Exploratory secondary objectives** 3. To assess the duration of disease control (DDC), defined as the time of initial diagnosis of response (SD, PR or CR) until diagnosis of progression, after treatment with ^{177}Lu-edotreotide compared to everolimus 4. To determine disease control rates (DCR), defined as the proportion of patients achieving stable disease (SD), PR or CR as best outcome 5. To determine response rate (RR), considering Cg-A and specific hormones (where increased at baseline) 6. To assess the safety and tolerability of ^{177}Lu-edotreotide in GEP-NET patients 7. To determine the health-related quality of life (HRQL) in GEP-NET patients during and after therapy (EORTC QLQ-C30 questionnaire) 8. To evaluate symptomatic tumour response (EORTC GI.NET21 questionnaire) 9. To evaluate the impact of patient characteristics (time from primary diagnosis, time from diagnosis of progression, number of prior therapies (1st vs 2nd line), type of prior therapies, KPS at randomisation) on tumour response 10. To evaluate the impact of tumour histology (histological entity, tumour grade, Ki-67 expression, SSTR expression, functional

	state) as determined in primary or current bioptic tumour specimen on tumour response **Tertiary objectives** (in ^{177}Lu-edotreotide patients) 1. To assess differences in tumour and kidney radiation dose estimates, obtained with conventional 2D (planar), compared to hybrid (2D/3D), and 3D (SPECT) imaging 2. To evaluate the value of pre-therapeutic SSTR imaging (SRI) to predict tumour response (globally/at lesion level) 3. To evaluate the relationship between PRRT radiation dose (in Gy) and tumour response (globally/at lesion level) 4. To assess metabolic stability and excretion pattern of ^{177}Lu-edotreotide 5. To assess bone marrow radiation dose
Project code	ITM-LET-01
Investigational Medicinal Product (IMP)	^{177}Lu-edotreotide, an octreotide-derived somatostatin analogue containing the chelator DOTA, radiolabelled with n.c.a. lutetium-177, a radio-lanthanide, emitting β- and γ-radiation.
Name of active ingredients	^{177}Lu-edotreotide (synonyms, e.g.: ^{177}Lu-Edo, ^{177}Lu-DOTATOC)
Doses	A maximum of four cycles of 7.5 ± 0.7 GBq ^{177}Lu-edotreotide, each containing a mass dose of 150 µg of DOTATOC. The cumulative ^{177}Lu-edotreotide dose will be up to 30 GBq, gauged individually not to exceed an absorbed dose of 23 Gy to the kidneys.
Route of administration	Slow intravenous infusion/injection (IV)
Duration of treatment	4 cycles, 90 (±14) days apart (total duration: 270 days/9 months)
Reference product (RP)	Everolimus, an mTOR inhibitor
Name of active ingredients	Everolimus
Doses	10 mg/d
Route of administration	Oral
Duration of treatment	Continuous daily treatment until diagnosis of progression or EOS
Indication	Treatment of patients with well-differentiated, somatostatin receptor-positive, unresectable or metastatic neuroendocrine tumors (NETs) of gastroenteric or pancreatic origin
Diagnosis and main criteria for inclusion	All patients must meet all of the following criteria: 1. Written informed consent 2. Male or female ≥18 years of age 3. Histologically confirmed diagnosis of well-differentiated neuro-endocrine tumour of non-functional gastroenteric origin (GE-NET) or both functional or non-functional pancreatic origin (P-NET), tumour grade G1 or G2 (Ki-67 ≤20%), unresectable or

	metastatic, in a patient who is either treatment-naïve (1st line) or who has progressed under prior therapy (2nd line) 4. Availability of existing biopsy specimen from primary tumour or metastasis or, if unavailable, willingness to undergo current biopsy for secondary central analysis 5. Measurable disease per RECIST 1.1, on CT/MRI scans, defined as at least 1 lesion with ≥1 cm in longest diameter, and ≥2 radiological tumour lesions in total. A maximum of 5 target lesions visible on CT/MRI will be defined, thereof not more than 2 lesions per organ 6. Somatostatin receptor positive ($SSTR^+$) disease, as evidenced by SSTR imaging (SRI) within 4 months prior to randomisation, as locally authorised, by: • ^{68}Ga-based SSTR positron emission tomography (PET) imaging (^{68}Ga-edotreotide or ^{68}Ga-DOTATATE), or • ^{111}In-pentetreotide SSTR SPECT/planar imaging, or • ^{99m}Tc-octreotide SSTR SPECT/planar imaging • ^{64}Cu-based SSTR PET imaging (^{64}Cu-DOTATATE), if approved, according to local regulations All target lesions and ≥90% of non-target lesions need to be positive for SSTR; this relates to lesions of at least 15 mm in diameter acquired on SRI images with SPECT, and of at least 10 mm in diameter acquired on SRI images with PET systems. 7. The patient must have progressive disease based on RECIST 1.1 Criteria as evidenced by two morphological imaging examinations made with the same imaging method (either CT or MRI), within a maximum of 36 months prior to randomisation. The most recent scan must not be older than 90 days prior to randomisation date. The minimum interval between the two scans must be ≥90 days. 8. Karnofsky performance status (KPS) scale ≥70 9. Life expectancy allows the patient to participate in the study based on the investigator's assessment 10. Glomerular filtration rate (GFR, CKD-EPI) ≥60 mL/min/1.73 m^2 11. For patients included in France only, verification and confirmation of their affiliation with a social security 12. Patients with functional P-NETs who require SSA for symptom control may continue SSA treatment throughout the study, on condition that: a) they have been on a stable dose for at least three months prior to study enrolment b) that progressive disease has been diagnosed while under such stable dose

Exclusion criteria	A patient will be excluded from participation in the trial if one or more of the following criteria are met: 1. Known hypersensitivity to edotreotide or everolimus 2. Known hypersensitivity to DOTA, lutetium-177, or any excipient of edotreotide or everolimus or any other Rapamycin derivative 3. Known hypersensitivity to lysine, arginine, or any excipient of the nephroprotective amino acid solution 4. Prior exposure to any peptide receptor radionuclide therapy (PRRT), including ^{177}Lu-edotreotide, ^{90}Y-edotreotide or other SSTR-targeting agents (e.g. ^{177}Lu-octreotate or high-dose ^{111}In-pentetreotide) 5. Prior therapy with mTOR inhibitors 6. Prior EFR (external field radiation) to GEP-NET lesions within 90 days before randomisation or radioembolisation therapy (e.g. ^{90}Y microspheres, ^{131}I-lipiodol) with administration to the liver 7. Prior therapy with chemotherapy, immunotherapy, interferon, chemo-embolisation, bland embolisation, cyclosporine-A within 4 weeks before randomisation; any new cancer treatment between screening and randomisation 8. Therapy with an investigational compound and/or medical device within 30 days or 5 half-life periods (whichever is longer) prior to randomisation 9. Subjects who have received a live vaccine up to 4 weeks prior to first dose 10. Current therapy with any prohibited medication (see Section 6.1.1) 11. Ongoing toxicity grade 2 according to CTCAE version 4.03 from previous standard or investigational therapies 12. Indication for surgical lesion removal with curative potential 13. Planned (for the period of study participation): chemotherapy, immunotherapy, interferon, radiation therapy, chemo-embolisation, bland embolisation, radio-embolisation, treatment with cyclosporine-A 14. Neuroendocrine tumours, not meeting the inclusion criteria: • With known non-GEP-NET origin (e.g. pulmonary or gonadal primaries) • Functional GE-NET • Explicit diagnosis of unknown primary (CUP) • G3 neuroendocrine tumours and neuroendocrine carcinomas • NET for which no histological specimen for secondary histological analysis can be obtained 15. Total hepatic tumour burden >70% 16. Brain metastases 17. Other malignancy within previous 5 years (except basal cell carcinomas and in situ squamous cell carcinomas of the skin)

	18. Serious non-malignant disease (e.g. psychiatric, infectious, autoimmune or metabolic), that may interfere with the objectives of the study or with the safety or compliance of the subject, as judged by the investigator 19. Clinically relevant renal, hepatic, cardiovascular, or haematological organ dysfunction, potentially interfering with the safety of the study treatments, as follows: • Renal ○ Renal obstruction • Hepatic ○ Total bilirubin >1.5 x ULN ○ AST or ALT >2.5 x ULN ○ Alkaline phosphatase >5 x ULN ○ Albumin <3 g/dL, unless prothrombin time is within normal range • Cardiovascular ○ New York Heart Association classification III & IV ○ Uncontrolled hypertension • Haematopoietic ○ Platelets ≤80 × 10^9/L ○ Absolute neutrophil count (ANC) <1 x 10^9 cells/L 20. Pregnant or breast-feeding women. Female patients of childbearing potential or male patients with female partners of childbearing potential, unless willing to practice full and true sexual abstinence or who are surgically/permanently sterile (bilateral tubal occlusion, hysterectomy, or vasectomy), or female patients whose male partners have medically successful vasectomy (provided the partner is the sole sexual partner of the female patient of childbearing potential), or who are not willing to practice highly effective contraception in combination with a barrier method of contraception (e.g. condom). Contraception methods that are considered highly effective are: oral or non-oral (injected or implanted) non-oestrogen progesterone-based hormonal method; oral, intravaginal, or transdermal combined oestrogen and progesterone-based hormonal methods; and/or intrauterine device (IUD), and/or intrauterine hormone-releasing system (IUS). Sexual abstinence or the contraception methods described above must be followed throughout the entire study period and for 56 days after treatment in the everolimus group and 66 days in the PRRT group (10 half-lives of ^{177}Lu) after the last treatment cycle. 21. Subjects not able to declare meaningful informed consent on their own (e.g. with legal guardian for mental disorders) or any other vulnerable population to that sense (e.g. persons institutionalised, incarcerated etc.).
Study design	This will be a confirmatory, prospective, randomised, controlled, parallel group, open-label, multi-centre phase III study to evaluate

	the efficacy and safety of ^{177}Lu-edotreotide in comparison to molecular targeted therapy with everolimus in patients with inoperable, progressive, somatostatin receptor-positive (SSTR^{+}), neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET). In total, 300 GEP-NET patients will be randomised in 2:1 fashion to receive either • PRRT with ^{177}Lu-edotreotide consisting of a maximum of four cycles (7.5 ± 0.7 GBq ^{177}Lu-edotreotide, each), administered as IV infusion at 3-monthly intervals for 9 months, or until diagnosis of progression (200 patients), or • 10 mg everolimus (Afinitor®) daily, administered orally as a tablet until diagnosis of progression (100 patients) Study duration per patient will be 30 months. Collection of survival data and information on further antineoplastic treatments as well as the development of secondary malignancies will be continued for 5 years (60 months) after EOS. The primary endpoint is progression-free survival (PFS). Diagnosis of progression and liver tumour burden will be established based on radiological information from morphological imaging (MRI and/or CT) according to RECIST 1.1. Stratification will be made for primary tumour origin (GE-NET vs. P-NET) and prior medical therapy (1st line vs. 2nd line). Tumour grade (G1, G2), and baseline Karnofsky score will be used for further statistical subgroup analyses. Secondary endpoints include parameters of morphological and biomarker tumour response such as objective response rate (ORR), overall survival (OS), disease control rates (DCR), as well as duration of disease control (DDC), safety, health-related quality of life (HRQL). Furthermore, exploratory analyses will be performed on patient and tumour characteristics, as well as the degree of ^{177}Lu-edotreotide uptake for traits predicting PRRT efficacy. The study is designed to confirm the trial hypothesis of a progression-free survival benefit, relative to comparator with a power of at least 0.8 and significance level (p) of <0.05 (two-sided). The sample size will also be sufficient, to confirm a progression-free survival benefit with a power (P) of 0.90 and significance level (p) of <0.01 (two-sided), if the difference in mPFS is more than 11 months. Patients with histologically confirmed diagnosis of GEP-NET will be recruited globally by approximately 60 oncological centres specialised in endocrinology or gastroenterology, and with local access to or own experience in PRRT. Confirmatory histology from existing or current specimens will be centrally performed to uniformly characterise the study population. All successfully screened patients will be randomised in a 2:1 fashion to undergo PRRT with ^{177}Lu-edotreotide or everolimus treatment, respectively, and will be followed-up for outcome for a maximum of 30 months.

	^{177}Lu-edotreotide therapy usually requires short-term hospitalisation at a radionuclide therapy ward for each administration (details subject to local radiation safety regulations). Biodistribution of ^{177}Lu-edotreotide, and consequently the absorbed dose (AD) to kidneys varies considerably between subjects. To minimise the risk of radiation-induced renal damage, the cumulative ^{177}Lu-edotreotide dose (D1 - D4) will be individually monitored, so that the resulting AD to kidneys does not exceed 23 Gy, generally considered to be safe. However, if the predicted absorbed dose to the kidneys is likely to exceed 23 Gy upon administration of the next PRRT cycle, dosing can be continued up to a maximum of 29 Gy, provided that a pre-PRRT tubular extraction rate (TER, ^{99m}Tc-MAG3 renal scintigraphy) is >50% of the value at baseline. In addition, before receiving the next ^{177}Lu-edotreotide treatment after cycle 1, all patients in the PRRT arm will be assessed for specific safety criteria during the pre-treatment evaluations on Day 90 post first cycle, including hematological as well as renal safety parameters. If the safety criteria are not met, the patients will not receive the next dose. After administration of D1, patients will be subjected to sequential dosimetric whole body imaging immediately after end of infusion (approximately 0.5 h p.i, prior to voiding, preceded by a blank and a transmission scan), 6, 24 and 72 – 96 h p.i. using conventional planar scintigraphy, complemented by abdominal SPECT imaging at 24 h. Based on the first cycle, the cumulative AD to kidneys from the planned full dose of four doses of 7.5 ± 0.7 GBq ^{177}Lu-edotreotide will be estimated. In selected patients, the accuracy of AD predictions made based on the first cycle will be verified by repeated dosimetry in cycles D2 – D4 (Sub-study A). ^{177}Lu-edotreotide dosimetry will be centrally analysed for the absorbed kidney and target tumour doses in a standardised fashion. Dosimetry will be performed according to the current regulatory standard (conventional planar (2D) dosimetry), and according to the emerging clinical standard (2D/3D hybrid dosimetry) for a more accurate determination of the kidney dose. Quantitative SPECT reconstruction is a recent option to directly derive quantitative information on ^{177}Lu activity distribution *in vivo*, allowing to assess absorbed doses to kidneys (safety) and tumour (efficacy) with higher accuracy, compared to planar scintigraphy. In selected study sites, ^{177}Lu-edotreotide SPECT/CT (3D) will be performed at each time point in addition to planar scintigraphy (2D). Data will be quantitatively reconstructed, and dosimetrically analysed in comparison to planar (2D) and hybrid (2D/3D) dosimetry (Sub-study B). To assess in vivo stability of ^{177}Lu-edotreotide, urine will be collected from all voids beginning immediately post-dose to 1 hour, and in intervals of 1-6, 6-24 and 24-48 hours post-injection in a subgroup of 20 patients at selected sites only and will be analysed using radio-

	HPLC and gamma-counting (Sub-study C). In addition, bone marrow dosimetry will be assessed by measuring radioactivity in blood samples taken at pre-defined intervals between end of ^{177}Lu-edotreotide injection to 7 days post-injection. Sub-study C will be performed during any one of the four ^{177}Lu-edotreotide treatment cycles (the choice of which of the four cycles to collect urine and blood samples for Sub-study C will be at the investigator's discretion). In order to facilitate the patient recruitment in the regulatory required Sub-study C, [redacted] at the sites participating in Sub-study C and only at those sites: Following approval of this Study Protocol Amendment and activation of [redacted] by the Sponsor, the patients who consent to participate in Sub-study C and who comply with all protocol inclusion and exclusion criteria will directly be allocated to the PRRT arm until a global cumulative number of 20 evaluable patients is reached for the Sub-study C. [redacted] the tests conducted for Sub-study C, the treatment regimen and patient care management will remain identical to that implemented in the main study. [redacted] The patients at Sub-study C participating sites who consent to participate in the main study but not in the Sub-study C, or the patients who are consented and screened out of or after the end [redacted] can be randomised in the main study provided they comply with all protocol inclusion and exclusion criteria. The sites not participating in the Sub-study C continue to only enroll patients using the randomization procedure of the main study. Everolimus: Patients randomised to everolimus therapy will undergo out-patient visits only. Patients will receive a standard dose of 10 mg daily, which may be reduced, where required for acceptable tolerability, according to manufacturer´s product information. For both study arms: Study visits will be monthly in the first 12 months, thereafter 3-monthly until end of study at month 30 or until progression (whatever occurs first). For symptom control, all patients are allowed to receive somatostatin analogues (SSA), as clinically indicated (best supportive care) in required doses, not to exceed licensed doses. In the ^{177}Lu-edotreotide arm, clinically established wash-out periods prior to ^{177}Lu-edotreotide dosing have to be considered (1 day for immediate release, and 28 days for sustained release SSA). Safety, tolerability and symptom control parameters, as well as tumour markers are captured at regular intervals. To assess efficacy, serial morphological imaging, comprising native liver and contrast-enhanced liver and 3-regional (pelvis, abdomen, thorax) MRI or CT (see Clinical Imaging Manual for details), is scheduled every three months, consistently using baseline methods. In case of clinically suspected tumour progression, investigators may

	schedule appropriate diagnostic imaging at any time. Diagnosis of progression will be made by the local investigator. All image analyses will be confirmed centrally. For establishment of PFS (primary endpoint) blinded reading in duplicate, with appropriate adjudication in case of discordance will be used. Patients who progressed under everolimus may be offered ^{177}Lu-edotreotide therapy based on the personal judgement of the Investigator, if he/she considers it appropriate and likely to be beneficial for the individual patient.
Study participation duration	• Screening period: 90 days (day -90 to day -1) • Study period: - Treatment period IMP: Four single doses administered on days 0, 90, 180 and 270, unless diagnosis of progression or EOS. - Treatment period RP: Daily oral administration from day 0 until diagnosis of progression or EOS. - Study period: day 0 – month 30 (or until diagnosis of progression, whichever is earlier). • Post-study Follow-up (5 years [60 months] post-EOS): - ^{177}Lu-edotreotide therapy for patients (having progressed under everolimus therapy): Administration and follow-up as for study patients, until secondary progression. - All patients: Collection of overall survival (OS) and progression data, as well as information on further cancer treatments and the development of secondary malignancies.
Methodology	Tumour characterisation and staging 1. Somatostatin receptor imaging (SRI) To clinically establish somatostatin receptor expression at baseline, patients undergo somatostatin receptor imaging (SRI) according to local guidelines, preferably with ^{68}Ga-based PET (^{68}Ga-edotreotide or ^{68}Ga-DOTATATE). Where not available, ^{111}In-pentetreotide (OctreoScan®), ^{99m}Tc-octreotide SPECT/CT imaging or, less preferable, planar imaging can be used. 2. Histology Central histological re-assessment will be made at baseline using tissue specimens from primary diagnosis or, where unavailable, a current biopsy to characterise histological entity, tumour grade, SSTR, Ki-67 expression status, and others. 3. Morphological imaging (MRI or CT) To document tumour lesions in the body, and tumour burden in the liver, at baseline, one native liver and contrast-enhanced liver and 3 regional (pelvis, abdomen, thorax) MRI or CT (see Clinical Imaging Manual for details) must be available (performed within 28 days prior to randomisation) or has to be repeated as baseline MRI/CT. Where established, combined imaging (e.g. abdominal MRI / thoracic CT) can be used. The baseline imaging method

has to be used consistently throughout the whole study period. Where a 3-monthly imaging follow-up schedule departs from clinical routine, MRI is preferred for radiation protection reasons. All image analyses will be made according to RECIST 1.1. classification criteria.

4. Tumour markers

   Chromogranin A (CgA) will be determined at baseline, and then monthly until month 12, thereafter in 3-monthly intervals until diagnosis of progression or EOS. In addition, specific hormones related to clinical symptoms (e.g. gastrin, insulin, etc.) will be determined in patients, if showing elevated levels at baseline work-up.

<u>^{177}Lu-edotreotide dosimetry</u>

- ^{177}Lu-edotreotide planar scintigraphy

  ^{177}Lu-edotreotide whole body 2D planar images will be obtained at four points of time after first dosing (D1, day 0) of ^{177}Lu-edotreotide: immediately after end of infusion (approx. 0.5 h, prior to voiding), 6 h, 24 h and 72-96 h post-infusion.

  a) Tumour targeting will be assessed qualitatively (signal accumulation in liver region).

  b) Whole body 2D planar scintigraphy in anterior and posterior projection, in conjunction with cobalt-57 or technetium-99m sheet source or if available whole body CT-based attenuation correction data and an external calibration source, will be used to determine ^{177}Lu-edotreotide 2D standard dosimetry (reference method), with emphasis to kidney (safety) and target tumours (efficacy).

- ^{177}Lu-edotreotide SPECT/CT

  Abdominal SPECT/CT scans, covering kidneys and liver (usually 1 to 2 bed positions) will be acquired in supine position 24 h after each ^{177}Lu-edotreotide infusion (D1 to D4) in all sites.

  Where established (Sub-study B), abdominal SPECT/CT (or SPECT) scans may be acquired in addition to planar images at all other imaging time points (0.5, 6, 72-96 h p.i.). CT-derived information will be used for attenuation and scatter correction.

  a) Tumour targeting will be assessed by demonstration of ^{177}Lu-edotreotide binding inside or in the vicinity of the target lesion, seen on structural imaging using SPECT/CT acquired 24h post-infusion.

  b) To take superimposition and self-absorption of abdominal organs into consideration, quantitatively reconstructed abdominal SPECT images (Bq/mL) from a single time point (24h p. i.) will be used to calibrate time-activity curves derived from 2D planar scans (reference method/regulatory standard) for dosimetry of kidneys and target tumours (2D/3D hybrid dosimetry/emerging clinical standard).

  c) Sub-study B (3D dosimetry): available full dosimetric SPECT/CT series (4 time points), will be quantitatively

	reconstructed, and analysed for kidney and tumour dosimetry (3D dosimetry). Dosimetry evaluations will be centrally analysed using a) the phantom-based MIRD methodology, and b) the Voxel-S methodology, which considers individual anatomy of the patient, allowing a more precise description of doses to tumours. • Pharmacokinetic urine analysis (Sub-study C) To assess in vivo stability of ^{177}Lu-edotreotide, urine will be collected from all voids beginning immediately at 0 min post-dose into 4 pooled samples in intervals from 0 min post-dose to 1 hour, and 1-6, 6-24 and 24-48 hours post-injection in a subgroup of 20 patients at selected sites only. Urine will be analysed with gamma-counting and radio-HPLC in order to investigate the radiochemical purity of the eliminated compound. • Bone marrow dosimetry (Sub-study C) As the radioactivity in blood was shown to be similar to that in bone marrow, bone marrow dosimetry will be assessed by measuring radioactivity in blood samples at pre-defined intervals from 10 minutes to 7 days post-injection of ^{177}Lu-edotreotide in a subgroup of 20 patients at selected sites only. <u>Safety and tolerability</u> 1. Kidney function A possible impact of study therapy on kidney function will be monitored assessing o Tubular extraction rate (TER, ^{99m}Tc-MAG3 renal scintigraphy) o GFR calculated from serum creatinine o Kidney volume (abdominal MRI/CT baseline, 3-monthly follow-up) 2. General a) Standard laboratory b) Adverse event recording c) Concomitant medication recording <u>Health-related quality of life (HRQL) and symptom control</u> 1. EORTC QLQ-C30 and 2. EORTC GI.NET21 questionnaire	
Type of control	Reference therapy: Everolimus 10 mg orally daily until progression	
Planned study dates (year)	**Start of study/ recruitment** 2017	**End of recruitment** 2021 **End of study** 2024
Planned number of study centres/countries	Approximately 60 centres/10-15 countries (Europe, North America, South Africa, Australia)	

Number of patients	**Total:** 300 subjects with morphologically progressive GEP-NET To facilitate patient recruitment in the Sub-study C, [redacted] at all sites participating in the Sub-study C until 20 evaluable patients are obtained globally. [redacted] **Total number based on statistical rationale:** Sample size based on estimation, considering published outcome data for RP (everolimus), and evidence of ^{177}Lu-edotreotide efficacy in GEP-NET from the Bad Berka academic study.
Primary variable	**Progression-free survival** a) Progression-free survival (PFS)
Secondary variables	**Key secondary variables** a) Objective response rate (ORR), % patients achieving PR or CR as best outcome b) Overall survival (OS) **Exploratory efficacy variables** c) Percentage patients progression-free at 2 years (% 2y-PFS) d) Disease control rate (DCR), % patients achieving PR, CR and SD e) Duration of disease control (DDC) f) Duration of response (DoR) g) Association between RECIST 1.1 tumour response and CgA and/or specific hormone levels. If relevant, percentage patients experiencing biomarker tumour response (CgA, specific hormones), classified as SD, PR, CR, PD **Safety and tolerability** a) Measured TER, percentage depart from baseline value b) Calculated GFR, percentage depart from baseline value c) Renal volume (V_{kidney}), percentage depart from baseline value d) Frequency of occurrence and severity of abnormal findings in safety investigations (vital signs, 12-lead ECG, clinical laboratory, adverse events) **Health-related quality of life (HRQL)** a) Maximum HRQL improvement (EORTC QLQ-C30 and GI.NET21 questionnaires) total scores, relative to baseline b) Duration of maximum HRQL improvement c) Time to HRQL deterioration, defined as the time from randomisation to first HRQL deterioration **Dosimetry** a) Full dosimetry assessments of target organs and tumour lesions

	b) Cumulative absorbed dose (in Gy) from ^{177}Lu-edotreotide to target tumour lesions, estimated from ^{177}Lu-edotreotide dosimetry after first dose c) Sub-study A patients: cumulative absorbed dose to kidneys and to tumour lesions extrapolated from absorbed dose estimated at D1 compared with the cumulative absorbed dose measured at the different administration times (i.e. D1 to D4) d) Sub-study B patients: absorbed dose (in Gy) determined by 3D dosimetry compared to absorbed dose values obtained by planar (2D) and hybrid (2D/3D) dosimetry e) Sub-study C patients: bone marrow absorbed dose (in Gy) extrapolated from blood radioactivity **Pharmacokinetics (Sub-study C)** a) Urine radioactivity in percentage of injected activity (%IA) at pre-defined intervals within 48 hours post-injection to assess excretion pattern b) Blood radioactivity in %IA at pre-defined time points within 7 days post-injection to assess clearance pattern c) Radiochemical purity assessed through HPLC of urine samples collected within 48 hours post-injection

Plan for statistical analysis	Stratified randomisation will be used to control for primary tumour origin (GE-NET vs. P-NET) and for prior medical therapy (1st line vs. 2nd line, as well as types of previous therapies). **Sample size considerations:** Considering that everolimus will be used as comparator in the planned study, a sample size estimation was conducted, based on a median PFS of 11.0 months reported for everolimus (Yao et al. 2011, 2016) and a median PFS of 32 months in NET patients (34.5 months in GEP-NET patients), as determined for ^{177}Lu-edotreotide in subjects, treated with ≥2 PRRT cycles in the retrospective study (van Echteld 2015; Baum et al. 2016). [redacted] The study was planned to last for 48 months of which subject accrual occurs in the first 24 months. The accrual across time is uniform. Of note, the trial sample size was not revised (i.e. decreased) after the protocol amendment that extended the patient follow-up from 24 months to 30 months. Based on this HR a total sample size of 300 will compensate for a dropout rate (censored data) of 15% for primary endpoint analysis. Switching from the one group to the other is not allowed in this study and therefore not considered in the sample size calculation. With regard to overall response rates, group sample sizes of 200 in the ^{177}Lu-edotreotide group and 100 in the everolimus group achieve [redacted] power to detect an odds ratio between the group ORRs of [redacted] (that corresponds to rates of [redacted] and [redacted]). The proportion in the ^{177}Lu-edotreotide group is assumed to be [redacted] under the null hypothesis and [redacted] under the alternative hypothesis. The proportion in the everolimus group is assumed to be 5% according to results of the RADIANT-3 study (Yao et al., 2011). The test statistic used is the two-sided Fisher's Exact Test. The significance level of the test is 5%. A dropout rate of 15% is included in this calculation using PASS software.

With regard to overall survival, a two-sided logrank test with an overall sample size of N=300 subjects ([redacted] events; [redacted], N1=100 subjects [redacted] in the everolimus group and N2=200 subjects [redacted] events] in the ^{177}Lu-edotreotide group) achieves [redacted] power at a [redacted] significance level to detect a hazard ratio (HR) of [redacted] when the everolimus group median overall survival time is 44 months as in the RADIANT-3 study (Yao et al., 2016; i.e., a difference of an additional 23 months in the ^{177}Lu-edotreotide group).

The sample size of 300 patients was chosen, as the primary variable and the 2 key secondary endpoints are to be tested in a confirmatory manner.

[redacted]

Interim analysis and Multiplicity:

[redacted]

	[redacted]

Table 1 (Study Flow Chart): ^{177}Lu-Edotreotide vs. Everolimus in GEP-NET (COMPETE Study) – ^{177}Lu-Edotreotide Patients

			Treatment																																EOS	Early withdrawal[U]	Post-study FU
Examination / Evaluation			**Dose 1**									**Dose 2**					**Dose 3**					**Dose 4**					**2nd year**										
Time point	Month	Baseline	0							1[AAA]	2[AAA]	3			4[AAA]	5[AAA]	6			7[AAA]	8[AAA]	9			10[AAA]	11[AAA]	12[AA]	15[AA]	18[AA]	21[AA]	24[AA]	27[AA]	30[AA]		
	Day	-90 to -1	-28 to -1	0					1	3	30 ± 7	60 ± 7	90 ± 14	91	93	120 ± 7	150 ± 7	180 ± 14	181	183	210 ± 7	240 ± 7	270 ± 14	271	273	300 ± 7	330 ± 7	± 21	± 21	± 21	± 21	± 21	± 21	± 21	within 28 days after withdrawal	6 monthly for 5 years
	h*			Pre-dose[AA]	Tx Dose 1	0.5 ±0.25	5 ± 1	6 ± 1	24 ± 3	72-96[E]			Tx[A, AA] Dose 2	24 ± 3	72-96[E]			Tx[A, AA] Dose 3	24 ± 3	72-96[E]			Tx[A, AA] Dose 4	24 ± 3	72-96[E]											
Informed Consent		X																																		
Review Inclusion / Exclusion Criteria		X	X																																	
Randomisation			X[T]																																	
General																																				
Medical History		X	X																																	
Physical Examination		X	X	X							X	X	X			X	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	
Vital Signs		X	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Haematology			X	X[B]							X[B]	X	X[B]			X[B]	X	X[B]			X[B]	X	X[B]			X[B]	X	X	X	X	X	X	X	X	X	
Serum Chemistry[X]			X	X			X		X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	
Clotting Parameters			X	X							X	X	X			X	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	
Urinalysis			X	X							X	X	X			X	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	
Tumour Markers[C]			X	X							X	X	X			X	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[D]			X	X[D]							X	X	X			X	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	
12-Lead ECG			X	X						X			X		X			X		X			X				X		X		X		X	X		
Current Biopsy[F]		X																																		
Tumour Histology[G]		X																																		
EORTC QLQ-C30 and GI.NET21			X								X	X	X			X	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	
Concomitant Medications		X	X	X ⟶																														X	X	
Symptomatic Medication (SSA)[H]			X	X ⟶																														X	X	
Adverse Events / Baseline Findings			X	X ⟶																														X[Y]	X[Y]	
Overall Survival																																				X
Antineoplastic Treatments																																				X
Imaging Inclusion, Outcome & Safety																																				
Somatostatin Receptor Imaging (SRI)[I]		X																																		
Morphological Imaging (MRI / CT)		X[K]	X[K, L]										X					X					X					X[ZZ]	X[ZZ]	X[ZZ]	X[ZZ]	X[ZZ]	X[ZZ]	X	X[ZZ]	
^{99m}Tc-MAG-3 Renogram			X[M]															X[M]					(X[M])					X[M]		X[M]		X[M]		X	X	
Eligibility for continued PRRT[MM]													X																							
Treatment[ZZZ]																																				
Amino-Acid Solution Infusion[N]			X										X					X					X													
^{177}Lu-Edotreotide Infusion				X									X					X					X													
^{177}Lu Whole Body Planar Imaging			X[Z]		X[O]		X[O]	X[O]	X[O]				X[P]	X[P]	X[P]			X[P]	X[P]	X[P]			X[P]	X[P]	X[P]											
^{177}Lu Abdominal SPECT/CT Imaging[Q]					X[R]		X[R]	X	X[R]					X					X					X												
Hospitalisation			X ⟷						X				X ⟷		X			X ⟷		X			X ⟷		X											

*hours post last dose

Table 1 – ^{177}Lu-Edotreotide – (footnotes):

(A) Pre- and post dosing procedures, as described for dose D1.
(AA) (Pre-dose) procedures (e.g. MRT / CT) may be performed within 7 days before visit. Investigations should be performed as close to PRRT as organisationally possible and as clinically appropriate.
(AAA) Blood-sampling can be perfomed up to 72 hours prior to the visit according to local practice and as clinically appropriate.
(B) Bi-weekly controls of haematology for 8 weeks following 177Lu-edotreotide administration, to occur in week 2, 4, 6, 8 post dosing (GP acceptable).
(C) Tumour biomarkers in serum: chromogranin-A (CgA) in all patients; disease-specific homones, if positive at baseline work-up.
(D) Pregnancy test for all premenopausal female patients during screening. To be repeated, if dosing starts >14 days after screening. To be repeated monthly until EOS.
(E) All scheduled evaluations may be performed 72 - 96 h (± 3 h) post infusion.
(F) Mandatory, unless prior tumour specimen (paraffin block) available. Biopsy sample to be sent to CPL before randomisation.
(G) Local histolopathology report to be sent to the CPL with the biopsy sample.
(H) Somatostatin agonists (SSA) for symptom control are allowed, if a) not exceeding the licensed posology and b) sufficient wash-out prior to ^{177}Lu-edotreotide dosing is observed (24 h for immediate, 28 d for sustained release galenics).
(I) SRI using PET/CT, SPECT/CT or planar imaging, as locally authorised (by ^{68}Ga-edotreotide, ^{68}Ga-DOTATATE, ^{111}In-pentetreotide,or ^{99m}Tc-octreotide) within 4 months prior to randomisation.
(K) MRI / CT showing radiological tumour progression based on RECIST 1.1 as evidenced by two scans obtained within a maximum of 36 months prior to randomisation, with at least 90 days interval between them. The most recent scan should not be older than 90 days at randomisation.
(L) One native liver and contrast-enhanced liver and 3 regional (pelvis, abdomen, thorax) MRI or CT, not older than 28 days at the time of randomisation. Baseline method must be followed throughout the study period.
(M) ^{99m}Tc-MAG-3 renogram to be performed within 28 days prior to randomisation; 7 days prior to administering the cycle D3 (month 6) dose; and if the predicted absorbed kidney dose likely exceeds 23 Gy but not 29 Gy prior to dose D4 (month 9). To be performed within 7 days prior to month 12, 18, and 24 visits.
(MM) See Sections 5.4.1.2 and 5.4.3 of the protocol for details on dosing after Cycle 1.
(N) Nephroprotective amino acid solution has to be started 30-60 min. before ^{177}Lu-Edotreotide infusion and should be administered for 4-6 h.
(O) Planar emission imaging, serial (4 time points) with calibration standard. Optional 5th time point 7 days post infusion.
(P) Sub-study A (at selected sites): Full dosimetry imaging (see O + Z) to be repeated for doses D2 - D4, in order to a) validate kidney and tumour dose predictions (AD), based on cycle 1, and b) evaluate the possibility of single time point dosimetry estimations, based on cycle 1 information.
(Q) SPECT/CT in all patients @24 h p. inj. for verification of tumour targeting and 2D/3D hybrid dosimetry.
(R) Sub-study B (at selected sites): SPECT imaging serial at 0.5, 6, and 72 - 96 h in addition to 24 h scan, for full 3D dosimetry (complementary to serial planar imaging).
(T) ^{177}Lu-edotreotide arm: Drug ordered at day of randomisation. The first dose of ^{177}Lu-edotreotide should be administered within 21 days of randomisation. In the case of any delay, the site should check with the Sponsor via the site monitor and the reason for the delay should be documented accordingly.
(U) In case of early withdrawal, all evaluations, as specified for EOS shall be performed, wherever possible.
(X) Hyperkalaemia is a known side effect of the Amino-Acid Solution. If K^+ is elevated: additional clinical chemistry blood samples will be collected at the discretion of investigator
(Y) AEs ongoing at EOS have to be followed up until resolved or for a period up to a maximum of 30 days by the investigator.
(Z) Transmission scan and blank scan using either a Co-57 or Tc-99m sheet source or if available at the site whole body low dose CT scan. These scans can be performed up to 7 days prior to PRRT. For Tc-99m blank and transmission scan have to be performed together (one followed by the other) due to the short half-life of Tc-99m.
(ZZ) MRI / CT to be performed within 7 days prior to month 12, 15, 18, 21, 24, and 27 visits. For early withdrawal, MRI / CT not to be repeated in case of progression.
(ZZZ) Sub-study C (at selected sites in a subgroup of 20 patients): Urine samples for PK - urine will be collected from all voids beginning immediately at 0 min post-dose into 4 pooled samples in intervals from 0 min post-dose to 1 hour, and 1-6, 6-24 and 24-48 hours post-injection. Blood samples of 1 mL, each, will be drawn at 0 min, 10 min, 1 h, 3 h, 6 h, 24 h, 48 h, 3 d, and 7 d post end of infusion. Blood samples on D0 can be taken within ±5 min of the scheduled time, as long as the exact sampling times are recorded in the CRF. Sub-study C will be performed during any one of the four ^{177}Lu-edotreotide treatment cycles (the choice of which of the four cycles to collect urine and blood samples for Sub-study C will be at the investigator's discretion).

Sampling Schedule Sub-study C

Time post-infusion	Day 0						D 1	D 2	D 3	D 7
	0 min	10 min	30 min	1h	3h	6h	24 ± 3 h	48 ± 3 h	72 ±12h	168 ±12h
Urine	X	→	→	X	→	X	X	X		
Blood	X	X	X	X	X	X	X	X	X	X

Table 2 (Study Flow Chart): ^{177}Lu-Edotreotide vs. Everolimus in GEP-NET (COMPETE Study) – Everolimus Patients

Examination / Evaluation				Treatment 1st year												Treatment 2nd year						EOS	Early withdrawal[U]	Post-study FU
Time point	Month	Baseline		0		1[AAA]	2[AAA]	3[AA]	4[AAA]	5[AAA]	6[AA]	7[AAA]	8[AAA]	9[AA]	10[AAA]	11[AAA]	12[AA]	15[AA]	18[AA]	21[AA]	24[AA]	27[AA]	30[AA]	within 28 days after withdrawal	6 monthly for 5 years
	Day	-90 to 1	-28 to -1	0		30 ± 7	60 ± 7	90 ± 14	120 ± 7	150 ± 7	180 ± 14	210 ± 7	240 ± 7	270 ± 14	300 ± 7	330 ± 7	± 21	± 21	± 21	± 21	± 21	± 21	±21		
	h*			Pre-dose[AA]	0.5 ±0.25																				
Informed Consent		X																							
Review Inclusion / Exclusion Criteria		X	X																						
Randomisation			X[V]																						
General																									
Medical History		X	X																						
Physical Examination		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Haematology			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clotting Parameters			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tumour Markers[C]			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[D]			X	X[D]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG			X	X				X			X			X			X		X		X		X	X	
Current Biopsy[F]		X																							
Tumour Histology[G]		X																							
EORTC QLQ-C30 and GI.NET21			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications		X	X	X←																			X	X	
Symptomatic Medication (SSA)[H]			X	X[H]←																			X	X	
Adverse Events / Baseline Findings			X	X←																			X[Y]	X[Y]	
Overall Survival																									X
Antineoplastic Treatments																									X
Imaging Inclusion, Outcome & Safety																									
Somatostatin Receptor Imaging (SRI)[I]		X																							
Morphological Imaging (MRI / CT)		X[K]	X[K, L]					X			X			X			X[ZZ]	X[ZZ]	X[ZZ]	X[ZZ]	X[ZZ]	X[ZZ]	X	X[ZZ]	
^{99m}Tc-MAG-3 Renogram			X[M]								X						X[M]		X[M]		X[M]		X	X	
Comparator Arm																									
Everolimus Administration[S]				X[S]←																			X		
Study Visits				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense of diary					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
^{177}Lu-Edotreotide Therapy[W]																									X

*hours post last dose

Table 2 – Everolimus – (footnotes):

(AA) (Pre-dose) procedures (e.g. MRI / CT) may be performed within 7 days before visit. Investigations should be performed as close to dosing as organisationally possible and as clinically appropriate.

(AAA) Blood-sampling can be perfomed up to 72 hours prior to the visit according to local practice and as clinically appropriate.

(C) Tumour biomarkers in serum: chromogranin-A (CgA) in all patients; disease-specific hormones, if positive at baseline work-up.

(D) Pregnancy test for all premenopausal female patients during screening. To be repeated, if dosing starts > 14 days after screening. To be repeated monthly until EOS.

(F) Mandatory, unless prior tumour specimen (paraffin block) available. Biopsy sample to be sent to CPL before randomisation.

(G) Local histopathology report to be sent to the CPL with the biopsy sample.

(H) Somatostatin agonists (SSA) for symptom control are allowed, if not exceeding the licensed posology

(I) SRI using PET/CT, SPECT/CT or planar imaging, as institutionally available/locally acceptable (e.g. ^{68}Ga-edotreotide, ^{68}Ga-DOTATATE, ^{111}In-pentetreotide, ^{99m}Tc-octreotide) within 4 months prior to randomisation.

(K) MRI / CT showing radiological tumour progression based on RECIST 1.1 as evidenced by two scans obtained within a maximum of 36 months prior to randomisation, with at least 90 days interval between them. The most recent scan should not be older than 90 days at randomisation.

(L) One native liver and contrast-enhanced liver and 3 regional (pelvis, abdomen, thorax) MRI or CT, not older than 28 days at the time of randomisation. Baseline method must be followed throughout the study period.

(M) ^{99m}Tc-MAG-3 renogram to be performed within 28 days prior to randomisation; and within 7 days prior to month 12, 18, and 24 visits.

(S) Everolimus, 10 mg (per os, once daily) until diagnosis of progression. Dose may be modified according to protocol appendix 4.

(U) In case of early withdrawal, all evaluations, as specified for EOS shall be performed, wherever possible.

(V) If patient was randomised to everolimus, treatment should be initiated as soon as possible (preferably no later than 21 days after randomisation). The randomisation visit can then be taken as day 0 of treatment if all required pre-dose examinations were performed on the same day.

(W) ^{177}Lu-Edotreotide therapy for patients (having progressed under everolimus therapy): Administration and follow-up as for study patients, until secondary progression.

(Y) AEs ongoing at EOS have to be followed up until resolved or for a period up to a maximum of 30 days by the investigator.

(ZZ) MRI / CT to be performed within 7 days prior to month 12, 15, 18, 21, 24, and 27 visits. For early withdrawal, MRI / CT not to be repeated in case of progression.

Table of Contents

List of Tables, Figures, Equations and Attachments

Tables:

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List of Abbreviations

^{177}Lu-Edo	^{177}Lu-edotreotide
3D	Three-dimensional
AAS	Amino acid solution
AD	Absorbed dose
ADR	International Carriage of Dangerous Goods by Road
AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the curve
BSA	Body surface area
CIM	Clinical imaging manual
CCL	Creatinine clearance loss
CgA	Chromogranin A
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum serum concentration
C_{min}	Minimum serum concentration
CPS	Central pathology services
CPL	Central pathology lab
CR	Complete response
CRA	Clinical research associate, monitor
CRF	Case report form
CRO	Clinical research organisation
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common toxicity criteria – adverse events (version 4.03)
CUP	Cancer of unknown primary origin
CYP2D6	Cytochrome P450 (3A4)
CYP3A4	Cytochrome P450 (2D6)
D1-4	Dose 1 to 4
DCR	Disease control rate

DDC	Duration of disease control
DMT	Dose-modifying toxicity
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTATATE	DOTA-octreotate
DOTATOC	Edotreotide
EBRT	External Beam Radiation Therapy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFR	External Field Radiation
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of study
EphMRA	European pharmaceutical Market Research Association
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration (USA)
FDG	Fluorodeoxyglucose
FOV	Field of view
FSH	Follicle stimulating hormone
GBq	Gigabecquerel
GE-NET	Gastroenteric NET
GEP-NET	Gastroenteropancreatic NET
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
Gy	Gray
HBsAg	Hepatitis B virus surface antigen
HCV	Hepatitis C virus
HE	Haematoxylin and eosin stain
HES	Hydroxyethyl starch
HR	Hazard ratio
HIV	Human immunodeficiency virus
HPF	High power field
HRQL	Health-related quality of life
IATA	International Air Transport Association

ICL	Image core laboratory
IEC	Institutional Ethics Committee
IDSMB	Independent data safety monitoring board
IMP	Investigational medicinal product
INN	International non-proprietary name
INR	International normalised ratio
IRB	Institutional Review Board
IRC	Independent image review committee
ISF	Investigator's site file
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
Ki-67	Antigen Ki-67
KPS	Karnofsky performance status
MAG3	Mercaptoacetyltriglycine
Max	Maximum
MBq	Megabecquerel
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
Min	Minimum
mNET	Metastasised neuroendocrine tumours
mOS	Median overall survival
mPFS	Median progression-free survival
mP-NET	Metastasised P-NET
MRI	Magnetic resonance imaging
mTOR	Mechanistic target of rapamycin
n.c.a.	Non carrier added
NEC	Neuro-endocrine carcinoma
NET	Neuro-endocrine tumours
NF	Non-functional
NM	Nuclear medicine
n.s.	not significant
OA	Octreotide acetate
OR	Overall morphological response
ORR	Objective response rate
OS	Overall survival
p.i., p.inj.	Post injection

%IA	Percent injected activity
PET	Positron emission tomography
PD	Progressive disease
PFS	Progression-free survival
PgP	P-glycoprotein
PI	Principal investigator
P-NET	Pancreatic NET
PP	Per protocol
PR	Partial response
PRRT	Peptide receptor radionuclide therapy
Q25	25% quartile
Q75	75% quartile
QLQ	Quality of life questionnaire
QOF	Quality of life
RCT	Randomised, controlled trial
RECIST	Response criteria in solid tumours
RFA	Radiofrequency Ablation
RP	Reference product
RR	Response rate
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Stable disease
SEER	Surveillance, epidemiology, and end results
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPECT	Single-photon emission computed tomography
SPSS®	Statistical package for social sciences
SRI	Somatostatin receptor imaging
SSA	Somatostatin agonist
SSTR	Somatostatin receptor
TER	Tubular extraction rate
TLS	Tumour lysis syndrome
TMF	Trial master file
ToC	Time of calibration
TSH	Thyroid stimulating hormone

ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information
VIP	Vasoactive intestinal peptide

Study Administrative Structure

Responsibility	Name	Affiliation/Address
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The principal investigator of each centre must sign the protocol signature sheet before patient recruitment may start at the respective centre. Likewise, all protocol amendments must be signed and dated by the principal investigator before coming into effect at the respective centre.

A complete list of all participating centres and their investigators, as well as all required signature documents, will be maintained in the trial master file (TMF).

1 Introduction

1.1 Background

Neuroendocrine neoplasms arise from neuroendocrine cells present in specialised endocrine glands or as isolated endocrine cells in most tissues throughout the body. The current WHO 2010 classification distinguishes between well-differentiated neuroendocrine tumours (NETs) and poorly differentiated neuroendocrine carcinomas (NECs) of small or large cell type (Rindi et al., 2010). The incidence of NETs has been rising over the past 30 years (Modlin et al., 2008), which is partly explained by improved diagnosis. About 72% of NETs arise in gastrointestinal structures, including the pancreas, which are collectively referred to as gastro-entero-pancreatic NETs (GEP-NETs). About 25% of NETs are bronchopulmonary in origin, and less than 5 % arise from other sites (e.g. thymus, breast). Frequently, NETs are discovered late when already metastatic or locally advanced disease is present, and potentially curative surgical treatment is no longer possible. Common sites of metastasis are mesenteric lymph nodes and the liver via the portal vein. NETs may remain clinically silent until a significant liver tumour burden is present, or obstructive symptoms occur. If tumours produce endocrine hormones, they are referred to as functional NET. Functional tumours are associated with clinical syndromes, characteristic for the type of hormone released (e.g. carcinoid syndrome with flushing and diarrhoea in serotonin secreting tumours). Beyond surgery, therapeutic options for NETs include loco-regional therapies (bland embolisation, radio-embolisation, RFA, EFR), interferon, and chemotherapy, or molecular targeted agents, which address individual metabolic pathways. Most NETs strongly express somatostatin receptors (SSTRs), predominantly of the sst2 subtype (Appetecchia et al., 2010), providing the basis of antisecretory and antiproliferative therapy with somatostatin agonists (SSA), such as octreotide or lanreotide (Rinke et al., 2009; Caplin et al., 2014). Peptide receptor radionuclide therapy (PRRT), using therapeutically radio-labelled SSTR receptor ligands, directed against SSTRs is an innovative modality for NET treatment, which has shown highly promising outcomes, even in patients with advanced disease (Bodei et al, 2013).

The largest group of GEP-NETs are found in the small intestine (carcinoids) and constitute approximately 50% of all GEP-NETs (Öberg et al., 2012). Of these carcinoids, approximately 30% are functional and present with the carcinoid syndrome, including flushing, diarrhoea and endocardial fibrosis. Neuroendocrine tumours of pancreatic origin (P-NETs) constitute approximately 30% of all GEP-NETs. 45-60% of P-NETs are non-functional, and 40–55% are functional (Öberg et al., 2012). Characteristic hormone-related syndromes include the Zollinger–Ellison syndrome (gastrin), hypoglycemia syndrome (insulin), glucagonoma syndrome (glucagon), in addition to which a large variety of very rare conditions exists, associated with the excessive production of VIP, somatostatin and other hormones.

According to the United States (US)-American SEER database, the overall annual incidence of GEP-NETs is 3.65/100,000, which is subdivided into 0.33 for stomach, 1.08 for small intestine, 0.43 for pancreas and 1.65 for colon and rectum (Lawrence et al., 2011). However, it should also be noted that considerable variations in incidence occur depending on country, race and gender (Lawrence et al., 2011, Öberg et al., 2012, Ramage et al., 2012). Non-functional GEP-NETs are usually diagnosed late in the course of the disease, and seem to have a slightly worse prognosis, compared to functional

tumours. When symptomatic, the most common presenting symptoms are abdominal pain (35-78%), weight loss (20–35%), anorexia and nausea (45%). The 5-year survival rate was found to be highest in rectal NETs at 89% and the lowest in P-NETs at 38% (Lawrence et al., 2011). The presence of distant metastases and the degree of differentiation are the most powerful predictors of poor survival (Falconi et al., 2012). Histologically, GEP-NETs are graded based on the number of mitoses per HPF (high power field), and the percentage of cells expressing the proliferation marker Ki-67 (Rindi et al. 2006) into grades G1 (Ki-67 ≤2%), G2 (Ki-67 3-20%), and G3 (Ki-67 >20%). Histological criteria for assessing the prognosis of endocrine pancreatic neoplasms are shown in Table 3. Similar criteria apply to gastroenteric neuroendocrine tumours.

Table 3: Criteria for Assessing the Prognosis of Endocrine Pancreatic Neoplasms

According to Falconi et al., 2012

Biological behaviour	WHO classification	Metastases	Invasion	Tumour size, cm	Angio-invasion	Ki-67 index [%]
Benign	NET G1 or G2	-	-	≤ 2	-	Usually around 2
Benign or low-grade malignant	NET G1 or G2	-	-	>2	±	Usually around 2
Low-grade malignant	**NET G1 or G2**	**+**	**+**	**any**	**+**	**Usually >2**
High-grade malignant	NEC or G3	+	+	any	+	>20

The present protocol aims to investigate metastasised and/or locally advanced, inoperable GEP-NET of grade G1 and G2, with radiologically proven progression.

Current treatment guidelines for metastasised GEP-NET published by ENETS (European Neuroendocrine Tumour Society), recommend as 1st line treatment for G1 midgut tumours somatostatin analogues (Pavel 2012). For P-NETs, a number of 1st line therapy options are presented, including streptozotocin-based chemotherapy in combination with 5-FU and/or doxorubicin (Jensen et al., 2012; Falconi et al., 2012; Pavel 2012). Streptozotocin is not generally licensed for the treatment of P-NET in the European Union (EU). In contrast, the mTOR inhibitor everolimus (Afinitor®, Novartis) and the tyrosine kinase inhibitor sunitinib, (Sutent®, Pfizer) have been licensed for treatment of P-NET in the EU and the USA. Most recently, everolimus has also been licensed for treatment of non-functional GE-NETs by both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). While everolimus has been quickly adopted clinically, sunitinib has remained a reserve medication, due to relatively poor tolerability. A further compound increasingly used for treatment of mP-NET – albeit off-label – is the chemotherapeutic agent temozolomide (Temodar®, MSD), which has shown outstanding tolerability and promising evidence of tumour control (Ekeblad et al., 2007). For non-resectable G1 P-NET tumours with demonstrated SSTR expression, treatment with long-acting somatostatin analogues (SSA), such as octreotide acetate (OA,

Sandostatin®, Novartis) or lanreotide (Somatuline®, Ipsen) is a further therapeutic alternative, which can alleviate hormone release symptoms, and provide some antiproliferative effect.

PRRT with radiolabelled SSTR-ligands, such as ^{90}Y-DOTATOC or ^{177}Lu-DOTATATE has shown great promise in the treatment of NET (Bushnell et al. 2010; Kwekkeboom et al. 2008), with median progression-free survival (mPFS) of 18.2 and 33.0 months, and disease control rates (DCR, proportion of patients with stable disease, partial or complete response) of 74.4% and 65%, respectively. To date, however, a direct comparison of PRRT vs. medical therapy has not been performed. As GEP-NET disease is typically slowly progressing and chronic, patients undergo mostly sequential treatments with SSA, chemotherapy, and/or molecular targeted therapy (everolimus or sunitinib). The order and selection of individual agents varies considerably between institutions and patients. PRRT, where institutionally available, is traditionally performed rather late in the disease course, although its earlier use might be beneficial (Kwekkeboom et al. 2010).^{177}Lu-edotreotide (synonym: ^{177}Lu-DOTATOC) is an innovative PRRT agent, with favourable safety profile, and promising efficacy. Compared to ^{90}Y-edotreotide, ^{177}Lu-edotreotide PRRT in NET was found to be less haematotoxic, and associated with a longer mOS (45.5 vs. 35.9 months, n.s.), which was highly significant for patients with low tumour uptake ($p < 0.001$), extra hepatic ($p < 0.012$), and solitary metastases ($p < 0.02$) (Romer et al., 2014). Compared to other ^{177}Lu-labelled somatostatin receptor ligands in clinical use, ^{177}Lu-edotreotide has the lowest uptake/dose ratio delivered to normal organs and highest tumour-to-kidney ratio (Schuchardt et al., 2013), rendering it particularly promising as a PRRT agent for the treatment of NETs, considering both safety and efficacy. In patients with progressive, inoperable GEP-NETs treated with two or more cycles of ^{177}Lu-edotreotide PRRT, a median PFS of 34.5 months and a disease control rate (DCR: SD, PR and CR) of 100.0% was observed in an academic study, conducted at the ENETS centre of excellence in Bad Berka, Germany (van Echteld et al., 2015; Baum et al., 2016). Based on these data, the EMA granted an Orphan Drug Designation to ^{177}Lu-edotreotide for the treatment of GEP-NET.

Therefore, ^{177}Lu-edotreotide will be developed in the indication GEP-NET. Everolimus (Afinitor®) was selected as a comparator, based on the strength of scientific evidence of efficacy, and the high clinical acceptance this product has gained soon after marketing authorisation. However, everolimus received marketing authorisation for both functional and non-functional P-NETs but for GE-NETs only for non-functional tumours. Everolimus inhibits the so-called mechanistic target of rapamycin (mTOR), involved in the control of cell division and angiogenesis. Pharmacologically, everolimus acts by preventing tumour cell division and reducing the blood supply to tumours by inhibiting angiogenesis.

Further details on the study drug ^{177}Lu-edotreotide can be found in the investigator's brochure, whereas further details concerning the comparator everolimus (Afinitor®) are described in the local product information for the countries participating in this study (Afinitor®, current version of Summary of Product Characteristics [SmPC] for the EU and South Africa; US Prescribing Information [USPI] for the US; Information for Professionals for Switzerland; and Product Information for Australia).

1.2 Rationale of the Study

Current ENETS guidelines recommend PRRT for 2nd line treatment in patients having failed on medical therapy (Jensen et al., 2012; Pavel et al., 2012). Although PRRT is considered an established

treatment modality in such cases, having shown impressive evidence of efficacy (PFS, OS, objective response rates) in non-comparative (single arm) studies, so far only one randomised prospective evaluation of PRRT has been performed with ^{177}Lu-DOTATATE – the NETTER-1 study. The results of an interim analysis of the NETTER-1 study conducted at the primary endpoint (PFS) have very recently been published (Strosberg et al., 2017): Of the 229 patients with well-differentiated, metastatic midgut neuroendocrine tumours included in this study, 116 received ^{177}Lu-Dotatate, and 113 received octreotide LAR. At the data cut-off date for the primary analysis, the estimated rate of progression-free survival at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the ^{177}Lu-Dotatate group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The response rate was 18% in the ^{177}Lu-Dotatate group versus 3% in the control group (P<0.001). In the planned interim analysis of overall survival, 14 deaths occurred in the ^{177}Lu-Dotatate group and 26 in the control group (P=0.004). With regard to safety, ^{177}Lu-Dotatate was associated with low rates of grade 3 or 4 hematologic toxic effects and, when administered together with a renal protective agent, showed no evidence of renal toxic effects during the observation period (median duration of follow-up, 14 months). Based on the results of the NETTER-1 trial, ^{177}Lu-Dotatate has recently received Marketing Authorisation in the EU and the USA as Lutathera® for the second-line treatment of unresectable or metastatic, progressive, somatostatin receptor positive gastroenteropancreatic neuroendocrine G1 and G2 tumours (GEP-NETs) in adults.

However, the NETTER-1 study only enrolled patients with midgut neuroendocrine tumours, and patients with primaries in stomach, pancreas, descending colon and rectum were not included. Furthermore, the previously mentioned academic study, conducted at the ENETS centre of excellence in Bad Berka, Germany (van Echteld et al., 2015, Baum et al., 2016) showed an unprecedented objective response rate of 54% for inoperable GEP-NETs treated with two or more cycles of ^{177}Lu-edotreotide.

The purpose of the present study, therefore, is to evaluate efficacy and safety of PRRT with ^{177}Lu-edotreotide in patients with metastatic GEP-NET, in comparison to established medical therapy using a prospective randomised controlled trial (RCT) design. As comparator drug, everolimus (Afinitor®), has been selected, a drug licensed for the treatment of unresectable or metastatic, well or moderately differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease and recently also for the treatment of unresectable or metastatic, well-differentiated (G1 or G2) non-functional neuroendocrine tumours of gastrointestinal origin. Everolimus has an innovative mode of action, high clinical acceptance, and a well-documented evidence of efficacy. This study will further be designed to allow a meaningful subgroup analysis of GE-NETs and P-NETs. In addition, by inclusion of both, 1st line and 2nd line GEP-NET patients, the issue of optimum timing of PRRT during the disease course will also be addressed by the trial.

1.3 Benefit-Risk Assessment

The prognosis of GEP-NET patients is poor in most cases, since the disease is typically diagnosed at a late stage once the tumour has become non-resectable and/or has metastasised already (Modlin et al., 2008). For patients with metastasised P-NET (mP-NET), the observed 5-year survival rates are the lowest reported and vary between 25%-60% (Öberg et al., 2012),27-43% (Ramage et al., 2012) and 38% (Lawrence 2011), in spite of using all available treatment options, including surgery,

symptom control with SSA and/or chemotherapy. Everolimus (Afinitor®) and sunitinib (Sutent®) are two drugs currently licensed for treatment of P-NET in the EU and USA, based on a median PFS (vs. placebo) of 11.0 (vs. 4.6) (Yao et al., 2011) and 10.2 (vs. 5.4) (Blumenthal et al., 2012) months, respectively. Lanreotide (Somatuline®) has also been approved by the FDA for GEP-NET. Study results showed a median PFS of 18.0 months for placebo (Caplin et al., 2014) and recently a corrected median PFS of 30.8 months for lanreotide (Caplin et al., 2016), but none of the enrolled patients in this study was in progression. Most recently, everolimus (Afinitor®) was also licensed both in the USA and the EU for treatment of non-functional GE-NET and lung NET based on a median PFS of 11.0 months vs. 3.9 months in placebo (Yao et al., 2016).

Well-documented evidence of clinical safety and efficacy of ^{177}Lu-edotreotide in patients with mNET is available from the academic study, mentioned above (van Echteld et al. 2015, Baum et al., 2016). Fifty-six (56) patients (27 female, 29 male, mean age 64.4 years) presenting with progressive NET disease, were administered 1 to 4 doses of ^{177}Lu-edotreotide PRRT as sole treatment option until a new diagnosis of disease progression.

For patients with metastasised GEP-NET, who received ≥ 2 ^{177}Lu-edotreotide cycles, a median PFS of 34.5 months was reported (van Echteld et al. 2015, Baum et al., 2016). It is, therefore assumed, that patients assigned to ^{177}Lu-edotreotide treatment may experience a significant individual benefit, compared to those assigned to standard treatment.

While everolimus treatment is chronic, acting by continuous inhibition of tumour and vascular growth, PRRT acts cumulatively by destroying sensitive tumour cells, similarly as fractionated EFR. For instance, in the Bad Berka academic study, most responding patients (34/37, 92%) showed their first response after the first PRRT cycle, but 5% of patients (2/37) required two, and one patient required three ^{177}Lu-edotreotide cycles for induction of an initial response.

In 65% (24 of 37) of patients the best response was observed after the first PRRT cycle. However, 32% (12 of 37) of patients required 2 cycles for induction of their best response, while latency was more than 9 months from start of treatment in 7 of these patients and in 2 patients, latency was even more than 22 months. One patient required three ^{177}Lu-edotreotide cycles for induction of the best response. Interestingly, 47% (9 of 19) of all objective responses (PR, CR) took more than nine months to develop from start of treatment. In 35% the best therapeutic response was observed only after their last PRRT cycle (late responders), without receiving further antineoplastic therapy. In addition to direct cytocidal effects of PRRT, mediated by lethal DNA double strand breaks, secondary antineoplastic effects may be induced, which can further improve the treatment outcome even months after the last PRRT cycle, without further specific treatment.

^{177}Lu-edotreotide PRRT will be administered as a maximum of four cycles of a 7.5 ± 0.7 GBq dose, referred to as dose 1 – dose 4 (D1 – D4), administered in 3-monthly intervals over a period of 9 months. Although current guidelines on PRRT (Bodei et al., 2013; Zaknun et al., 2013; IAEA 2013) advise 200 mCi (=7.4 GBq) as maximum for a single dose, we have chosen to employ a 7.5 GBq dose based on SI-units. The advised number of cycles is three to five with a 6-12 weeks interval, from which we derived a maximum number of four cycles with a 3 months interval, based on the academic study, mentioned before (van Echteld et al. 2015, Baum et al., 2016). This dose and dose regimen were approved on several protocol discussion meetings with key opinion leaders.

Due to tubular re-absorption of radiolabelled peptide agents, radiation-induced kidney disease is the main safety concern for PRRT. Both, acute renal toxicity with increased serum creatinine and long-term nephropathy with creatinine clearance loss (CCL) of 5 to more than 10% per year (Bodei et al., 2008) may occur. Nephropathy is reported to be more pronounced in patients with renal risk factors (arterial hypertension, diabetes mellitus), pre-existing renal impairment or those who have received earlier nephrotoxic treatment modalities (chemotherapy, local EFR, prior PRRT) (Bodei et al., 2008).

All patients in the above-mentioned academic study were pre-treated with a nephroprotective amino acid solution, administered IV starting 30 min to and lasting 3 – 4 h after the start of the PRRT infusion, according to current guidelines (Bodei et al., 2013; Zaknun et al., 2013; IAEA 2013). Such regimen has been shown to decrease the renal absorbed radiation dose by 50% without reducing the tumour uptake (Rolleman et al., 2010). Using this regimen, no clinically relevant nephrotoxicity following PRRT with ^{177}Lu-edotreotide was observed, as evaluated by extended renal function testing (glomerular filtration rate [GFR], creatinine, tubular extraction rate [TER], K^+ and BUN).

In the context of the planned trial, a similar nephroprotective regimen will be used. In addition, patients with impaired renal function (GFR <60mL/min/1.73 m²), or ill-controlled renal risk factors will be excluded from participation. As a further safety measure, absorbed organ doses to the kidneys will in principle be restricted to ≤ 23 Gy, as per current guidelines on PRRT (Bodei et al., 2013; Zaknun et al., 2013; IAEA 2013). If the predicted absorbed dose to the kidneys likely exceeds 23 Gy upon administration of the next PRRT cycle, additional measurement of renal function must be performed. In case this pre-therapeutic TER (^{99m}Tc-MAG3 renal scintigraphy) is >50% of baseline, dosing can be continued. However, the absorbed dose is not allowed to exceed 29 Gy, as suggested by Konijnenberg et al. (2007).

Patients assigned to comparator treatment with everolimus will receive licensed standard treatment. Potential side effects include among others anaemia, fatigue, diarrhoea, hyperglycaemia, and diabetes mellitus (see Afinitor®, current version of manufacturer's instruction and local product information for the countries participating in this study). The selected dose (10 mg/d) corresponds to manufacturer´s recommendations.

PRRT with ^{177}Lu-edotreotide has been administered in a relevant number of patients with NET in the context of the above-mentioned academic study. A promising impact on progression-free survival and objective response rate has been observed in these patients with advanced and progressive disease. At the same time, a safety profile favourable for an anti-cancer agent was established. For participating patients, the potential of an individual benefit is substantial, considering both an improved efficacy, and better safety and tolerability, compared to the licensed comparator medication everolimus. Furthermore, because of the expected substantial difference in PFS between ^{177}Lu-edotreotide PRRT and everolimus (Afinitor®) treatment, a 2:1 randomisation has been chosen, respectively. This allows a larger number of patients the direct potential benefits and low risks of ^{177}Lu-edotreotide PRRT.

In summary, considering the expected favourable benefit-risk ratio for study participation of patients with progressive GEP-NET, the recommended ^{177}Lu-edotreotide dosing, consisting of four cycles of 7.5 ± 0.7 GBq, is justified to maximise therapeutic benefit, provided that individualised dosimetry shows the cumulative renal absorbed radiation dose not to exceed 23 Gy. Exceptionally, dosing up

to 29 Gy renal absorbed radiation dose is permitted, only if kidney function is not compromised and additional pre-therapeutic TER (^{99m}Tc-MAG3 renal scintigraphy) is proven to be >50% of baseline.

In view of the expected benefit for patients with advanced cancer, the planned Phase 3 dosing regimen represents an optimum balance of risk (nephrotoxicity) and therapeutic benefit, in line with current guidelines and similar therapies under investigation.

2 Study Objectives

Primary objective

The primary objective is to demonstrate the efficacy of PRRT with ^{177}Lu-edotreotide to prolong progression-free survival (PFS) in patients with inoperable, progressive, SSTR+ GEP-NET, compared to everolimus.

Key secondary objectives

The key secondary objectives of this study are:

1. To assess objective response rates (ORR), defined as the proportion of patients achieving partial response (PR) or complete response (CR) as best outcome, after treatment with ^{177}Lu-edotreotide compared to everolimus

2. To assess overall survival (OS) defined as the time from date of randomisation until death

Exploratory secondary objectives

The exploratory secondary objectives of this study are:

3. To assess the duration of disease control (DDC), defined as the time of initial diagnosis of response (SD, PR or CR) until diagnosis of progression, after treatment with ^{177}Lu-edotreotide compared to everolimus

4. To determine disease control rates (DCR), defined as the proportion of patients achieving stable disease (SD), PR or CR as best outcome

5. To determine response rate (RR), considering CgA and specific hormones (where increased at baseline)

6. To assess the safety and tolerability of ^{177}Lu-edotreotide in GEP-NET patients

7. To determine the health-related quality of life (HRQL) in GEP-NET patients during and after therapy (EORTC QLQ-C30 questionnaire)

8. To evaluate symptomatic tumour response (EORTC GI.NET21 questionnaire)

9. To evaluate the impact of patient characteristics (time from primary diagnosis, time from diagnosis of progression, number of prior therapies (1st vs 2nd line), type of prior therapies, KPS at randomisation) on tumour response

10. To evaluate the impact of tumour histology (histological entity, tumour grade, Ki-67 expression, SSTR expression, functional state), as determined in primary or current tumour specimen, on tumour response

Tertiary objectives (in ^{177}Lu-edotreotide patients)

1. To assess differences in tumour and kidney radiation dose estimates, obtained with 2D (planar) compared to hybrid (2D/3D), and 3D (SPECT) imaging

2. To evaluate the value of pre-therapeutic SSTR imaging (SRI) to predict tumour response (globally/at lesion level)

3. To evaluate the relationship between PRRT radiation dose (in Gy) and tumour response (globally/at lesion level)

4. To assess metabolic stability and excretion pattern of ^{177}Lu-edotreotide

5. To assess bone marrow radiation dose

3 Overview of Methodology and Design

3.1 Study Design

This will be a confirmatory, prospective, randomised, controlled, parallel group, open-label, multi-centre phase III study to evaluate the efficacy and safety of ^{177}Lu-edotreotide in comparison to molecular targeted therapy with everolimus in patients with inoperable, progressive, somatostatin receptor-positive (SSTR+), neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET).

In total, 300 GEP-NET patients will be randomised in a 2 : 1 fashion to receive either:

- PRRT with ^{177}Lu-edotreotide consisting of a maximum of four cycles (7.5 ± 0.7 GBq ^{177}Lu-edotreotide, each), administered as IV infusion at 3-monthly intervals for 9 months, or until diagnosis of progression (200 patients), or

- 10 mg everolimus (Afinitor®) daily, administered orally as a tablet (100 patients).

The duration of study participation for the patients will be 30 months. Due to the extension of the duration of study participation from 24 months to 30 months, patients already in the post-study follow-up will be contacted again if applicable and re-consented for performing the visits at 27 and/or 30 months. The duration of the entire study is planned to be 90 months. Collection of survival data and information on further antineoplastic treatments as well as the development of secondary

malignancies will be continued for five years after EOS. To enable a meaningful subgroup analysis, randomisation will be stratified for primary tumour origin with ideally equal numbers of GE-NETs (150 patients) and P-NETs (150 patients). Furthermore, a sufficient number of treatment-naive patients (1st line) and patients with previous therapies (2nd line) must be enrolled to allow conclusions on efficacy in each of the sub-populations.

^{177}Lu-edotreotide PRRT will be administered as a maximum of four cycles of a 7.5 ± 0.7 GBq dose referred to as dose 1 – dose 4 (D1 – D4), administered in 3-monthly intervals over a period of 9 months. The administration of each dose may require a short-term hospitalisation of typically 3 days on a suitable radionuclide therapy ward. Individual hospitalisation requirements will be as specified per the locally applicable radiation safety regulations for each study site. Biodistribution of ^{177}Lu-edotreotide, and consequently the absorbed dose (AD) to kidneys may vary considerably between subjects. Therefore, following current guidelines, the absorbed organ doses to the kidneys will in principle be restricted to ≤ 23 Gy (Bodei et al., 2013; Zaknun et al., 2013; IAEA 2013).

To this end, after administration of D1, patients will be subjected to sequential dosimetric whole body imaging at 0.5 (prior to voiding, preceded by a blank and a transmission scan or if available at the site whole body low dose CT scan), 6, 24, and 72–96 h p.i. using conventional planar scintigraphy, complemented by abdominal SPECT/CT imaging at 24 h (optional planar scintigraphy on day 7). Based on the first cycle, the cumulative AD to kidneys from the planned full treatment course of four doses of 7.5 ± 0.7 GBq ^{177}Lu-edotreotide will be estimated. However, if the predicted absorbed dose to the kidneys likely exceeds 23 Gy upon administration of the next PRRT cycle, dosing can be continued up to a maximum of 29 Gy, provided that a pre-PRRT TER (^{99m}Tc-MAG3 renal scintigraphy) is >50% of the value at baseline (see Section 5.4.3). In selected patients, the accuracy of AD predictions made based on the first cycle will be verified by repeated dosimetry in cycles D2 – D4 (Sub-study A).

In addition, before receiving the next ^{177}Lu-edotreotide treatment after cycle 1, all patients in the PRRT arm will be assessed for specific safety criteria during the pre-treatment evaluations on Day 90 post first cycle, including hematological as well as renal safety parameters. If the safety criteria are not met, the patients will not receive the next dose (see Section 5.4.1.2).

^{177}Lu-edotreotide dosimetry will be centrally analysed for the absorbed kidney and target tumour doses in a standardised fashion. Resulting mandatory prescriptions for additional ^{99m}Tc-MAG3 renal scintigraphy before continued administration of ^{177}Lu-edotreotide doses D2 - D4, ensuring a safe kidney dose exposure, will be derived and communicated to the sites by the central lab. Dosimetry will be performed according to the current regulatory standard (conventional planar (2D) dosimetry), and according to the emerging clinical standard (2D/3D hybrid dosimetry) for a more accurate determination of the kidney dose.

Quantitative SPECT reconstruction is a recent option to directly derive quantitative information on ^{177}Lu activity distribution *in vivo*, allowing to assess absorbed doses to kidneys (safety) and tumour (efficacy) with higher accuracy, compared to planar scintigraphy. In selected study sites, ^{177}Lu-edotreotide SPECT/CT (3D) will be performed at each time point in addition to planar scintigraphy (2D). Data will be quantitatively reconstructed, and dosimetrically analysed in comparison to planar (2D) and hybrid (2D/3D) dosimetry (Sub-study B).

To assess in-vivo stability of ^{177}Lu-edotreotide, urine will be collected from all voids beginning immediately post-dose to 1 hour, and in intervals of 1-6, 6-24 and 24-48 hours post-injection in a subgroup of 20 patients at selected sites only. Urine will be analysed using gamma counting and radio-HPLC in order to investigate the radiochemical purity of the eliminated compound, as well as the excretion pattern of ^{177}Lu-edotreotide (Sub-study C). In addition, bone marrow dosimetry will be assessed in Sub-study C by measuring radioactivity in blood samples at pre-defined intervals from 0 minutes to 7 days post-injection of ^{177}Lu-edotreotide.

Following administration of each ^{177}Lu-edotreotide dose (D1 – D4), blood has to be drawn for safety laboratory examinations (haematology) in 2-weekly intervals for 8 weeks. Where these time points will not coincide with formal study visits, blood may be drawn in local medical institutions, if a visit of the study site is not reasonably feasible.

Everolimus: Patients randomised to everolimus therapy will undergo out-patient visits only. Patients will receive a standard dose of 10 mg daily, which may be reduced, where required for acceptable tolerability, according to manufacturer´s product information (see Appendix 4).

Both study arms: Study visits will be monthly in the first 12 months, thereafter 3-monthly until end of study at month 30 or until progression (whatever occurs first). For symptom control, all patients are allowed to receive somatostatin analogues (SSA), as clinically indicated (best supportive care) in required doses, not to exceed licensed doses. In the ^{177}Lu-edotreotide arm, clinically established wash-out periods prior to ^{177}Lu-edotreotide dosing have to be considered (1 day for immediate release, and 28 days for sustained release SSA).

Safety, tolerability and symptom control parameters, as well as tumour markers are captured at regular intervals.

To assess efficacy, serial morphological imaging, comprising native liver and contrast-enhanced liver and 3 regional (pelvis, abdomen, thorax) MRI or CT (see Clinical Imaging Manual for details), is scheduled every three months, consistently using baseline methods. Evaluation of tumour response will be performed by local investigators using RECIST 1.1 criteria.

In case of clinically suspected tumour progression, investigators may schedule appropriate diagnostic imaging at any time.

Image analyses will also be conducted centrally. For establishment of PFS (primary endpoint) blinded reading in duplicate, with adjudication in case of discordance will be used.

Patients who progressed under everolimus may be offered ^{177}Lu-edotreotide therapy based on the personal judgement of the Investigator, if he/she considers it appropriate and likely to be beneficial for the individual patient (see Section 7.4.2).

To further evaluate tumour response, the tumour marker Chromogranin A (Cg-A) will be determined at baseline, and then monthly until month 12, thereafter in 3-monthly intervals until diagnosis of progression or end of study. Cg-A represents a secretory protein present in dense-core vesicles of neuroendocrine (NE) cells. It is being expressed in most secretory, but also non-functional NET. Cg-A is the best circulating neuroendocrine marker available up to now for the management of differentiated

neuroendocrine malignancies irrespective of tumour location and functional status (Singh et Law, 2012).

The European Organisation for Research and Treatment of Cancer (EORTC) has issued an integrated system of quality of life questionnaires (QLQ) for assessing the health-related quality of life (HRQL) of cancer patients participating in international clinical trials. The QLQ-C30 and QLQ-GI.NET21 will be used in the current trial.

QLQ-C30 is a copyrighted instrument, which has been translated and validated into 81 languages and is used in more than 3,000 studies worldwide. The first version of QLQ-C30 was released in 1993. Since then, several new versions have been developed and issued. Version 3.0, a 30-item questionnaire, is currently the standard version of the QLQ-C30, and should be used for all new studies unless compatibility to previous studies is intended. It is supplemented by disease specific modules for e.g. Breast, Lung, Head & Neck, Oesophageal, Ovarian, Gastric, Cervical cancer, Multiple Myeloma, Oesophago-Gastric, Prostate, Colorectal Liver Metastases, Colorectal and Brain cancer which are distributed from the EORTC Quality of Life Department. Other disease-specific modules are under development but not yet validated.

The QLQ-C30 supplement QLQ-GI.NET21 is intended for use among patients with GI-related neuroendocrine tumours, who vary in disease stages and treatments. The module comprises 21 questions assessing disease symptoms, side effects of treatment, body image, disease related worries, social functioning, communication, and sexuality (see Appendix 2). The module has been recently validated within an international multicentre study in 253 patients with gastrointestinal neuroendocrine tumours. All patients were requested to complete two quality of life questionnaires – the EORTC Core Quality of Life questionnaire (QLQ-C30) and the QLQ-GI.NET21 – at baseline, and at 3 and 6 months post-baseline; the psychometric properties of the questionnaire were then analysed. It was concluded that QLQ-GI.NET21 is a valid and responsive tool for assessing quality of life in the gut, pancreas and liver neuroendocrine tumours (Yadegarfar et al., 2013). The GI.NET21 has been translated into several European languages.

During treatment phase monthly QOL assessments will be performed as in the everolimus group the continuous daily treatment may lead to changes in quality of life which are not consistent to treatment intervals in the ^{177}Lu-edotreotide group.

3.2 Study Endpoints

The primary endpoint is progression-free survival (PFS). Diagnosis of progression will be established based on morphological imaging (MRI and/or CT) according to RECIST 1.1. Progression-free survival (PFS) will be determined as time elapsed between randomisation, and the date of first objective report of tumour progression (evaluated by RECIST criteria, 1.1), or death. Stratification will be made for primary tumour origin (GE-NET vs. P-NET) and prior medical therapy (1st line vs. 2nd line). Tumour grade (G1, G2), and baseline Karnofsky score will be used for further statistical subgroup analyses

Secondary endpoints include parameters of morphological and biomarker tumour response, such as objective response rate (ORR), overall survival (OS) , disease control rates (DCR), and duration of

disease control (DDC), as well as safety, and health-related quality of life (HRQL). Furthermore, exploratory analyses will be performed on patient and tumour characteristics, as well as the degree of ^{177}Lu-edotreotide uptake as possible predictors of PRRT efficacy.

3.3 Justification of the Design

For the evaluation of a new treatment modality, a prospective, randomised, controlled trial (RCT) design is appropriate. Ideally, a double-blind setting should be implemented to minimise observational bias. Due to the nature (radioactive vs. non-radioactive) and the administration schemes of investigational and comparator drugs, a blinded design is not possible, as the treatments are substantially different. ^{177}Lu-edotreotide therapy is administered in 3-monthly intervals at most four times as intravenous infusion with concurrent infusion of a nephroprotective amino acid solution. This therapy involves a short-term hospitalisation for each dose and several imaging procedures (for dosimetry and tumour targeting). In contrast, everolimus is a systemic therapy administered per os on an outpatient basis.

While for pivotal phase III oncology trials “overall survival” (OS) is generally seen as the ideal primary outcome parameter (FDA, Guidance for Industry, 2007), “progression-free survival” (PFS) is widely accepted as alternative primary endpoint. Since GEP-NET patients typically are treated with various medications during their disease course, study participants are likely to undergo further treatments after study participation, rendering the interpretation of OS difficult. For this reason, PFS has been selected as primary endpoint, which requires appropriate randomisation, blinding and consistent definition of tumour progression criteria.

To achieve blinding, although not feasible in the clinical setting, the diagnosis of progression (primary endpoint) will be independently confirmed by a centralised blinded read, in duplicate, with adjudication, as appropriate for a phase III study (Yao et al., 2011).

Considering that licensed medications for the treatment of GEP-NET are available, a placebo-controlled design as in earlier pivotal studies (Raymond et al., 2011; Yao et al., 2011) appears no longer adequate from an ethical and medical perspective. Also, products in current clinical use for treatment of GEP-NET, but not licensed (off-label use, e.g. temozolomide chemotherapy), are considered not adequate as comparators for a confirmatory study. The mTOR antagonist everolimus is currently the only product licensed worldwide for the treatment of inoperable, advanced low-grade and intermediate-grade GEP-NET, which is the indication ^{177}Lu-edotreotide is being developed for. The license for GE-NET is limited to non-functional GE-NETs and granted in both the USA and EU. Consequently, everolimus (Afinitor®) was selected as the most suitable comparator. It will be administered using a standard dose of 10 mg/d, with the option of dose reduction in case of inadequate tolerability, according to the recommendations of the manufacturer (Appendix 4: Afinitor dose adjustment recommendations).

An independent data safety monitoring board (IDSMB) will closely review safety data at regular intervals throughout the study. If there are any signs of safety issues, the IDSMB may suggest terminating the trial (see also Section 11 on premature termination of the study).

3.4 Justification of the Dose

The clinical dose regimen was selected based on biodistribution and dosimetry data from a subset of patients with neuroendocrine tumours, belonging to the same group of 140 patients of the Bad Berka retrospective study treated with ^{177}Lu-edotreotide (Schuchardt et al., 2013; van Echteld et al., 2014; Baum et al., 2016), supported by detailed pharmacokinetics and biodistribution data of ^{86}Y-edotreotide from Novartis Phase I clinical studies (Jamar et al., 2003; Barone et al., 2005). Furthermore the recommendations of the joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours (Zaknun et al., 2013) have been taken into consideration.

The detailed examination of the pharmacokinetics and biodistribution of therapeutic radiolabelled edotreotide was performed in a Phase I, single-centre, open label, cross-over study of 24 GEP-NET patients (Jamar et al., 2003) and in a subset of 18 GEP-NET patients enrolled in a Phase-I multicentre study (Barone et al., 2005), using the positron emitting isotope yttrium-86 (^{86}Y) and the inherent quantitative advantages of positron emission tomography (PET) imaging. ^{86}Y-edotreotide is an appropriate surrogate to quantitatively predict the in vivo behaviour of the therapeutic compound, not only radiolabelled with chemically identical ^{90}Y, but also when radiolabelled with chemically very similar ^{177}Lu. Since Y(III) and Lu(III) belong to the same group of trivalent rare-earth elements with very similar chemical properties, Y(III) and Lu(III) reveal almost identical nine-coordinate structure and thermodynamic stability of the complexes with DOTA-chelator (Viola-Villegas & Doyle, 2009). Furthermore, the ^{86}Y half-life of 14.74 h allows quantitative PET investigations up to 48 h p.i., which is adequate for the pharmacokinetics and biodistribution analysis of therapeutic ^{90}Y- and ^{177}Lu-edotreotide.

The main outcome of the Novartis Phase-I pharmacokinetics and biodistribution studies was a large variability in individual renal uptake. Kidney uptake and retention of ^{86}Y-edotreotide varied between patients by a factor of 3 and indicated a wide range of absorbed doses during therapies, whereas body surface area only ranged between 1.50 and 2.06 m^2. Given the known safety profile and dose limiting renal toxicity, the dosing of the therapeutic agent has been proposed based on the individualised dosimetry approach (Barone et al., 2005), rather than based on body mass.

The same observation was reported in 59 patients treated with ^{177}Lu-edotreotide and undergoing dosimetric evaluation by means of SPECT (Schuchardt et al., 2013). The mean kidney absorbed dose was 0.6 with a wide variation in range 0.3 – 1.6 mGy/MBq.

Figure 1 shows a selection of 19 patients from the Bad Berka dosimetry data base, who received 7.5 ± 0.4 GBq ^{177}Lu-edotreotide (= 7.5 GBq ± 5%). These patients belong to the same group of 140 patients of the above mentioned retrospective study. Similar to the results reported from Novartis Phase-I clinical trials, these data serve to support fixed dosing as opposed to body weight-guided dosing, since no correlation whatsoever is found between kidney absorbed dose and body weight for the same administered ^{177}Lu-edotreotide dose. Furthermore, these data also serve to emphasise the importance of individual dosimetry-guided dosing, since we observe a 3-fold variation in absorbed kidney dose for the same administered ^{177}Lu-edotreotide dose.

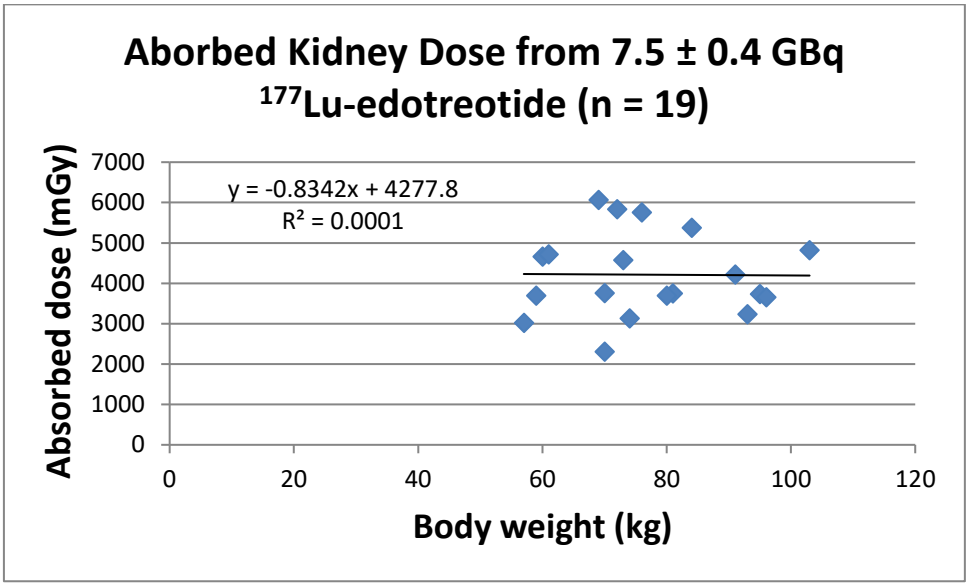

Figure 1: Absorbed kidney dose from 7.5 ± 0.4 GBq ^{177}Lu-edotreotide (Schuchhardt et al., 2013)

In summary, the selected ^{177}Lu-edotreotide dosing is a regime of up to four cycles of a fixed 7.5 GBq dose per cycle, based on individual dosimetry not to exceed a 23 Gy cumulative renal absorbed radiation dose or maximally 29 Gy, provided that additional measurements of renal function (^{99m}Tc-MAG3 renal scintigraphy) are >50% of baseline. In addition, this clinical dose regimen is in line with the recommendations from recent literature and based on leading experts' opinions of joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours (Zaknun et al., 2013).

3.5 Protocol Adherence

Strict adherence to all specifications laid down in this protocol is required for all aspects of the study conduct; the investigator may not modify or alter the procedures described in this protocol. If protocol modifications are necessary, all alterations that are substantial and not solely of an administrative nature require a formal protocol amendment which has to be approved by the Institutional Ethics Committee(s) IEC(s) / Institutional Review Board(s) IRB(s) and Competent Regulatory Agencies/Authorities according to national regulations before the amendments can be implemented and the study may continue (see Section 13.1 for the role of IECs / IRBs and Competent Regulatory Agencies/Authorities).

If an investigator has deviated from the protocol in order to eliminate an immediate hazard to patients or for other inevitable medical reasons, the investigator shall document all such deviations, including the reasons thereof, and submit the document to the sponsor, the IEC(s) / IRB(s) and the relevant Competent Regulatory Agencies/Authorities if applicable, and according to national regulations.

As an exception only during the COVID-19 pandemic, the Sponsor acknowledges that some organisational and/or logistical adjustments might be necessary at the investigational sites. Deviations from this protocol that might arise in case of exceptional circumstances must be documented and

discussed with the Sponsor without delay. Every effort should be made to ensure the continuity of this study as per this study protocol and to avoid delays, treatment discontinuation, missing assessments, and study dropout.

3.6 Sub-studies (^{177}Lu-Edotreotide patients only)

To obtain additional exploratory data, three sub-studies will be performed at selected sites with adequate technical capabilities. Patients will be informed about sub-studies during the informed consent process (see Section 13.2). Participation requires additional consent for each sub-study.

3.6.1 Sub-study A: Repetitive Full Dosimetry Imaging (D1 – D4)

The total absorbed doses (AD) to kidneys and tumour from four cycles of ^{177}Lu-edotreotide (D1 - D4) will be estimated, by linear extrapolation of the AD measured on D1 with 7.5 ± 0.7 GBq to the full dose of 30 GBq. Dosimetry will be measured, using serial planar and single time point SPECT imaging (see Section 8.2.2). To verify the accuracy of total AD estimations, based on a linear extrapolation of AD measured during D1, full dosimetric imaging will be repeated during subsequent cycles (D2 – D4) in a subgroup of approximately 20 patients, ready and able to undergo repetitive dosimetric imaging. For further details please refer to Clinical Imaging Manual.

3.6.2 Sub-study B: 3D Dosimetry SPECT/CT Imaging

Traditionally, dosimetry imaging has been performed using serial planar scintigraphic imaging only (2D), which is still considered the standard reference methodology by regulatory authorities. Clinically, though, the combination of serial planar with single time point SPECT imaging (2D/3D hybrid imaging) has emerged as new standard with improved spatial resolution. Especially in the abdomen, where the superposition of critical organs (e.g. kidneys, intestine, liver) renders the anatomic attribution of activity to individual organs difficult, 2D/3D dosimetry has been found to be superior to 2D dosimetry.

Full 3D dosimetry (3D), is based on serial SPECT/CT imaging only, which is quantitatively reconstructed yielding activity distributions of Bq/mL in the field of view (FOV). Serial planar imaging to capture the total adminstered and organ bound activities (% ID) is no longer required.

In selected sites, with SPECT/CT systems, where serial 3D imaging is clinically established, abdominal SPECT images (1-2 bed positions, covering liver, kidneys, tumour, as appropriate) will be acquired in a subgroup of approximately 20 patients, in addition to the compulsory planar images at 0.5, 6, 24, and 72 – 96 h p. i. of ^{177}Lu-edotreotide. SPECT imaging will be performed after planar imaging.

AD determined by 3D dosimetry, will be analysed in comparison to AD values obtained by planar (2D) and hybrid (2D/3D) dosimetry. For further details please refer to Clinical Imaging Manual.

3.6.3 Sub-study C: Pharmacokinetic Urine Analysis and Bone Marrow Dosimetry

Due to the prolonged imaging procedure, patients of Sub-studies A and B cannot be included in Sub-study C. Sub-study C will be performed during any one of the four ^{177}Lu-edotreotide treatment cycles (the choice of which of the four cycles to collect urine and blood samples for Sub-study C will be at the investigator's discretion).

To assess in vivo stability of ^{177}Lu-edotreotide, urine will be collected from all voids beginning immediately at 0 min post-dose into 4 pooled samples in intervals from 0 min post-dose to 1 hour, and 1-6, 6-24 and 24-48 hours post-injection in a subgroup of 20 patients at selected sites only (see Section 8.2.2.4).

Urine will be analysed with gamma-counting and with radio-HPLC in order to investigate the radiochemical purity of the eliminated compound.

As the radioactivity in blood was shown to be similar to that in bone marrow (Forrer et al., 2009), bone marrow dosimetry will be assessed by measuring radioactivity in blood samples at pre-defined intervals between 0 minutes and 7 days post-infusion of ^{177}Lu-edotreotide in a subgroup of 20 patients at selected sites only.

Blood samples of 1 mL, each will be drawn at a site on the lower arm below the amino acid infusion site, and opposite the arm receiving the infusion of ^{177}Lu-edotreotide at 0 min, 10 min, 30 min, 1 h, 3 h, 6 h, 24 h, 48 h, 3 d, and 7 d post-injection (see Table 4, and Section 8.2.2.5). Radioactivity in the blood samples will be measured using a well-type gamma-counter.

The sampling schedule is featured in the footnotes of the flowchart in Table 1, as well as in Table 4, below: (All time points post-injection (p.i.) refer to post the start of injection.)

Table 4: Sampling Schedule Sub-study C

	Sampling Schedule Sub-study C‡									
Time	Day 0*						Day 1	Day 2	Day 3	Day 7
Post-injection	0 min	10 min	30 min	1 h	3 h	6h	24±3h	48±3h	72±12h	168±12h
Urine	X†	→	→	X	→	X	X	X		
Blood	X	X	X	X	X	X	X	X	X	X

* Blood samples can be taken within ± 5 minutes of the scheduled time, as long as the exact sampling times are recorded in the CRF.
† Urine will be collected from all voids beginning immediately at 0 min post-dose into 4 pooled samples in intervals from 0 min post-dose to 1 hour, and 1-6, 6-24 and 24-48 hours post-injection.
‡ Sub-study C will be performed during any one of the four ^{177}Lu-edotreotide treatment cycles (the choice of which of the four cycles to collect urine and blood samples for Sub-study C will be at the investigator's discretion).

In order to facilitate the patient recruitment in the regulatory required Sub-study C, [redacted] at the sites participating in Sub-study C and only at those sites:

Following approval of this Study Protocol Amendment and activation of [redacted] by the Sponsor, the patients who consent to participate in Sub-study C and who comply with all

protocol inclusion and exclusion criteria will directly be allocated to the PRRT arm (See Section 3.1) until a global cumulative number of 20 evaluable patients is reached for the Sub-study C.

Aside from this [redacted] and the tests conducted for Sub-study C (see above), the treatment regimen and patient care management will remain identical to that implemented in the main study. However, [redacted]

After this [redacted] Sub-study C cohort is closed or if not activated or during the time this cohort is activated for the patients who consent to participate in the main study but not in the Sub-study C, the patients have the possibility to be randomised in the main study untill study termination provided they comply with all protocol inclusion and exclusion criteria.

The sites not participating in the Sub-study C continue to only enroll patients using the randomization procedure of the main study.

4 Study Population

4.1 Patient Population

It is planned to randomise 300 patients with histologically confirmed well-differentiated neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET), which have inoperable, progressive, and somatostatin receptor positive (SSTR+) disease, as evidenced by somatostatin receptor imaging (SRI). To uniformly and consistently characterise the study population according to current classification systems, a central pathologist will confirm histological diagnoses, based on historical or current tumour specimens.

To facilitate the patients recruitment in the Sub-study C, [redacted] at all sites participating in the Sub-study C until 20 evaluable patients are obtained globally. [redacted]

4.2 Eligibility

4.2.1 Inclusion Criteria

All patients must meet all of the following criteria:

1. Written informed consent
2. Male or female ≥18 years of age

3. Histologically confirmed diagnosis of well-differentiated neuroendocrine tumour of non-functional gastroenteric origin (GE-NET) or both functional or non-functional pancreatic origin (P-NET), grade G1 or G2 (Ki-67 ≤20%), unresectable or metastatic, in a patient who is either treatment-naïve (1st line) or who has progressed under prior therapy (2nd line)

4. Availability of existing biopsy specimen from primary tumour or metastasis or, if unavailable, willingness to undergo current biopsy for secondary central analysis

5. Measurable disease per RECIST 1.1, on CT/MRI scans, defined as at least 1 lesion with ≥1 cm in longest diameter, and ≥2 radiological tumour lesions in total. A maximum of 5 target lesions visible on CT/MRI will be defined, thereof not more than 2 lesions per organ (Eisenhauer et al., 2009)

6. Somatostatin receptor positive (SSTR+) disease, as evidenced by SSTR imaging (SRI) within 4 months prior to randomisation, as locally authorized, by:

   - ^{68}Ga-based SSTR PET imaging (^{68}Ga-edotreotide or ^{68}Ga-DOTATATE), or
   - ^{111}In-pentetreotide SSTR SPECT/planar imaging, or
   - ^{99m}Tc-octreotide SSTR SPECT/planar imaging
   - ^{64}Cu-based SSTR PET imaging (^{64}Cu-DOTATATE) if approved according to local regulations

   All target lesions and ≥90% of non-target lesions need to be positive for SSTR; this relates to lesions of at least 15 mm in diameter acquired on SRI images with SPECT, and of at least 10 mm in diameter acquired on SRI images with PET systems.

7. The patient must have progressive disease based on RECIST 1.1 Criteria as evidenced by two morphological imaging examinations made with the same imaging method (either CT or MRI), within a maximum of 36 months prior to randomisation. The most recent scan must not be older than 90 days prior to randomisation date. The minimum interval between the two scans must be ≥90 days.

8. Karnofsky performance status (KPS) scale ≥70 (see Appendix 3)

9. Life expectancy allows the patient to participate in the study based on the investigator's assessment

10. Glomerular filtration rate (GFR, CKD-EPI) ≥60mL/min/1.73 m^2 (see Section 8.3.9)

11. For patients included in France only, verification and confirmation of their affiliation with a social security

12. Patients with functional P-NETs who require SSA for symptom control may continue SSA treatment throughout the study, on condition that:

    a) they have been on a stable dose for at least three months prior to study enrollment

b) that progressive disease has been diagnosed while under such stable dose

4.2.2 Exclusion Criteria

A patient will be excluded from participation in the trial if one or more of the following criteria are met:

1. Known hypersensitivity to edotreotide or everolimus or any other Rapamycin derivative
2. Known hypersensitivity to DOTA, lutetium-177, or any excipient of edotreotide or everolimus
3. Known hypersensitivity to lysine, arginine, or any excipient of the nephroprotective amino acid solution
4. Prior exposure to any peptide receptor radionuclide therapy (PRRT), including ^{177}Lu-edotreotide, ^{90}Y-edotreotide or other SSTR-targeting agents (e.g. ^{177}Lu-octreotate or high-dose ^{111}In-pentetreotide)
5. Prior therapy with mTOR inhibitors
6. Prior EFR (external field radiation) to GEP-NET lesions within 90 days before randomisation or radioembolisation therapy (e.g. ^{90}Y microspheres, ^{131}I-lipiodol) with administration to the liver
7. Prior therapy with chemotherapy, immunotherapy, interferon, chemo-embolisation, bland embolisation, cyclosporine-A within 4 weeks before randomisation; any new cancer treatment between screening and randomisation
8. Therapy with an investigational compound and/or medical device within 30 days or 5 half-life periods (whichever is longer) prior to randomisation
9. Subjects who have received a live vaccine up to 4 weeks prior to first dose
10. Current therapy with any prohibited medication (see Section 6.1.1)
11. Ongoing toxicity grade 2 from previous standard or investigational therapies (NCI-Common Terminology Criteria for Adverse Events [CTCAE] version 4.03)
12. Indication for surgical lesion removal with curative potential
13. Planned (for the period of study participation): chemotherapy, immunotherapy, radiation therapy, chemo-embolisation, bland embolisation, radio-embolisation, treatment with cyclosporine-A
14. Neuroendocrine tumours, not meeting the inclusion criteria:
    - With known non-GEP-NET origin (e.g. pulmonary or gonadal primaries)
    - Functional GE-NET
    - Explicit diagnosis of unknown primary (CUP)

- G3 neuroendocrine tumours and neuroendocrine carcinomas
- NET for which no histological specimen for secondary histological analysis can be obtained

15. Total hepatic tumour burden >70%

16. Brain metastases

17. Other malignancy within previous 5 years (except basal cell carcinomas and in situ squamous cell carcinomas of the skin)

18. Serious non-malignant disease (e.g. psychiatric, infectious, autoimmune or metabolic), that may interfere with the objectives of the study or with the safety or compliance of the subject, as judged by the investigator

19. Clinically relevant renal, hepatic, cardiovascular, or haematological organ dysfunction, potentially interfering with the safety of the study treatments, as follows:

    - Renal
        - Renal obstruction
    - Hepatic
        - Total bilirubin >1.5 x ULN
        - AST or ALT >2.5 x ULN
        - Alkaline phosphatase >5 x ULN
        - Albumin <3 g/dL, unless prothrombin time is within normal range
    - Cardiovascular
        - New York Heart Association classification III and IV
        - Uncontrolled hypertension
    - Haematopoietic
        - Platelets ≤80 × 10^9/L
        - Absolute neutrophil count (ANC) <1 x 10^9 cells/L

20. Pregnant (see Section 8.3.6) or breast-feeding women. Female patients of childbearing potential or male patients with female partners of childbearing potential, unless willing to practice full and true sexual abstinence or who are surgically/permanently sterile (bilateral tubal occlusion, hysterectomy, or vasectomy), or female patients whose male partners have medically successful vasectomy (provided the partner is the sole sexual partner of the female patient of childbearing potential), or who are not willing to practice highly effective contraception in combination with a barrier method of contraception (e.g. condom). Contraception methods that are considered highly effective are: oral or non-oral (injected or implanted) non-oestrogen progesterone-based hormonal method; oral, intravaginal, or

transdermal combined oestrogen and progesterone-based hormonal method; and/or intrauterine device (IUD), and/or intrauterine hormone-releasing system (IUS). Sexual abstinence or the contraception methods described above must be followed throughout the entire study period and for 56 days after treatment in the everolimus group and, 66 days in the PRRT group (10 half-lives of ^{177}Lu) after the last treatment cycle (see Section 8.3.1.1).

21. Subjects not able to declare meaningful informed consent on their own (e.g. with legal guardian for mental disorders) or any other vulnerable population to that sense (e.g. persons institutionalised, incarcerated etc.)

4.3 Recruitment

Potential patients for this study will be recruited by approximately 60 oncological centres in Europe, North America, South Africa and Australia specialised in endocrine oncology (endocrinology, gastroenterology, nuclear medicine), and with local access to or own experience in PRRT. Study sites will be interdisciplinary, consisting of an endocrine oncology sub-site, and a nuclear medicine sub-site. Study visits will be typically conducted at the recruiting sub-site, or as institutionally appropriate. Treatment visits for patients randomised to ^{177}Lu-edotreotide will be performed in the collaborating nuclear medicine sub-site. Patients will be invited for study participation by the investigators in the context of specialised NET clinics. Interested patients will be provided with an information sheet and will undergo a detailed informed consent procedure prior to any study procedures (see Section 13.2). Recruitment will be continued until a sufficient number of patients has received at least one dose of PRRT treatment, or a sufficient number of events has been reached.

4.4 Withdrawal of Patients from Study Participation or Medication

4.4.1 Withdrawal

Patients may decide to withdraw from the study at any time for any reason without prejudice to their further medical care. The investigator may withdraw a patient for any of the following reasons:

- Adverse event: if patient is unwilling to continue because of an AE or if continued participation of the patient would be an unnecessary risk to the patient's health, in the opinion of the investigator.
- Non-compliance
- Protocol deviation
- Pregnancy
- Lost to follow-up

A female patient who becomes pregnant during the treatment phase of the study must be discontinued from study treatment. See Section 8.3.1.1 for follow-up procedures in the case of pregnancy.

4.4.2 Withdrawal Procedures

Although patients are not obliged to give their reason(s) for withdrawing prematurely from a trial, the investigator should make every effort to ascertain the reason(s) for withdrawal while fully respecting the patient's rights. The investigator will make every effort to contact the patient and complete the EOS page on the case report form (CRF) and if possible the assessments outlined on EOS visit.

An EOS CRF page is to be completed for every patient, whether or not the patient completed the study. The reason for any early discontinuation should be indicated on this form. The primary reason for a patient withdrawing prematurely should be selected from the following standard categories of early termination:

- *Safety Reason/Adverse Event:* Clinical or laboratory events occurred that in the medical judgment of the investigator, for the best interest of the patient, are grounds for discontinuation. This includes serious and non-serious AEs regardless of relation to study medication. Criteria for dose-limiting toxicity are discussed in Section 5.4.3 and Table 9.

- *Protocol Violation:* The patient's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., drug non-compliance, failure to return for defined number of visits) as judged by the investigator or sponsor. The violation necessitated premature termination from the study.

- *Withdrawal of Consent:* The patient desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the patient gave a reason for withdrawing, it should be recorded.

- *Lost to Follow-Up:* The patient stopped coming for visits, and study personnel were unable to contact the patient (two unsuccessful phone contacts followed by registered letter and documentation in the source documents).

The date of study drug administration must be documented.

Appropriate follow-up of withdrawn patients will be performed, as required.

Attempts to contact a patient who withdraws from the study or is lost to follow-up must be documented.

Stopping rules for the entire study are described in Section 11.

4.4.3 Replacement

Patients who drop out of the study before first treatment administration will be replaced. Additional enrolment will be performed for patients who have received study medication, but who do not have analysable efficacy data. As this is an open study, no specific replacement scheme is needed.

4.5 Patient Identification

All patients who give informed consent will be identified by a unique identification number ("patient number") that consists of 5 digits in two parts:

1. The site number is a 3-digit number that is provided by the sponsor prior to the start of recruitment.

2. The screening number is a 2-digit number that is consecutively assigned by the site to each patient after informed consent.
   Example: The first patient screened by site "101" will receive patient number 101-01.
   Example: The third patient at site "112" will receive patient number 112-03.

Investigational sites are required to keep a patient identification list, identifying their patients by name, date of birth, patient number and status (screen failure/completed study/withdrawn). This list will be reviewed by assigned monitors, but has to stay on site and will not be collected, in order to protect confidentiality.

4.6 End of the Study

For regulatory purposes, the end of the study is defined as the last visit of the last patient or the last date of follow-up of toxicities, if required (whichever is later).

The end of study for each individual patient is the visit at month 30, unless disease progression, withdrawal from the study, or death occurs earlier.

4.7 Study Duration

After providing informed consent, subjects will be screened for study enrolment, for up to 90 days prior to the first study treatment. Once enrolled and randomised to treatment, subjects will stay in the study until disease progression is established per RECIST 1.1 criteria, an alternative treatment for GEP-NET is initiated, the subject is withdrawn from the study, or for 30 months, whichever occurs first.

A subject randomised to everolimus (Afinitor®) who has disease progression must end study participation but may be offered ^{177}Lu-edotreotide therapy based on the personal judgement of the Investigator, if he/she considers it appropriate and likely to be beneficial for the individual patient (see Section 7.4.2).

The maximum duration of participation for individual subjects is 30 months. The observation time for overall survival will be 5 years (60 months) after EOS for all patients (see Section 7.4).

5 Study Drug

5.1 Identity

5.1.1 Chemical Properties of ^{177}Lu-Edotreotide

The PRRT agent to be evaluated in the present study is ^{177}Lu-edotreotide. Its chemical name is lutetium-177-Nα-[(4, 7, 10- triscarboxymethyl- 1, 4, 7, 10-tetraazacyclododec-1-yl)acetyl]-D-phenylalanyl-L-hemicystyl-L-tyrosyl-D-tryptophyl- L-Lysyl- L-threonyl- L-hemicystyl- L-threoninol cyclic (2→7) disulphide. Synonyms are:

- ^{177}Lu-DOTATOC, (DOTA(0)-Phe(1)-Tyr(3)) octreotide, and
- ^{177}Lu-DOTA-Tyr^3-octreotide.

^{177}Lu-edotreotide is radiolabelled with carrier-free lutetium-177 (^{177}Lu), a synthetic, low-energy beta and gamma emitting isotope of lutetium, the last element in the lanthanide series of metallic elements. Carrier-free ^{177}Lu is generated by neutron irradiation of the isotope ytterbium-176 (^{176}Yb) and subsequent fractionation of ^{177}Lu and ^{176}Yb with cation chromatography. Key physical characteristics of ^{177}Lu are summarised in Table 5.

Table 5: Radiological Properties of Lutetium-177

Physical half-life T½	Decay product	Main β^- emission	Maximum range (β^-)	Main γ emission
6.647 d	^{177}Hf	498 keV	1.7 mm	208 keV 113 keV

The structural formula of ^{177}Lu-edotreotide is shown in Figure 2.

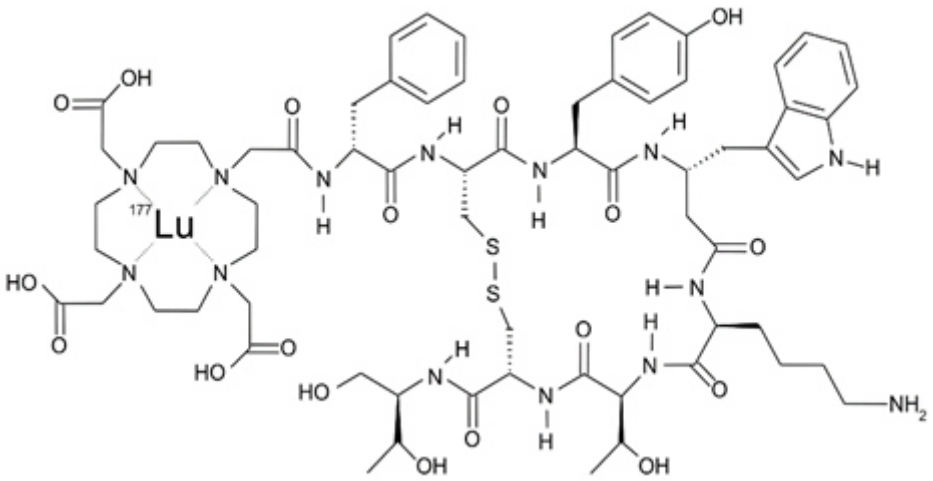

Figure 2: Structural formula of ^{177}Lu-edotreotide

The chemical formula of ^{177}Lu-edotreotide is $Lu_1C_{65}H_{89}N_{14}O_{18}S_2$. The molar weight is 1595.6 g/mol for ^{177}Lu-edotreotide and 1421.6 g/mol for edotreotide alone.

5.1.2 Chemical Properties of Everolimus

As reference product (RP), the mTOR inhibitor everolimus (Afinitor®) will be used. The chemical name of everolimus is:

(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentone.

Everolimus is a macrocyclic lactone. Its structural formula is shown in Figure 3.

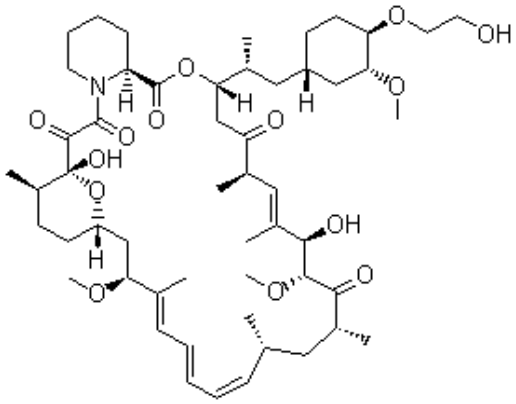

Figure 3: Structural formula of everolimus (www.chemblink.com)

The molecular formula is $C_{53}H_{83}NO_{14}$ and the molar weight is 958.2 g/mol.

5.1.3 Pharmaceutical Properties of ^{177}Lu-Edotreotide

^{177}Lu-edotreotide is administered intravenously.

A description of ^{177}Lu-edotreotide solution for infusion is shown in Table 6.

Table 6: ^{177}Lu-Edotreotide Solution

Pharmaceutically active component	^{177}Lu-edotreotide
Physical dose	7.5 ± 0.7 GBq / cycle
Substance dose	150 µg edotreotide
Primary unit dose container	20 mL glass vial containing 16 – 20 mL of stabilised aqueous solution
Appearance	[redacted]
pH	[redacted]
Bacterial Endotoxin	[redacted] EU/Dose
Radionuclidic purity	^{177}Lu [redacted] %
Sterility	Sterile

The labelled drug product is produced, tested and released under GMP conditions by a licensed radiopharmaceutical contract manufacturer as a sterile solution for injection/infusion, ready for use. The labelled drug product will be manufactured upon individual order and delivered directly to the study sites globally.

5.1.4 Pharmaceutical Properties of Everolimus (Afinitor®)

Everolimus has been licensed for the treatment of several types of cancer including progressive neuroendocrine tumours of pancreatic origin (P-NET) and non-functional gastroenteric origin (GE-NET) with unresectable, locally advanced or metastatic disease.

Afinitor® tablets are supplied for oral administration and contain 10 mg of everolimus. For patients not tolerating the regular dose of 10 mg, tablets containing 5 mg will also be available, to be administered according to the manufacturer´s instructions for dose reduction. The tablets also contain anhydrous lactose, butylated hydroxytoluene, crospovidone, hypromellose, lactose monohydrate, and magnesium stearate as inactive ingredients. The tablets are white to slightly yellow, elongated with a bevelled edge and no score, and engraved with “UHE” on one side and “NVR” on the other.

Everolimus will be purchased from licensed commercial sources, and labelled by the central pharmacy, according to the requirements of the participating countries. Details will be described in the separate document Investigational Medicinal Product (IMP)-Management Plan.

5.1.5 Storage and Handling

See Section 5.6.

5.2 Treatment Assignment and Randomisation

All successfully screened patients will be randomised in a 2:1 fashion, to receive:

a) ^{177}Lu-edotreotide (at most four ^{177}Lu-edotreotide doses, administered 3-monthly) or

b) Everolimus (Afinitor®, administered daily).

Randomisation will follow a confidential, pre-defined scheme under direct control of the Study Data Management. Details of treatment assignment procedure, from the initial request down to the delivery of the requested IMP will be described in the IMP-Management Plan.

Stratified randomisation, using four randomisation lists, will be used to ensure in both study arms a balanced frequency of GE-NET patients vs. P-NET patients and a balanced frequency of patients naive to medical treatment (1st line patients) vs. patients who have received prior medical therapies (2nd line patients). Prior therapies may include chemotherapy, SSA, targeted therapy (e.g. sunitinib), and others; the types of prior therapies will have to be recorded in the CRF (see also Section 9.2.3.2). Furthermore, inclusion of an equal number of GE-NET and P-NET will be attempted, but any ratio will also be acceptable as long as it allows meaningful subgroup analysis.

Randomisation should be performed as soon as all necessary information for patient eligibility from screening assessments is available. Start of treatment should commence as soon as possible after randomisation, e.g. on the day of randomisation (everolimus group). In the ^{177}Lu-edotreotide group, the study drug needs to be ordered on the day of randomisation. The first dose of ^{177}Lu-edotreotide should be administered within 21 days of randomisation. In case of any delay, the site should check with the Sponsor via the site monitor and the reason for delay should be documented accordingly.

5.3 Blinding

Not applicable, since this is an open label study.

For blinded Image Data Analysis please refer to Section 8.7.

5.4 Dosage and Administration

5.4.1 ^{177}Lu-edotreotide Group

Patients assigned to ^{177}Lu-edotreotide treatment will undergo at most four cycles of 7.5 ± 0.7 GBq ^{177}Lu-edotreotide, each containing a mass dose of 150 µg edotreotide. The cumulative ^{177}Lu-edotreotide dose will be up to 30 GBq with treatment cycles every 3 months.

^{177}Lu-edotreotide will be administered as a slow intravenous infusion over 10 – 20 min, via a flexible cannula into the cubital vein of the non-dominant arm (i.e. left arm in right-handers and vice versa). Concomitantly to the administration of ^{177}Lu-edotreotide patients will receive a nephroprotective amino acid solution (starting 30 – 60 min before IMP, and lasting 4 - 6 h) as described in Section 6.1.3.

In most regulatory environments, ^{177}Lu-edotreotide administration requires a short-term hospitalisation in a radionuclide therapy ward for radiation protection reasons, in order to minimise irradiation of others, and in order to collect radioactive excretions. During cycle 1 (D1), patients will undergo planar scintigraphy and SPECT/CT imaging (see Section 8.2.2), to determine the absorbed dose (AD) to kidneys and tumour from ^{177}Lu-edotreotide from this first cycle (D1). AD to kidneys will be determined centrally by image core laboratory (ICL), to ensure methodological uniformity across all sites. Dosimetry prescription information will be returned to the sites by the central ICL in a timely manner, sufficiently in advance before the subsequent cycle.

Patients randomised to the ^{177}Lu-edotreotide group experiencing progressive disease under treatment must stop study participation.

5.4.1.1 Absorbed Dose from ^{177}Lu-Edotreotide PRRT to the Kidneys

Traditionally, an absorbed dose (AD) to the kidneys, not exceeding 23 Gy has been recommended to effectively avoid radiation-induced toxicity to the kidneys (IAEA PRRNT guideline 2013). Current dosimetric studies and clinical observations demonstrate, however, that an AD of 23 Gy does not correlate with kidney toxicity in PRRT, and that radiation tolerance of the kidneys for PRRT is actually higher than 23 Gy (Barone et al., 2005; Strosberg et al., 2017). Absorbed doses to kidneys have been described to vary considerably between patients, while at the same time variation of AD does not predictably correlate with body weight (Barone et al., 2005; Schuchardt et al., 2013, Strosberg et al., 2017) (see Section 3.4).

For safety reasons, therefore, AD to kidneys will be measured in all PRRT patients after their 1st PRRT cycle in this study. The absorbed dose to the kidneys (in Gy/GBq) is calculated based on AD to kidneys from ^{177}Lu-edotreotide activity (in GBq) administered during the first cycle. From this, the cumulative AD to kidneys (in Gy) can be estimated for the cumulative activity dose (GBq) administered during the study, individually for each patient. If it can be anticipated that according to the individual AD per GBq of ^{177}Lu-edotreotide, the traditional limit of a total of 23 Gy would be exceeded in a subsequent treatment cycle, no further treatment cycle will be administered, unless a) clinically relevant tubular renal dysfunction (see below) can be excluded, and b) the investigator considers it in the best interest of the patient to undergo a next cycle.

A PRRT cycle leading to transgression of an AD to kidneys of >23 Gy may only be administered on condition that a) the TER (^{99m}Tc-MAG3 renal scintigraphy) determined before this cycle, is >50% of the value at baseline (a value not associated with GFR changes), and b) and that the resulting AD to kidney will not exceed a maximum of 29 Gy (Konijnenberg et al., 2007; Bodei et al., 2013; Barone et al., 2005; Strosberg et al., 2017).

5.4.1.2 Eligibility for Continued Administration of ^{177}Lu-edotreotide after Cycle 1

Prior to receiving further ^{177}Lu-edotreotide administration, subsequent to cycle 1, the following general eligibility criteria should be met for safety reasons in all patients in the PRRT arm, the latest by day 90 (±14) calculated from the date of the first ^{177}Lu-edotreotide cycle, to be determined during the pre-treatment evaluations, in the investigator's opinion:

- Hb concentration ≥5.0 mmol/L (≥8.0 g/dL); WBC ≥2 x 10^9/L (2000/mm^3); platelets ≥75 x 10^9/L (75 x 10^3/mm^3).
- Total bilirubin ≤3 x ULN.
- Serum albumin >3.0 g/dL, or serum albumin ≤3.0 g/dL, but normal prothrombin time.
- KPS ≥60.
- Serum creatinine ≤150 µmol/L (≤1.7 mg/dL) and eGFR (estimated GFR) ≥50 mL/min/1.73 m². In all cases, where the eGFR is ≥ 50 mL/min/1.73m² and ≤60 mL/min/1.73m², the eGFR needs to be confirmed by a non-radioactive plasma clearance method (e.g. collection of 24 h urine for creatinine clearance determination), prior to administration of the subsequent ^{177}Lu-edotreotide cycle. In cases where eGFR is >60 mL/min/1.73m², no confirmation by a non-radioactive plasma clearance method is required. GFR will be calculated using the recommended CKD-EPI formula* (Levey et al., 2009).

  *GFR = 141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if female] × 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

5.4.2 Everolimus Group

Patients assigned to RP receive a standard dose of 10 mg everolimus (Afinitor®) per os once daily at the same time every day. Reduction of dose is permitted according to the recommendations of the manufacturer (see Appendix 4). Everolimus needs to be administered either consistently with food or consistently without food and should be swallowed in whole with a glass of water.

Patients randomised to everolimus experiencing progressive disease under treatment must stop study participation but may be offered ^{177}Lu-edotreotide therapy based on the personal judgement of the Investigator, if he/she considers it appropriate and likely to be beneficial for the individual patient (see Section 7.4.2). The administration of this individual treatment requires the patient's consent. Administration, assessments and follow-up should be according to the schedule described for the ^{177}Lu-edotreotide arm of the study.

5.4.3 Dose-Modifying Toxicity

As different types of toxicities are likely to occur under Everolimus and ^{177}Lu-edotreotide PRRT, specific dose-modifying toxicity criteria are to be used for each of the study treatments. In general, the evaluation of patients for potential dose modifying toxicities (DMT) is defined according to NCI CTCAE v 4.03.

5.4.3.1 DMT under Everolimus

Dose reductions in the everolimus group are to be done according to manufacturer's recommendations (see Appendix 4).

5.4.3.2 DMT during ^{177}Lu-Edotreotide PRRT

Dose modifying toxicity (DMT) during ^{177}Lu-edotreotide treatment is defined as any of the following conditions which are ongoing on day 90 following the preceding PRRT cycle (i.e. at the time of the next scheduled PRRT cycle, as established during the respective pre-treatment evaluations):

- Grade 2 CTCAE or above toxicity for platelet count
- Grade 4 CTCAE lymphopenia
- Grade 3 CTCAE or above toxicity for any other haematological parameter
- 40% increase over baseline in serum creatinine
- decrease of over 40% in creatinine clearance from baseline
- any other Grade 4 CTCAE toxicity considered at least possibly related to study drug, regardless of duration, with the exception of liver enzymes (ASAT, ALAT, AP), which will not be used to define DMT.

Patients experiencing DMT from ^{177}Lu-edotreotide treatment may receive subsequent PRRT cycles, provided that toxicity has subsided below the values defined above by week 16 following the non-tolerated PRRT administration.

With regard to renal DMT, further PRRT cycles may only be administered, if the following additional conditions are met by week 16:

- Serum creatinine level must be classified CTCAE Grade 0,
- Calculated creatinine clearance must have improved to within 20% from baseline (i.e. at least 80% of initial value)
- The GFR is at least ≥ 50 ml/min/1.73 m². A GFR value below 50 ml/min/1.73 m² will preclude further administration of ^{177}Lu-edotreotide.

In patients with renal DMT, the eGFR (estimated GFR), needs to be confirmed by a non-radioactive plasma clearance method (e.g. 24 h creatine collection in urine), prior to administration of further administration of ^{177}Lu-edotreotide, in all cases, where the eGFR is ≥50 ml/min/1.73m² and ≤60 mL/min/1.73m² at 16 weeks. In cases where eGFR is >60 mL/min/1.73m² at 16 weeks, no confirmation by a non-radioactive plasma clearance method is required.

As only standard ^{177}Lu-edotreotide doses of 7.5 GBq ± 0.7 GBq are used in this study, dose modification will not be achieved by reducing the next planned dose, but by delaying the next treatment cycle up to a maximum of 4 weeks (week 16 (+ 2). In such a situation, subsequent PRRT cycles and evaluations (except for evaluation of tumour response based on morphological imaging RECIST 1.1) will be performed in intervals of 90 (±14) days, calculated from the delayed PRRT cycle. In case toxicity has not recovered by week 16, a patient cannot receive further PRRT cycles, but will remain in the study.

Following the second occurrence of DMT, the patient is excluded from further treatment, but will remain in the study.

5.5 Packaging and Labelling

^{177}Lu-edotreotide will be supplied in vials for injection in appropriate packaging.

Everolimus will be delivered as commercially available blisters which will be specially labelled for the use in this clinical trial.

The outer packaging of all study drugs will contain label(s) which will include the following minimum information:

- Name and address of sponsor
- Study number
- Investigator identification
- Name of study drug and formulation
- Dosage strength
- Batch number
- Patient number
- Expiry date (or retest date)
- Storage instructions
- “For Clinical Trial Use only”.

A system of medication numbering in accordance with all requirements of Good Manufacturing Practice (GMP) and any other applicable regulatory requirement will be used for all study drugs. This will ensure that for each patient, any dose of study drug can be identified and traced back to the

original bulk ware of the active ingredients. Lists linking all numbering levels will be maintained by the institutions in charge of study drug packaging.

5.5.1 ^{177}Lu-edotreotide

^{177}Lu-edotreotide will be delivered in 20 mL injection vials, labelled according to pharmaceutical requirements, governing investigational medicines, as described above. In addition, the vial will bear a radioactive warning symbol. The vial will be shipped in a lead-shielded transport container, bearing a radioactive warning symbol in accordance with radioactive pharmaceutical requirements. The labelled lead shield is packaged with absorbent material to minimise radioactive spill in case of vial damage within special packaging designed to conform to all applicable agreements concerning International Air Transport Association (IATA) and International Carriage of Dangerous Goods by Road (ADR) regulations and requirements for shipment of radioactive materials.

5.5.2 Everolimus (Afinitor®)

Commercial drug product will be purchased from the manufacturer (Novartis Pharma Stein AG; Stein, Switzerland) or a licensed pharmaceutical wholesaler, able to provide lot documentation and will be labelled according to the requirements as described above.

Tablets will be available with the following strengths: 10 mg and 5 mg.

5.6 Drug Logistics and Accountability

5.6.1 Storage, Dispensation and Return of ^{177}Lu-Edotreotide

^{177}Lu-edotreotide will be shipped at ambient temperature, should be stored without freezing, and should be used by the expiration date and time printed on the label. ^{177}Lu-edotreotide contains radioactive material and should only be handled by personnel trained in the use of radioactive isotopes with proper shielding and monitoring. Receipt and use of ^{177}Lu-edotreotide is limited to institutions holding an appropriate handling permit by their competent national or regional authority.

Storage, handling and destruction must be performed according to local guidelines regarding radioactive waste management. Details are outlined in the IMP management plan.

5.6.2 Storage, Dispensation and Return of Everolimus

Everolimus (Afinitor®) is shipped at and should be stored not above 25°C, and should be used by the expiration date printed on the label. Everolimus for study purposes should be stored in a locked cabinet (separate from other medication for clinical use). As an exception only during the COVID-19 pandemic, sites are allowed to ship everolimus directly to the patients.

Unless the site has a specific Standard Operating Procedure (SOP) for reconciliation of unused or remaining everolimus, in the absence of sites' SOP for reconciliation, unused or remaining everolimus

will be kept at the site until reconciliation and approval of the site CRA to return it to the CRO. Details are outlined in the IMP management plan.

5.6.3 Drug Accountability

The investigator (or pharmacist, whatever applicable in certain countries) will confirm receipt of the study drug in writing and will use the study drug only within the framework of this clinical study and in accordance with this study protocol. He/she will keep a record of the study drug dispensed.

Receipt, distribution and return of the study drug must be properly documented on the forms provided by the sponsor giving at least the following information: study protocol number, sender, receiver, date, mode of transport, quantity, batch number, expiration date and retest date, if applicable.

5.7 Treatment Compliance

A record of the number of ^{177}Lu-edotreotide doses and everolimus tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Details of each study drug administration will be recorded in appropriate source documents and then reported in the CRF.

- ^{177}Lu-edotreotide:

  ^{177}Lu-edotreotide will be administered by study personnel at the trial site only. In any case of interruption of ^{177}Lu-edotreotide infusion, the infused and discarded amounts will be recorded. ^{177}Lu-edotreotide is to be ordered on the day of randomisation. The first dose of ^{177}Lu-edotreotide should be administered within 21 days of randomisation. In case of any delay, the site should check with the Sponsor via the site monitor and the reason for delay should be documented accordingly.

- Everolimus:

  Subjects will be asked to maintain a dosing diary to record their daily administration of everolimus. At each visit, the subject should return the dosing diary. An evaluation of subject compliance with study treatments taken will be performed. The investigator will make every effort to bring non-compliant subjects into compliance. Compliance with dosing will be assessed through querying the subject during site visits and will be documented in the source documents and in the CRF, including treatment start and stop dates, dates for treatment delays and/or dose reductions.

The following deviations are defined as major protocol deviations, leading to exclusion from the PP set (see Section 9.3.3):

- ^{177}Lu-edotreotide arm:
  - Subjects with incomplete ^{177}Lu-edotreotide infusion, in which less than 50% of the total pre-scribed activity (GBq) based on initially dosimetry assessment was injected.
  - Subjects in whom a dose was administered more than 30 days outside the per protocol date.

- Everolimus arm:
    - Subjects missing more than 14 doses, within a visit interval of 30 days (with exception of treatment interruptions due to toxicity, see Section 5.4.3.1).

Regardless whether a patient is compliant or non-compliant, the investigator must make every effort to perform all investigations according to the protocol for the entire duration of study participation.

5.8 Treatment of Overdose

- ^{177}Lu-edotreotide:

  ^{177}Lu-edotreotide has a very favourable safety profile (see Section 1.3).

  The risk of overdosing is minimal in this trial, as individual doses will be prepared centrally by a radiopharmaceutical contract manufacturer. Nevertheless, if accidental overdosing of radio-labelled product should occur, it will result in increased radioactive tissue exposure, with kidney and bone marrow as the critical organs.

  In the event of an overdose of ^{177}Lu-edotreotide, no specific treatments are available, and the patient should be treated at the discretion of the investigator.

- Everolimus:

  Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been given with acceptable acute tolerability (EU: SmPC, Afinitor®, current version). General supportive measures should be initiated in all cases of overdose.

6 Therapies other than Study Drug

6.1 Prior and Concomitant Therapy

Prior medications (up to 4 weeks prior to the screening visit) and all medications taken from baseline until EOS (including herbal products) must be recorded in the patient's file. The indication for each drug, generic name, dosage form, strength, dose, frequency of dosing, route of administration, start date and, if applicable, stop date should also be recorded in the CRF. All medications will be encoded according to WHO-DD classification.

6.1.1 Prohibited Medications

Patients will not be permitted to enter the study if they have received any of the following therapies:

- Prior exposure to any PRRT, including ^{177}Lu-edotreotide, ^{90}Y-edotreotide or other SSTR-targeting agents (e.g. ^{177}Lu-octreotate or high-dose ^{111}In-pentetreotide)
- Prior mTOR inhibitor therapy

- Prior EFR (external field radiation) to GEP-NET lesions or radioembolisation therapy (e.g. ^{90}Y microsphere, ^{131}I-lipiodol) administration to the liver
- Prior therapy with an investigational compound and/or medical device within 30 days or 5 half-life periods (whichever is longer) prior to randomisation.
- Any new cancer treatment between screening and randomisation

The following therapies are prohibited from 4 weeks before randomisation until the end of the study: chemotherapy, immunotherapy, interferon, radiation therapy, chemo-embolisation, bland embolisation, radioembolisation, cyclosporine-A, or any other cancer therapy. In the event that any prohibited medication is given to a patient during the study, any such medication needs to be recorded in the CRF. The patient will then be excluded from further participation.

Subjects in the everolimus group must not receive live vaccines during the study and for eight weeks after final dose. Potent inhibitors of CYP3A4 and PgP, and potent inducers of CYP3A4 are also prohibited for everolimus patients (see Section 6.1.5.2).

6.1.2 Somatostatin Analogues

Somatostatin analogues are currently standard therapies for NETs. Somatuline® (Lanreotide) and Sandostatin® LAR (octreotide) are both licensed for the treatment of specific types of GEP-NETs. To prevent evaluation bias and simultaneously allow adequate symptomatic treatment for functional tumours, the following rules apply:

- Patients with non-functional NETs who have experienced progressive disease under SSA treatment for their tumours (i.e. inefficacy of SSA to control tumour growth) will have to discontinue their SSA therapy prior to randomisation.
- Patients with functional P-NETs who require SSA for symptom control may continue SSA treatment throughout the study, on condition that:
  a) they have been on a stable dose for at least three months prior to study enrolment
  b) that progressive disease has been diagnosed while under such stable dose, and
  c) they will remain on a stable dose during study participation.

  The doses for symptomatic treatment must not exceed 30 mg Octreotide/Sandostatin LAR every 4 weeks, or 120 mg Lanreotide/Somatuline every 4 weeks, respectively (maximum doses according to label). The morphological MRI/CT scan demonstrating progression during screening will be obtained after establishment of a stable dose of SSAs in functional P-NET patients, and preferably before the next dose of long-acting SSA is due (trough).
- Patients with primarily functional GE-NETs are excluded from the study. However, if a patient with a primarily non-functional tumour develops a hormone-release (e.g. carcinoid) syndrome in the course of the study, he/she may receive SSA for symptom control using a stable dose to be maintained throughout study participation, not exceeding Octreotide/Sandostatin LAR every 4 weeks, or 120 mg Lanreotide/Somatuline every 4 weeks, respectively (maximum doses according to label).

- Patients on stable doses of SSA who develop exacerbation of symptoms due to clinical fluctuation of a hormone-release (e.g. carcinoid) syndrome during the study, may receive SSA rescue medication, as clinically appropriate, at the discretion of the investigator. Rescue medication type, dosing, duration, and clinical symptomatology will be recorded in detail. Such patients will remain in the study and receive further study treatments as scheduled. Subcutaneous, short-acting Somatostatin Analogue injections may be used as rescue medication, in accordance with the manufacturer's prescribing information.

Concomitant SSA use will be recorded throughout the study. Data of all patients receiving any SSA while on study will be statistically analysed for a possible impact on the primary endpoint (sensitivity analysis).

6.1.3 Scheduled Nephroprotective Amino-Acid Solution for Patient Management

Nephroprotective AAS aims to reduce the risk of acute and chronic radiation nephropathy, by inhibiting undesired renal ^{177}Lu-edotreotide uptake, thereby allowing administration of higher therapeutic doses to the tumour. Efficient nephroprotection, therefore, does increase the therapeutic index of PRRT. To ensure comparable safety and efficacy of a given therapeutic dose across sites in the present study, a standardised nephroprotection protocol will be used, which is based on the concomitant administration of an amino acid solution (AAS) according to the recommendations of different international Societies of Nuclear Medicine for the management of PRRT in NET (Bodei et al., 2013).

No commercially available amino acid solution, optimised for nephroprotection in PRRT exists. Available products vary considerably in their composition in different countries. For the study, therefore, a standardised amino acid solution optimised for PRRT will be used.

The AAS to be used in this study will contain a mixture of 25 g lysine-HCl and 25 g arginine-HCl diluted in 2000 mL of electrolyte solution, infused over 4 - 6 h, starting 30 – 60 min before PRRT. The AAS should preferably be co-infused with the radiopeptide via a three-way stop cock.

Amino acid infusion causes elevation of serum potassium levels due to induction of a shift of potassium ions from cells to the extracellular department. This shift can lead to significant hyperkalaemia in up to 19% of patients (Giovacchini et al., 2011). In this trial potassium levels are monitored at pre-dose, 4 - 6 h, and 24 h post ^{177}Lu-edotreotide infusion. If hyperkalaemia >6.0 mmol/l occurs, additional monitoring and/or therapeutic measures should be undertaken. Severe hyperkalaemia can lead to cardiac arrhythmias and subsequently circulatory arrest. Non-specific clinical signs include malaise, palpitations, muscle weakness and mild hyperventilation. Treatment options are e.g. IV calcium, IV loop diuretics (e.g. furosemide), inhaled salbutamol, and oral sodium polystyrene sulfonate/sorbitol.

Please note that the AAS should not be co-administered with plasma expanders, e.g. gelofusine or HES.

6.1.4 Antiemetic therapy

Amino acid infusion is frequently associated with nausea and vomiting (see Section 8.3.2.4). For this reason, administration of a standard antiemetic regimen prior to amino acid infusion is recommended according to current international guidelines (Bodei et al., 2013) If an antiemetic is given on the day of dosing, it should be recorded in the patient's records and transcribed onto the CRF form.

6.1.5 Medication Precautions

6.1.5.1 ^{177}Lu-edotreotide

PRRT may potentially induce hormonal dysregulation or interact with other medications, by virtue of its pharmacological effects on GEP-NET cells, especially in the following situations (see Section 8.3.2.4):

- Diabetes mellitus: Blood glucose levels should be monitored and anti-diabetic treatment adjusted accordingly, where needed.
- Gastritis
- Diarrhoea
- Gastroesophageal reflux
- Pain
- Nausea

Medical administration of radioactive therapies such as ^{177}Lu-edotreotide is guided by national radiation safety regulations, differing extensively between countries. Excretion limits acceptable for discharge will be defined by the investigators in compliance with the local regulations. The requirement of hospitalisation will be approximately for 3 days in most countries, but can be adapted at the discretion of the investigator, as appropriate.

The following safety precautions for patients apply during and after ^{177}Lu-edotreotide administration:

- Good hydration is recommended if not otherwise contraindicated.
- Subjects should be advised to observe rigorous hygiene in order to avoid risk of contamination of others using the same toilet facility.
- A double toilet flush is recommended.
- Subjects should wash their hands thoroughly every time after using the toilet.

It must be noted that if the predicted absorbed dose to the kidneys is likely to exceed 23 Gy upon administration of the next PRRT cycle, dosing can be continued up to a maximum of 29 Gy, provided that a pre-PRRT TER (^{99m}Tc-MAG3 renal scintigraphy) is >50% of the value at baseline (see Section 5.4.1.1 and 5.4.3.2) and the criteria for continued administration of study drug are fulfilled (see Section 5.4.1.2).

Patients should be carefully monitored for side effects. Pre-existing co-morbidities (e.g. pre-existing nephropathy and diabetes mellitus) must be assessed and appropriate monitoring and prophylactic measures are to be applied according to local standard of care.

Tumour lysis syndrome (TLS) was previously reported in patients receiving ^{177}Lu PRRT. Patients should be monitored for the development of TLS or cytokine release syndrome (CRS). In case of suspected TLS or CRS development, ^{177}Lu-edotreotide treatment must be discontinued and symptomatic treatment is to be given immediately according to local standard of care.

If hypersensitivity or anaphylactic reaction occurs, treatment with ^{177}Lu-edotreotide must be discontinued and appropriate treatment is to be given according to local standard of care.

6.1.5.2 Everolimus

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of PgP. Therefore, absorption and subsequent elimination of everolimus may be influenced by products that affect CYP3A4 and/or PgP. In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

For detailed information on known and theoretical interactions with selected inhibitors and inducers of CYP3A4 and PgP, see SmPC of everolimus.

CYP3A4 and PgP inhibitors increasing everolimus concentrations
Substances that are inhibitors of CYP3A4 or PgP may increase everolimus blood concentrations by decreasing metabolism or the efflux of everolimus from intestinal cells.

CYP3A4 and PgP inducers decreasing everolimus concentrations
Substances that are inducers of CYP3A4 or PgP may decrease everolimus blood concentrations by increasing metabolism or the efflux of everolimus from intestinal cells.

Agents whose plasma concentration may be altered by everolimus
Based on *in vitro* results, the systemic concentrations obtained after oral daily doses of 10 mg make inhibition of PgP, CYP3A4 and CYP2D6 unlikely. However, inhibition of CYP3A4 and PgP in the gut cannot be excluded. An interaction study in healthy subjects demonstrated that co-administration of an oral dose of midazolam, a sensitive CYP3A substrate probe, with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam AUC (0-inf). The effect is likely to be due to inhibition of intestinal CYP3A4 by everolimus. Hence everolimus may affect the bioavailability of orally co-administered CYP3A4 substrates. However, a clinically relevant effect on the exposure of systemically administered CYP3A4 substrates is not expected (EU: SmPC, Afinitor®, current version).

6.2 Post-Study Therapy

After withdrawal or EOS, patients will be treated according to clinical practice at the discretion of the investigator following completion of this study. This includes treatment of the tumour disease as well as any conditions that may arise during the trial (see also Section 7.4.2).

For French patients: please refer to the rollover study.

7 Schedule of Evaluations and Visit Description

7.1 Schedule of Evaluations

A detailed schedule of evaluations is shown in Table 1 and Table 2.

If more than one procedure is scheduled at the same time, the assessments will be performed in an order as clinically appropriate.

As an exception only during the COVID-19 pandemic, if a patient is unable to attend his/her institutional site visit per the protocol schedule, blood samples may be collected and tested in the patient's local centre in a laboratory certified as per local requirements. However, the physical examination, vital signs, and electrocardiogram (ECG) may be postponed to the next scheduled site visit. Any of these deviations from the protocol-specified schedule will be considered a minor protocol deviation. The principal investigator (or delegate) will follow up on the patient's status as needed.

Protocol measures introduced because of the COVID-19 outbreak are temporary (see also Section 5.6.2), and will be considered revoked as soon as there is a consensus that the period of the current public health crisis has passed.

7.2 Screening Phase

Screening is to take place between 90 days and 1 day before treatment (day -1). Screening evaluations can be divided; all necessary results need to be available prior to randomisation.

7.2.1 Baseline

After signing the informed consent form, patients will undergo the following screening investigations and procedures:

- Review of inclusion/exclusion criteria
- Medical history (not older than 28 days at the time of randomisation)
- Physical examination (not older than 28 days at the time of randomisation)
- Vital signs (not older than 28 days at the time of randomisation)
- Clinical laboratory tests (not older than 28 days at the time of randomisation)
    - Haematology
    - Serum chemistry and clotting parameters
    - Urinalysis

- Tumour serum biomarker tests (not older than 28 days at the time of randomisation)
- Pregnancy test (not older than 28 days at the time of randomisation)
- 12-Lead ECG (not older than 28 days at the time of randomisation)
- EORTC QLQ-C30 and GI.NET21 (not older than 28 days at the time of randomisation)
- Current biopsy (mandatory, unless prior tumour specimen is available, see Section 8.1.4)
- Tumour histology (see Section 8.1.4)
- Concomitant medications and SSA medications assessment (over a period of 28 days before randomisation)
- SSTR imaging (SRI), not older than 4 months must be available or has to be performed, by either:
    - preferably ^{68}Ga-based SSTR PET imaging (^{68}Ga-edotreotide or ^{68}Ga-DOTATATE), or, if unavailable,
    - ^{111}In-pentetreotide or ^{99m}Tc-octreotide SSTR SPECT/planar imaging
- Morphological imaging: native liver and contrast-enhanced liver and 3 regional (pelvis, abdomen, thorax) MRI or CT, must be available (performed within 28 days prior to randomisation) or has to be repeated as baseline MRI/CT
- ^{99m}Tc-MAG3 renal scintigraphy (performed within 28 days prior to randomisation)

If the patient meets all of the selection criteria, he/she will be randomly assigned to one of both treatment groups.

^{177}Lu-edotreotide is to be ordered on the day of randomisation. The first dose of ^{177}Lu-edotreotide should be administered within 21 days of randomisation. In case of any delay, the site should check with the Sponsor via the site monitor and the reason for delay should be documented accordingly.

If randomisation reveals assignment to the everolimus arm, treatment should be initiated as soon as possible (preferably no later than 21 days after randomisation). The randomisation visit can then be taken as day 0 of treatment if all required pre-dose examinations were performed on the same day.

If a patient is a screen failure, the following information is to be collected in the electronic case report for (eCRF):

- Date of informed consent
- Date of the screening visit
- Demography (see Section 8.1.1)
- Inclusion/exclusion criterion number not met
- Serious adverse event, if applicable
- EOS page of eCRF is to be completed with reason “Screen Failure”

7.3 Treatment Phase

Adverse events and concomitant medication are to be reported continuously from Day 0 until end of study. AEs ongoing at EOS have to be followed up until resolved or for a period up to a maximum of 30 days by the investigator (see Section 8.3.2.3). Pregnancy tests are to be performed monthly in all female patients from the start of treatment until EOS.

7.3.1 Month 0

7.3.1.1 Day 0

The following examinations and procedures will be performed on day 0:

Pre-dose:

Only ^{177}Lu-edotreotide group:

- Hospital admission (according to discretion of investigator and local regulations)
- Transmission scan and blank scan using either a Co-57 or Tc-99m sheet source or if available at the site whole body low dose CT scan. These scans can be performed up to 7 days prior to day 0. For Tc-99m, blank and transmission scan have to be performed together (one followed by the other) due to the short half-life of Tc-99m, but both scans can also be performed up to 7 days prior to day 0. For Co-57, blank and transmission scan can be acquired on different days within the defined period.

Only for everolimus group:

- Ambulatory visit, beginning pre-dose and ending approximately 3 h post-dose when all examinations and procedures are completed for day 0.

Both treatment groups:

- Physical examination
- Vital signs
- Clinical laboratory tests
    - Haematology
    - Serum chemistry and clotting parameters
    - Urinalysis
- Tumour serum biomarker tests
- Pregnancy test (if baseline pregnancy test was performed more than 14 days ago)
- 12-Lead ECG
- Concomitant medications and SSA medications continuously

- Adverse events

Pre-dose procedures may be performed within 7 days before Day 0 for both treatment groups. Investigations should be performed as close to PRRT or dosing as possible and as clinically appropriate.

Treatment

^{177}Lu-edotreotide group:

- Pre-medication with amino acid solution (see Section 6.1.3)
- Infusion/injection of undiluted ^{177}Lu-edotreotide dose 1 (D1) over 10 to 20 min according to locally established practice

Everolimus group:

- Start with everolimus administration, 10 mg p.o.

Post-Treatment (only ^{177}Lu-edotreotide group):

Assessments:

- Vital signs immediately after end of infusion and 6 h ± 1 h post start of infusion
- Serum chemistry 5 h ± 1 h post start of infusion
- Concomitant medications and SSA medications continuously
- Adverse events continuously

Imaging:

- ^{177}Lu whole body planar imaging immediately after vital signs assessment (approx. 0.5 h ± 0.25 h) and 6 h (± 1 h) post start of infusion
- *Sub-study B: Serial 3D SPECT/CT Imaging only: ^{177}Lu abdominal SPECT/CT 0.5 ± 0.25 h and 6 h ± 1 h post start of infusion*

Post-imaging urine and blood samples (Sub-study C only)

The following samples will be collected only if Sub-study C is performed during the first ^{177}Lu-edotreotide treatment cycle:

- Urine will be collected from all voids beginning immediately post-dose to 1 hour, and in intervals of 1-6 and 6-24 hours post-injection
- Blood samples of 1 mL, each will be drawn from a site on the lower arm below the amino acid infusion site, and opposite the arm receiving the infusion of ^{177}Lu-edotreotide at 0 min, 10 min, 30 min, 1 h, 3 h, and 6 h post-injection (see Section 8.2.2.5).

Post-Treatment (only Everolimus group):

- Vital signs 0.5 h ± 0.25 h after everolimus administration
- Concomitant medications and SSA medications continuously
- Adverse events continuously
- Patients receive compliance diary

7.3.1.2 Day 1 (only ^{177}Lu-edotreotide group)

Prior to Imaging:

- Vital signs 24 h ± 3 h post start of infusion
- Serum chemistry 24 h ± 3 h post start of infusion
- Concomitant medications and SSA medications continuously
- Adverse events continuously

Imaging:

- ^{177}Lu whole body planar imaging 24 h ± 3 h post start of infusion
- ^{177}Lu abdominal SPECT/CT imaging 24 h ± 3 h post start of infusion

Post-imaging urine and blood samples (Sub-study C only)

The following samples will be collected only if Sub-study C is performed during the first ^{177}Lu-edotreotide treatment cycle:

- Urine sampling interval from 6-24 hours post-dose ends and next sampling interval from 24-48 hours post-dose starts.
- Blood sample for dosimetry will be taken at 24 h ± 3 h post-injection.

7.3.1.3 Day 2 (only Sub-study C in ^{177}Lu-edotreotide group)

The following samples will be collected only if Sub-study C is performed during the first ^{177}Lu-edotreotide treatment cycle:

- Urine sampling ends at 48 h (± 3 h) post start of infusion
- Blood sample for dosimetry will be taken at 48 h ± 3 h post-injection

7.3.1.4 Day 3 (only ^{177}Lu-edotreotide group)

Prior to Imaging:

- Vital signs 72 – 96 h (± 3 h) post start of infusion
- 12-lead ECG 72 - 96 h (± 3 h) post start of infusion
- Concomitant medications and SSA medications continuously
- Adverse events continuously

Patients randomised to ^{177}Lu-edotreotide group will receive bi-weekly haematology controls for 8 weeks following ^{177}Lu-edotreotide administration at week 2, 4, 6, 8 post-PRRT (general practitioner acceptable).

Imaging:

- ^{177}Lu whole body planar imaging 72 - 96 h (± 3 h) post start of infusion
- *Sub-study B: Serial 3D SPECT/CT Imaging only: ^{177}Lu abdominal SPECT/CT imaging– 72 - 96 h* (± 3 h) *post start of infusion (same time as planar imaging)*
- Discharge of patients in the morning after day 3 or later, according to discretion of investigator and local regulations.

Optional ^{177}Lu whole body planar and – for Sub-study B – SPECT/CT imaging 7 days (± 2 d) post start of infusion may be performed at investigator's discretion.

The following sample will be collected only if Sub-study C is performed during the first ^{177}Lu-edotreotide treatment cycle: 1mL blood sample for dosimetry will be taken 72 ± 12 h post-injection.

7.3.1.5 Day 7: Sub-study C Only

The following sample will be collected only if Sub-study C is performed during the first ^{177}Lu-edotreotide treatment cycle: 1 mL blood sample for dosimetry will be taken 7 days ± 12 h post-injection.

7.3.2 Month 1 and Month 2

The visits have to be performed at day 30 and 60 with ± 7 days window calculated from day 0.

The following examinations and procedures will be performed in all patients:

- Physical examination
- Vital signs
- Clinical laboratory tests
    - Haematology
    - Serum chemistry and clotting parameters
    - Urinalysis
- Tumour serum biomarker tests
- Pregnancy test
- EORTC QLQ-C30 and GI.NET21
- Concomitant medications and SSA medications continuously
- Adverse events

- Everolimus patients receive their compliance diary

Blood-sampling can be performed up to 72 hours prior to the visit according to local practice and as clinically appropriate.

7.3.3 Month 3

It must be noted that if the predicted absorbed dose to the kidneys in patients receiving ^{177}Lu-edotreotide is likely to exceed 23 Gy upon administration of the next PRRT cycle, dosing can be continued up to a maximum of 29 Gy, provided that a pre-PRRT TER (^{99m}Tc-MAG3 renal scintigraphy) is >50% of the value at baseline (see Sections 3.1, 5.4.1.1, and 5.4.3.2) and the criteria for continued administration of study drug are fulfilled (see Section 5.4.1.2).

7.3.3.1 Day 90

Visit may be performed ±14 days calculated from day 0, whereby days 91 and 93 will be calculated from the actual day 90 visit date. Pre-dose procedures may be performed within 7 days before the Day 90 visit for both treatment groups. Investigations should be performed as close to PRRT or dosing as possible and as clinically appropriate.

The following examinations and procedures will be performed:

Pre-dose:

Only ^{177}Lu-edotreotide group:

- Hospital admission (according to discretion of investigator and local regulations)
- *Sub-study A: Repeated Full Dosimetry Imaging only:* Transmission scan and blank scan or if available at the site whole body low dose CT scan. For further details see Day 0 (Section 7.3.1.1).

Only for everolimus group:

- Ambulatory visit, beginning pre-dose and ending approximately 3 h post-dose when all examinations and procedures are completed for day 90

Both treatment groups:

- Physical examination
- Vital signs
- Clinical laboratory tests
  - Haematology
  - Serum chemistry and clotting parameters
  - Urinalysis
- Tumour serum biomarker tests

- Pregnancy test
- 12-Lead ECG
- EORTC QLQ-C30 and GI.NET21
- Concomitant medications and SSA medications continuously
- Adverse events
- Evaluation of tumour response: native liver and contrast-enhanced liver and 3 regional (pelvis, abdomen, thorax) MRI or CT, baseline method to be adhered to

Treatment:

^{177}Lu-edotreotide group:

- Pre-medication with amino acid solution (see Section 6.1.3)
- Infusion/injection of undiluted ^{177}Lu-edotreotide (dose D 2) over 10 to 20 min according to locally established practice

Everolimus group:

- Continuation of everolimus administration, 10 mg orally once daily
- Everolimus patients receive their diary

Post-Treatment (only ^{177}Lu-edotreotide group):

Prior to Imaging:

- Vital signs immediately after end of infusion and 6 h ± 1 h post start of infusion
- Serum chemistry 5 h ± 1 h post start of infusion
- Concomitant medications and SSA medications continuously
- Adverse events continuously

Imaging:

- *Sub-study A: Repeated Full Dosimetry Imaging only: ^{177}Lu whole body planar imaging immediately after vital signs assessment (approx. 0.5 h ± 0.25 h) and 6 h ± 1 h post start of infusion*

Post-imaging urine and blood samples (Sub-study C only)

The following samples will be collected only if Sub-study C is performed during the second ^{177}Lu-edotreotide treatment cycle:

- Urine will be collected from all voids beginning immediately post-dose to 1 hour, and in intervals of 1-6 and 6-24 hours post-injection
- Blood samples of 1 mL, each will be drawn from a site on the lower arm below the amino acid infusion site, and opposite the arm receiving the infusion of ^{177}Lu-edotreotide at 0 min, 10 min, 30 min, 1 h, 3 h, and 6 h post-injection (see Section 8.2.2.5).

7.3.3.2 Day 91 (only ^{177}Lu-edotreotide group)

Prior to Imaging:

- Vital signs 24 h ± 3 h post start of infusion
- Blood sample serum chemistry 24 h ± 3 h post start of infusion
- Concomitant medications and SSA medications continuously
- Adverse events continuously

Imaging:

- *Sub-study A: Repeated Full Dosimetry Imaging only: ^{177}Lu whole body planar imaging 24 h ± 3 h post start of infusion.*
- ^{177}Lu abdominal SPECT/CT imaging 24 h ± 3 h post start of infusion

Post-imaging urine and blood samples (Sub-study C only)

The following samples will be collected only if Sub-study C is performed during the second ^{177}Lu-edotreotide treatment cycle:

- Urine sampling interval from 6-24 hours post-dose ends and next sampling interval from 24-48 hours post-dose starts
- Blood sample for dosimetry will be taken at 24 h ± 3 h post-injection

7.3.3.3 Day 92 (only Sub-study C in ^{177}Lu-edotreotide group)

The following samples will be collected only if Sub-study C is performed during the second ^{177}Lu-edotreotide treatment cycle:

- Urine sampling ends at 48 h (± 3 h) post start of infusion
- Blood sample for dosimetry will be taken at 48 h ± 3 h post-injection

7.3.3.4 Day 93 (only ^{177}Lu-edotreotide group)

Prior to Imaging:

- Vital signs 72 - 96 h (± 3 h) post start of infusion
- 12-Lead ECG 72 - 96 h (± 3 h) post start of infusion
- Concomitant medications and SSA medications continuously
- Adverse events continuously

Patients randomised to ^{177}Lu-edotreotide group will receive bi-weekly safety controls for 8 weeks following ^{177}Lu-edotreotide administration including haematology.

Imaging:

- *Sub-study A: Repeated Full Dosimetry Imaging only: ^{177}Lu whole body planar imaging 72-96 h post start of infusion*
- Discharge of patients in the morning after day 93 or later, according to discretion of investigator and local regulations

An optional ^{177}Lu whole body planar imaging for Sub-study A 7 days post end of infusion may be performed at investigator's discretion.

The following sample will be collected only if Sub-study C is performed during the second ^{177}Lu-edotreotide treatment cycle: 1 mL blood sample for dosimetry will be taken 72 h ± 12 h post-injection.

7.3.3.5 Day 97: Sub-study C Only

The following sample will be collected only if Sub-study C is performed during the second ^{177}Lu-edotreotide treatment cycle: 1 mL blood sample for dosimetry will be taken 7 days ± 12 h post-injection.

7.3.4 Month 4 and Month 5

The visits have to be performed at day 120 and 150 with ± 7 days window calculated from day 0.
The examinations and procedures to be performed are identical to month 1.

7.3.5 Month 6

The visit has to be performed at day 180 with ± 14 days window calculated from day 0. Days 181 and 183 will be calculated from the actual day 180 visit date.

All patients will undergo a ^{99m}Tc-MAG3 renal scintigraphy.

All further examinations and procedures to be performed at month 6 are identical to month 3. Pre-dose procedures may be performed within 7 days before Day 180 for both treatment groups. Investigations should be performed as close to PRRT or dosing as possible and as clinically appropriate.

If Sub-study C is to be performed during the third ^{177}Lu-edotreotide treatment cycle, the urine and blood samples for Sub-study C are to be collected as described for month 3.

7.3.6 Month 7 and Month 8

The visits have to be performed at day 210 and 240 with ± 7 days window calculated from day 0
The examinations and procedures to be performed are identical to month 1.

7.3.7 Month 9

The visit has to be performed at day 270 with ± 14 days window calculated from day 0. Days 271 and 273 will be calculated from the actual day 270 visit date.

Patients randomised to ^{177}Lu-edotreotide will receive dose D4 at day 270 provided that the kidney function allows administration (see Sections 3.1 and 5.4.3.2).

All further examinations and procedures to be performed at month 9 are identical to month 3. Pre-dose procedures may be performed within 7 days before Day 270 for both treatment groups. Investigations should be performed as close to PRRT or dosing as possible and as clinically appropriate.

If Sub-study C is to be performed during the fourth ^{177}Lu-edotreotide treatment cycle, the urine and blood samples for Sub-study C are to be collected as described for month 3.

7.3.8 Month 10 and Month 11

The visits have to be performed at day 300 and 330 with ± 7 days window calculated from day 0. The examinations and procedures to be performed are identical to month 1.

7.3.9 Second Year

During the second year of the study, patients in the everolimus arm continue on everolimus, while patients in the ^{177}Lu-edotreotide arm will not receive further PRRT treatment until diagnosis of progression. Study visits during the 2nd year take place on an out-patient basis in 3-monthly intervals (12, 15, 18, 21, 24, and 27 months after day 0, with ± 21 day time window). For the management of patients impacted by the follow-up extension, see Section 3.1. Examinations comprise physical examination, vital signs, blood sampling for laboratory and tumour markers, pregnancy test, EORTC QLQ questionnaire, recording of AEs and concomitant medication, morphological MRI/CT imaging at every second year visit, as well as 12-lead ECG and ^{99m}Tc-MAG3 renal scintigraphy at months 12, 18, and 24 only. Morphological MRI/CT imaging and ^{99m}Tc-MAG3 renal scintigraphy should be performed within 7 days prior to the study visit, in order for the results to be available at the time of the visit. Pregnancy tests for the following months without visits at the study centre will be handed out to the patients at every visit. Blood-sampling can be performed up to 72 hours prior to each visit according to local practice and as clinically appropriate. Pregnancy tests are to be repeated monthly during year 2 until EOS. Everolimus patients continue to receive their patient diary at every visit.

7.3.10 End of Study (EOS)

The EOS visit will be performed 30 months from day 0, or after establishment of definitive disease progression, whatever occurs earlier (see Section 8.2.4). Study patients who experience disease progression established prior to the next planned visit are required to complete the EOS visit. For the management of patients impacted by the follow-up extension, see Section 3.1.

The following examinations and procedures will be performed:

- Physical examination

- Vital signs
- Clinical laboratory tests
  - Haematology
  - Serum chemistry and clotting parameters
  - Urinalysis
- Tumour serum biomarker tests
- Pregnancy test
- 12-Lead ECG
- EORTC QLQ-C30 and GI.NET21
- Concomitant medications and SSA medications
- Adverse events
- MRI (CT) evidencing radiological tumour progression by RECIST 1.1: native liver and contrast-enhanced liver and 3 regional (pelvis, abdomen, thorax) MRI or CT, baseline method to be adhered to - not to be repeated in case of progression
- ^{99m}Tc-MAG3 renal scintigraphy

7.3.11 Early Withdrawal Visit

In case of early withdrawal, the EOS visit is to be performed within 28 days after discontinuation. If the visit cannot be completely performed for any reason, the investigator must make every attempt to complete at least all safety-relevant evaluations:

- Physical examination
- Vital signs
- Pregnancy test
- Clinical laboratory tests
  - Haematology
  - Serum chemistry and clotting parameters
  - Urinalysis
- 12-Lead ECG
- Concomitant medications and SSA medications
- Adverse events
- ^{99m}Tc-MAG3 renal scintigraphy

The reason for withdrawal must be noted in patient's file, where known.

7.4 Post-Study Evaluations

7.4.1 All Patients

As this is an oncological study with overall survival and other progression parameters as secondary endpoints, survival information and progression status, as well as further cancer treatments and the development of late toxicities, including renal toxicity and secondary malignancies will be collected from all randomised patients (including drop-outs, non-compliant patients, other), in compliance with local legal regulations for five years after end of study for each patient. The sites will contact their patients at 6-monthly (± 1 month) intervals (i.e. at 6, 12, 18, 24, etc. months after EOS/Early withdrawal) and check the survival status and tumour progression of their patients.

For the management of patients impacted by the follow-up extension, see Section 3.1.

7.4.2 ^{177}Lu-edotreotide Therapy for Patients Progressing under Everolimus

Study patients experiencing disease progression under everolimus have to perform EOS visit and terminate study participation. Subsequently, a patient who progressed under everolimus may be offered ^{177}Lu-edotreotide therapy based on the personal judgement of the Investigator/treating physician, if he/she considers it to be appropriate and beneficial for the individual patient. In these cases, the investigator can request from the sponsor the provision of study drug to individual patients on a "named patient" basis, as a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his or her direct personal responsibility as a special needs request.

The administration of this individual treatment requires the patient's consent. ^{99m}Tc-MAG3 renal scintigraphy should be repeated if it was performed more than six months prior to the start of individual post-study ^{177}Lu-edotreotide therapy.

8 Procedures and Variables

Patients will provide written informed consent before any study-related procedures can be performed (see Section 13.2).

The schedule of assessments is provided in Table 1 and Table 2.

Unless otherwise specified, all examinations and procedures will be performed by the investigator or authorised study personnel. An additional visit can be scheduled at any time if the investigator considers it to be necessary. This applies especially, when there is clinical suspicion of disease progression. In this situation, the investigator will schedule all necessary clinical investigations, irrespective of the study schedule.

Patient-related events and activities, including specific instructions, procedures, concomitant medications, dispensing of study drug, and descriptions of AEs are to be recorded in the appropriate

source documents. Any findings and information resulting from the below described procedures will be recorded in the CRF (see Section 10.1).

8.1 Baseline Characteristics

8.1.1 Demographic Characteristics

The following demographic characteristics will be recorded:

- Date of birth or age, depending on local requirements on data protection
- Weight, height, ethnic origin, gender

8.1.2 Medical and Surgical History, Baseline Findings

Medical/surgical history and medical conditions present before randomisation will be recorded at the screening visits.

Detailed instructions on the differentiation between (i) medical / surgical history and (ii) baseline findings can be found in Section 8.3.1.1.

8.1.3 Prior and Concomitant Medication

Prior and concomitant medication will be recorded at screening and throughout the study, until the End-Of-Study visit (see Section 6).

8.1.4 Tumour Histology

Only patients with histologically proven, metastasised or unresectable, well-differentiated neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET) are eligible for this study. In case of GE-NET, clinical evidence of non-functionality needs to be provided. Central histological re-assessment will be made at baseline using tissue specimens from primary diagnosis or, where unavailable, from a current biopsy.

During screening, a histopathology report of the primary tumour and/or a current tissue specimen, specifying the histological diagnosis, needs to be available. A pseudonymised copy of such report(s) will be collected for the TMF by the monitor for each randomised patient.

Histological diagnosis will be centrally verified for consistency with the current WHO classification 5 (Fletcher et al., 2013). For this purpose, paraffin-embedded blocks or suitable slide-mounted tissue samples obtained during previous interventions will be retrieved from the site pathology and sent to the Central Pathology Laboratory (CPL) University of Bern, Institute of Pathology, Prof. Dr. Aurel Perren. If no prior sample is available, a fresh tumour sample must be obtained to verify diagnosis (inclusion criterion).

The Central Pathology Laboratory will assess:

- Histological entity
- Tumour grade
- Mitoses per high power field (HPF)
- Ki-67 expression
- SSTR expression
- Chromogranin (CgA) immune reactivity

Argyrophilia or hormone expression will not be assessed.

Only patients with a histology of well-differentiated GEP-NET, as confirmed by the CPL will be included in the per protocol analysis.

To avoid that central pathology review capacity delays enrolment of patients, randomisation and start of treatment may be performed, once availability of paraffin-embedded blocks or suitable slide-mounted tissue samples is confirmed at the study site.

In case the results obtained by the CPL cannot confirm the presence of GEP-NET of tumour grade G1 or G2, the corresponding patients may remain in the study, but will be included only in the safety analysis. If in the everolimus arm, it will be at the discretion of the treating physician to offer continued treatment off-label. The treating physician may also offer ^{177}Lu-edotreotide therapy if he/she considers it to be appropriate and beneficial for the individual patient.

8.2 Efficacy

8.2.1 Tumour Characterisation and Staging

8.2.1.1 Somatostatin Receptor Imaging (SRI)

To clinically establish somatostatin receptor (SSTR) expression at baseline, patients undergo somatostatin receptor imaging (SRI) according to local guidelines, preferably with ^{68}Ga-based PET/CT (e.g. ^{68}Ga-edotreotide (^{68}Ga-DOTATOC) or ^{68}Ga-DOTATATE). Where ^{68}Ga-based PET/CT is not available, ^{111}In-pentetreotide (OctreoScan®) or ^{99m}Tc-octreotide SPECT/CT imaging, less preferably planar or SPECT only imaging may be used.

Wherever possible, SRI tomographic hybrid imaging (PET/CT; SPECT/CT), providing three-dimensional information should be performed to alleviate the identification the target lesions, pre-defined per RECIST 1.1. (based on CT/MRI) on the SRI scan. Planar or “SPECT-only-SRI” should only be performed, where tomographic hybrid imaging is not established, as registration/ identification of target lesions with SRI-positive lesions is not easily possible.

All target lesions (up to 5) and ≥90% of non-target lesions need to show adequate tracer uptake, defined as being “clearly differentiable from background” (SSTR positive). This criterion relevant for

eligibility will be assessed by the local investigator. Criteria for SRI scoring are presented in Appendix 5: Tumour Scoring.

Subsequently, image analysis will be centrally verified by the ICL, see Section 8.7. Any differences between local and central assessment will be reported.

8.2.1.2 Morphological Imaging (MRI or CT)

Morphological imaging by MRI / CT will be used a) for the establishment of the radiologically confirmed progressive disease (key inclusion criterion), and b) for the determination of the primary endpoint (PFS).

Two MRI or CT scans obtained using the same method within a maximum of 36 months prior to randomisation, with at least 90 days interval between them, need to demonstrate progressive disease, as per RECIST 1.1. criteria. The most recent scan must not be older than 90 days at randomisation. The minimum interval between two scans must be ≥90 days.

At baseline, one native liver and contrast-enhanced liver and 3 regional (pelvis, abdomen, thorax) MRI or CT, must be available (performed within 28 days prior to randomisation) or has to be repeated as baseline MRI / CT. Where established, combined imaging (e.g. abdominal MRI / thoracic CT) can be used. The baseline imaging method has to be used consistently throughout the whole study period.

Tumour lesions in the body, and tumour burden in the liver at baseline will be documented, as far as visible on morphological imaging (performed within 28 days prior to randomisation). Tumour burden will be assessed semi-quantitatively/visually. According to RECIST 1.1., a maximum of 5 target lesions, visible on morphological imaging will be defined, in descending order of size. Per organ, only 2 target lesions may be defined. All other lesions are defined as non-traget lesions. Only after definition of target lesions on CT / MRI, SSTR expression of target and non-target lesions will be assessed, using SRI (see Section 8.2.1.1).

For follow-up, native liver and contrast-enhanced liver and 3 regional (pelvis, abdomen, thorax) MRIs or CTs will be obtained from all patients in 3-monthly intervals, starting at month 3, until diagnosis of progression or end of study. Additional MRI / CT scans may be performed at any other time if, in the investigator's clinical judgment, progressive disease is suspected. Diagnosis of progression will be made by the local investigator at the point of time when radiological progression criteria, according to RECIST (Eisenhauer et al., 2009) are first met. The RECIST 1.1 and the SRI evaluations performed locally at the study sites will be centrally verified by the ICL (see Section 8.7). For the primary endpoint PFS, the central ICL will perform blinded readings in duplicate, with adjudication in case of discordance will be used.

8.2.1.3 Tumour Markers

Chromogranin A (CgA) will be determined at baseline, and then monthly until month 12, thereafter in 3-monthly intervals until diagnosis of progression or end of study.

CgA serum concentrations will be considered for the assessment of response to therapy (see Section 8.2.4). In patients with an elevated baseline CgA, changes in CgA serum concentrations could be classified in analogy to published classifications (Bajetta et al., 1993) as follows: Complete biomarker response (CR): return to normal range; partial biomarker response (PR): decrease ≥50% from baseline, biomarker stable disease (SD): An increase by <25% or decrease by <50% from baseline; biomarker progressive disease (PD): increase in CgA by ≥25% from baseline, or compared to prior examination, in patients, where an initial improvement following therapy has been observed.

In addition, specific hormones related to clinical symptoms (e.g. gastrin, insulin, etc.) will be determined in patients, if showing elevated levels at baseline work-up. Response could be graded in analogy to CgA, where merited.

8.2.2 ^{177}Lu-edotreotide Biodistribution and Dosimetry

Biodistribution and dosimetry of ^{177}Lu-edotreotide will be determined using traditional, current, and innovative methods, in order to comply with regulatory expectations (planar 2D), correspond to the current clinical standard (2D/3D hybrid), and to evaluate innovative dosimetry methods (3D) currently under investigation at leading research institutions. These innovative methods may considerably reduce the effort for acquisition and analysis in the future, thereby greatly facilitating clinical dosimetry.

Dosimetry will be used, a) to determine the AD to kidney, the organ with highest dose exposure in PRRT (safety dosimetry), and b) to determine the AD to tumour lesions, as basis for establishing a dose response relationship, based on the Gy dose achieved in a tumour, rather than based on a Bq dose administered to the patient, as is the current practise. Dosimetry evaluations will be centrally analysed (ICL, see Section 8.7), using a) the MIRD methodology, which is based on a standard phantom to describe the spatial relationship between organs, and b) the Voxel-S methodology, which considers individual activity distribution of the patient, allowing a more precise description of doses to tumours.

8.2.2.1 ^{177}Lu-edotreotide Whole Body Planar Scintigraphy

^{177}Lu-edotreotide whole body 2D planar images will be performed in anterior and posterior projection, in conjunction with transmission/blank scan using ^{57}Co or ^{99m}Tc sheet source or if available at the site whole body low dose CT scan for attenuation correction (pre-dose) and an external calibration source. Serial scans will be obtained at four points of time after first dosing (D1, day 0) of ^{177}Lu-edotreotide: 0.5 h (prior to voiding), 6 h, 24 h and 72-96 h post-infusion. An additional ^{177}Lu whole body planar imaging 7 days post infusion may be performed at investigator's discretion.

Scintigraphy results will be used to determine ^{177}Lu-edotreotide traditional 2D dosimetry (reference method), with emphasis to kidney (safety) and target tumours (efficacy).

In selected patients, the accuracy of AD predictions made based on the first cycle will be verified by repeated dosimetry in cycles D2 – D4 (Sub-study A: verification of the accuracy of AD extrapolation based on AD determined after D1).

8.2.2.2 ^{177}Lu-edotreotide Abdominal SPECT/CT

Abdominal SPECT/CT scans, covering kidneys and liver will be acquired in a supine position (usually 1 - 2 bed positions), 24 h after each infusion of ^{177}Lu-edotreotide (D1 - D4). The scan following D1 will be quantitatively reconstructed, to yield absolute activity concentrations (Bq/ml) for 2D/3D hybrid dosimetry. The scans from D2 – D4 will be analysed qualitatively only, to demonstrate tumour targeting of ^{177}Lu-edotreotide. In subjects participating in Sub-study A, quantitative reconstruction will be made for all cycles (D1 – D4).

After the first dosing (D1) a SPECT/CT scan will be performed. CT-derived information data from this scan will be used for attenuation and scatter correction.

a) Tumour targeting

   Tumour targeting will be assessed by demonstration of ^{177}Lu-edotreotide binding inside or in the vicinity of the target lesion, seen on structural imaging using SPECT/CT acquired 24 h post-infusion.

b) 2D/3D hybrid dosimetry

   To take superimposition and self-absorption of abdominal organs into consideration, quantitatively reconstructed abdominal SPECT images (Bq/mL) from a single time point (24 h p. i.) of the first dose (D1) will be used to correct 2D planar dosimetry results (reference method), with emphasis to kidney and target tumours.

8.2.2.3 Serial ^{177}Lu-edotreotide SPECT/CT, (Sub-study B, only)

At sites, where 3D dosimetry is performed as routine, or research methodology, serial SPECT/CT imaging covering kidneys and tumour will be acquired in a supine position (usually 2 bed positions), in addition to the mandatory planar acquisitions (see Section 8.2.2.1). SPECT/CT images will be acquired subsequent to planar images and quantitatively reconstructed as described under Section 8.2.2.2.

8.2.2.4 Pharmacokinetic Urine Analysis (Sub-study C, only)

At selected sites, urine will be collected after any one of the 4 administrations of ^{177}Lu-edotreotide from all voids of patients in the ^{177}Lu-edotreotide arm, beginning immediately post-dose (0 min) to 1 hour, and in intervals of 1-6, 6-24 and 24-48 hours post-injection in a subgroup of 20 patients, to assess *in-vivo* stability of ^{177}Lu-edotreotide. Volume and radioactivity content of these voids should be recorded up to 48 hours. Radioactivity concentrations will be measured with a calibrated well-type gamma-counter. Urine will be analysed using radio-HPLC in order to investigate the radiochemical purity of the eliminated compound.

8.2.2.5 Bone Marrow Dosimetry (Sub-study C, only)

As the radioactivity in blood was shown to be similar to that in bone marrow (Forrer et al., 2009), bone marrow dosimetry will be assessed by measuring radioactivity in blood samples at 0 min, 10 min,

30 min, 1 h, 3 h, 6 h, 24 h, 48 h, 3 d, and 7 d post injection during any one of the 4 administrations of ^{177}Lu-edotreotide in a subgroup of 20 patients in the ^{177}Lu-edotreotide arm at selected sites only.

8.2.3 Health-Related Quality of Life (HRQL) and Symptom Control

To evaluate HRQL, self-rating questionnaires will have to be completed by the patient at baseline, and then monthly until month 12, thereafter in 3-monthly intervals until diagnosis of progression or end of study. Completion will be made prior to the administration of study medication, if applicable for this visit.

8.2.3.1 EORTC QLQ-C30

The QLQ-C30 questionnaire (version 3.0, in local language) will be used for the assessment of the general health state. It will not be considered for the diagnosis of progression or symptomatic tumour response (see Section 9.2.2).

8.2.3.2 EORTC QLQ-GI.NET21

The QLQ-GI.NET21 questionnaire (in local language) will be used for the assessment of symptomatic response to therapy, as well as for the diagnosis of symptomatic progression (see Section 9.2.2). In patients with elevated baseline GI.NET21 score, changes in the score will be classified as follows: Complete symptomatic response (CR_S): normalisation of score; partial response (PR_S): decrease ≥50% from baseline score; symptomatically stable disease (SD_S): An increase by <25% or decrease by <50% from baseline scores. Symptomatic progression (PD_S) will be defined as an increase in the GI.NET21 score of ≥25% from baseline, or compared to prior examination, in patients, where an initial improvement following therapy has been observed.

8.2.4 Assessment of Progression-free Survival

Primary endpoint

The primary endpoint is progression-free survival (PFS), determined as time elapsed between randomisation and the date of first objective report of tumour progression (evaluated by RECIST criteria, 1.1), or death. Diagnosis of progression will be established based on radiological information from morphological imaging (MRI / CT) using RECIST 1.1 (Eisenhauer et al. 2009). Status of disease will be defined as one of the following options: Complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

In addition to the evaluation by local investigators pseudonymised images will be transferred to the ICL (see Section 8.7), and analysed by independent radiologists not involved in the study in a blinded fashion in duplicate, with adjudication in case of discordance. In case of discordance reads, a third independent radiologist will act as an adjudicator.

A detailed description of the process of image handling, analysis and documentation will be outlined in a separate document, the image review charter (IRC).

8.3 Safety

8.3.1 Baseline Findings

8.3.1.1 Definition of Baseline Finding

Definition of a baseline finding

A baseline finding is defined as any untoward medical condition in a study patient who has signed the informed consent form but not yet received the first dose of the study drug. This includes conditions stabilised by treatment. By definition, a baseline finding cannot be causally related to study drug; however, it may be causally related to the study (e.g., caused by study-conduct-related investigations).

Differentiation between medical / surgical history and baseline findings

Conditions which started before signature of informed consent and for which no symptoms or treatment are present until the first administration of study drug (e.g., seasonal allergy without acute complaints) are recorded as medical / surgical history.

Conditions which started before signature of informed consent and for which new or worsening symptoms or further treatment are present between signature of informed consent and first administration of study drug (e.g., allergic pollinosis) are recorded as baseline findings.

Differentiation between baseline findings and adverse events

Conditions (e.g., abnormal physical examination findings, symptoms, diseases, laboratory, ECG) present before the first administration of study drug will be documented as baseline findings.

Conditions which started or deteriorated after the first administration of study drug will be documented as adverse events.

Pregnancy

Following the existing international guidelines on embryo-foetal Risk Mitigation and Risk Assessment of Medicinal and Investigational Medicinal Products on Human Reproduction and Lactation and in consideration with the absence of adequate data from the use of the reference study drug in pregnant women and its effects including known embryotoxicity and fetal toxicity as well as considering the known risks of radiation exposure to the embryo or foetus from therapeutic procedures with the administration of radioactive pharmaceuticals, highly effective contraceptive methods that can achieve a failure of less than 1% per year when used consistently and correctly are considered to be used in this study. Female patients of childbearing potential as well as male patients having female partners of childbearing potential, unless surgically/permanently sterile (bilateral tubal occlusion, hysterectomy, or vasectomy), will be excluded from participation in the study unless they are willing to: practice full and true sexual abstinence, or use highly effective contraception in combination with a barrier method of contraception (e.g. condom). Contraception methods that are considered highly effective are: oral or non-oral (injected or implanted) non-oestrogen progesterone-based hormonal

method; oral, intravaginal, or transdermal combined oestrogen and progesterone-based hormonal method; and/or IUD, and/or IUS. Sexual abstinence or the contraception methods described above must be followed throughout the entire study period and for 56 days after treatment in the everolimus group and 66 days in the PRRT group (10 half-lives of ^{177}Lu) after the last treatment cycle. True abstinence may be practised if this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are *not* acceptable methods of contraception. A partner who has a medically successful vasectomy is a highly effective birth control method provided the partner is the sole sexual partner of the female patient of childbearing potential.

Pregnancy is rather unlikely due to study design and presents an exclusion criterion for this study. Adequate pregnancy testing will be performed at regular intervals throughout the study (see Section 8.3.6). Should it nevertheless emerge, it will not be classified as an SAE except in cases where it can be shown that the effectiveness of the contraception was affected by the IMP/RP. A female patient who becomes pregnant during the treatment phase of the study must be discontinued from study treatment. All pregnancy cases (pregnant patient or a male patient who has impregnated a partner) except those emerging after 80 days (66 days per exclusion criteria and 14 days additional waiting period) after the last treatment cycle in the PRRT group and 70 days (56 days per exclusion criteria and 14 days additional waiting period) after treatment in the everolimus group, will be monitored and followed up in regular intervals in order to identify adverse events especially fulfilling the criteria for an SAE. If a pregnant patient or a male patient who has impregnated a partner withdraws from the study during the pregnancy, the pregnant patient/partner will be monitored and followed up on at regular intervals in order to identify adverse events especially fulfilling the criteria for an SAE until the end of the pregnancy. A pregnant patient will not have any further radiation-related follow-up assessments or other follow-up assessments that may interfere with the pregnancy, determined by investigator discretion.

8.3.1.2 Categories, Assessments and Documentation of Baseline Findings

The date and time of the first acute occurrence of the event is documented as the onset.

If the baseline finding is "continuing" into the treatment phase, no AE is to be recorded if, after start of study treatment, the event has the same or milder pattern and intensity/severity. If the finding worsens in terms of either the pattern or intensity/severity after study drug administration, the event must be documented as an AE.

If the event is concluded, this should be recorded in the CRF ("resolved"). If the event vanishes but re-occurs during treatment, an AE with a start date of its re-occurrence should be entered.

All baseline findings will be assessed and documented by the investigator according to the following categories:

- Seriousness: for each baseline finding, the seriousness must be determined according to the criteria given in Section 8.3.2.5. If serious, the baseline finding has to be handled in the same way as an SAE.
- Intensity/Severity

- Specific drug treatment
- Specific non-drug treatment
- Causal relationship to study conduct
- Outcome

The intensity/severity of an event, the causal relationship to study conduct, and the outcome of the baseline finding should be classified according to the same categories used for AEs, as specified in Section 8.3.2.

8.3.1.3 Serious Baseline Findings

Baseline findings will be regarded as serious if they meet the criteria used for defining serious adverse events (SAEs) (see Section 8.3.2.5).

Serious baseline findings will be reported on the SAE form described in Section 8.3.2.5.

8.3.2 Adverse Events

8.3.2.1 Definition of Adverse Event

The definition below follow International Conference on Harmonisation (ICH) – Good Clinical Practice (GCP) (see also ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting):

Adverse event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

By definition, for this study, all AEs are regarded as 'treatment emergent', i.e., not seen before treatment or, if already present before treatment, worsened after start of treatment. See Section 8.3.2.6 for exemptions.

8.3.2.2 Categories for Adverse Event Assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below. NCI-CTCAE version 4.03 will be used for this purpose.

Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 8.3.2.5.

Intensity/severity

The intensity of an AE is classified according to NCI-CTCAE version 4.03, taking into account the possible range of the intensity of the event (see Section 8.3.2.3).

- NCI-CTCAE Grade 1 (mild)
- NCI-CTCAE Grade 2 (moderate)
- NCI-CTCAE Grade 3 (severe)
- NCI-CTCAE Grade 4 (life-threatening)
- NCI-CTCAE Grade 5 (fatal)

An AE should be documented with the applicable diagnosis, if possible (rather than as a symptom, sign, or laboratory finding).

Main pattern

The main pattern of the AE is to be documented as follows:

Every drug administration:	Events that occur in a clear time relationship to every study drug administration
Intermittent:	Regular or irregular repeating events that are clearly of the same kind and same cause, but not clearly time related to study drug administration
Continuous:	Events that are continuously present within the whole time period which is covered by the form, but not clearly time related to study drug administration
Other:	All other patterns, need to be specified in the following text field

Study drug action

Any potential study drug action to resolve the AEs is to be documented as follows

- Drug withdrawn
- Dose reduced
- Dose not changed
- Other action (stopped: definitely, temporarily with exact dates)

Drug treatment

Non-drug treatment

Causal relationship to study drug

The assessment of a possible causal relationship between the AE and the administration of the study drug is based on the following question:

“Is there a reasonable likelihood that the event was caused by the study drug?”

Possible answers are:

- Related (plausible time relationship to the administration of IMP/RP. No plausible explanation by underlying/concurrent disease or other drugs/events),
- Possible (plausible time relationship to the administration of IMP/RP, but the AE can be also plausibly explained by the underlying/concurrent disease or other medicinal products/events),
- Unlikely (unlikely temporal relationship to the administration of IMP/RP. Other medicinal products, events, and the underlying/concurrent disease provide a plausible explanation)
- Not related (clear evidence that the AE is not connected to the IMP/RP administration)
- Not assessable (no evaluation possible based on present data, additional clarification and follow-up necessary)

Causal relationship to study conduct

The assessment of a possible causal relationship between the AE and the study conduct other than the relationship to study drug is based on the following question:

“Is there a reasonable likelihood that the event was caused by the study conduct?”

- Possible answers are “related”, “not related”, “not assessable.”

Outcome

The outcome of the AE is to be documented as follows:

- recovered
- recovered with sequelae, with additional details
- ongoing
- fatal
- unknown

8.3.2.3 Assessments and Documentation of Adverse Events

All adverse events which occur up to EOS, both those observed by study site personnel and those spontaneously reported by study patients, must be recorded on the ‘adverse event’ page(s) in the

CRF regardless of causality. AEs ongoing at EOS have to be followed up until resolved or for a period up to a maximum of 30 days by the investigator.

If an adverse event fulfils any of the criteria for a SAE, both the adverse event pages of the CRF and the Serious Adverse Event Form must be completed. SAEs are recorded for the entire duration of the study. For details of how to report SAEs see Section 8.3.2.5.

For both Serious and Non-serious AEs, documentation must be supported by an entry in the patient's hospital notes. Required information includes: the type of adverse event, seriousness of the event, start date, date of resolution, actions required, outcome, and an assessment of its relationship to study drug and an estimate of its severity (using NCI-CTCAE, version 4.03). NCI-CTCAE severity will be marked in the SAE Report Form using the numeric grades: grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening) and grade 5 (fatal).

All abnormal laboratory results, which are considered to be clinically relevant by the investigator, should also be recorded as adverse events. If an abnormal laboratory result meets any of the criteria for a SAE, this must also be reported on a Serious Adverse Event Form.

An AE should be documented with the applicable diagnosis, if possible (rather than as a symptom, sign, or laboratory finding).

All adverse events that meet the criteria for serious require the completion of a SAE Report Form, in addition to being recorded on the AE pages of the patients' CRF. This applies to all SAEs, whether or not they were considered to be related to study treatment.

8.3.2.4 Expected Adverse Events

Expected disease-related AEs

Neuroendocrine tumour disease has a serious cluster of symptoms. Common disease-related events are:

- Gastrointestinal hormone disorders including potential symptoms, e.g. hypoglycaemia, hyperglycaemia, gastritis, steatorrhea, cholecystolithiasis, weight loss, anorexia
- Skin irritations and sore skin
- Obstructive symptoms and vomiting
- Diarrhoea
- Indigestion
- Abdominal pain or back pain
- Gastroesophageal reflux
- Nausea

Expected conduct-related AEs

The use of an indwelling cannula for the purpose of blood sampling and administration of study drug may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the vessel

wall. After initial irritation, the presence of an indwelling cannula is usually painless and hardly noticeable. The same applies to single vein punctures for blood sampling.

Patients may also experience discomfort from the imaging facilities, e.g. back pain, claustrophobia, headache, chill, and others.

Expected AEs related to the nephroprotective amino acid solution

Amino acid infusion may cause elevation of serum potassium levels by inducing a shift of potassium ions from cells to the extracellular department. This shift can lead to significant hyperkalemia in up to 19% of patients (Giovacchini et al., 2011), leading to malaise, palpitations, muscle weakness and mild hyperventilation. Generalised flushing, fever, nausea and vomiting have also been reported during infusions of amino acid solutions. Prevention and treatment of these symptoms are described in Sections 6.1.3 and 6.1.4.

Expected AEs related to an investigational drug

Please refer to the IB (Section 6.8.2 Undesirable Effects Related to ^{177}Lu-edotreotide) for ^{177}Lu-edotreotide.

Patients should be carefully monitored for side effects. Pre-existing co-morbidities (e.g. pre-existing nephropathy and diabetes mellitus) must be assessed and appropriate monitoring and prophylactic measures are to be applied according to local standard of care.

TLS was previously reported in patients receiving ^{177}Lu PRRT. Patients should be monitored for the development of TLS or CRS. In case of suspected TLS or CRS development, ^{177}Lu-edotreotide treatment must be discontinued and symptomatic treatment is to be given immediately according to local standard of care.

If hypersensitivity or anaphylactic reaction occurs, treatment with ^{177}Lu-edotreotide must be discontinued and appropriate treatment is to be given according to local standard of care.

Please refer to the local product information for the countries participating in the study for everolimus.

Expected Adverse Drug Reactions

The definition below follows ICH-GCP (see also ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting):

Adverse drug reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered as ADR. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Unexpected Adverse Drug Reactions

An unexpected adverse drug reaction is defined as any adverse drug experience, the nature, specificity or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or Summary of Product Characteristics for an approved product). "Unexpected" as used in this definition refers to an adverse drug experience that has not been previously observed and included in the product information, rather than from the perspective of such experience not being anticipated from the pharmacological properties of the investigational product. Any unexpected adverse drug reaction, as of formal criteria of an SAE may not be met, (see above), has to be reported by the investigator immediately after informing the sponsor, using an SAE form.

8.3.2.5 Serious Adverse Events

Definition of Serious Adverse Events

Definition

The following SAE definition is based on ICH guidelines and the final rule issued by the FDA and effective 06-Apr-1998. It is to be applied to both, AEs (defined in Section 8.3.2.1) and baseline findings (defined in Section 8.3.1.1).

An SAE is classified as any untoward medical occurrence that at any dose

- Results in death, or
- Is life threatening, or
- Requires inpatient hospitalisation or prolongation of existing hospitalisation, or
- Results in persistent or significant disability / incapacity, or
- Is a congenital anomaly / birth defect, or
- Is a medically important event or reaction.

The term 'life threatening' in the definition 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 were more severe.

Medical and scientific judgment should be exercised in deciding whether it is appropriate to report an AE as serious also in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in inpatient hospitalisation; or development of drug dependency or drug abuse.

Actions and reporting obligations in case of serious adverse events

All adverse events that meet the criteria for serious require the completion of a SAE Report Form, in addition to being recorded on the AE pages of the patients' CRF. This applies to all SAEs, whether or not they were considered to be related to study treatment.

SAEs must be reported within 24 hours, once the investigator or other study site personnel are aware of the event. An initial written report should be prepared using the SAE Report Form and sent to the sponsor preferably per email (SAE-reporting@itm-radiopharma.com) or (in case of email system failure) per fax (+49 89 329 8986 6068). This report should provide a detailed description of the SAE. Any other relevant documents such as anonymised copies of hospital records may also be attached, if available. If it is not possible to notify the sponsor by email or fax within 24 hours, an initial notification to your assigned clinical research associate (CRA) should be made by telephone, to include the following information:

- Identification of the investigator and centre
- Patient number
- Confirmation of study medication given, with date and dose
- Concomitant medication and indication for using such medication
- Information on the event, including date and time of onset of symptoms, severity, resolution (if applicable), date of death or other outcome (as applicable)
- Relationship with study medication in the investigator's opinion

Toxic death should be reported immediately to the sponsor using the SAE Report Form. Also death as a result of progression of disease (no relatedness to study medication) needs to be reported using the SAE Report Form (option "not related" in the SAE reporting form section "relatedness to study medication"). A detailed description of the cause of death should be provided. Autopsy reports, if available, should also be sent to the sponsor as soon as they become available. Any additional information which becomes known to the investigator should be provided in a follow-up report. The severity of SAEs will be graded according to NCI-CTCAE 4.03 (see Section 8.3.2.3). SAEs must be followed up until a definite outcome can be documented, the event has resolved or stabilised, or the event is diagnosed as a chronic condition.

Also all pregnancy cases must be reported within 24 hours on the corresponding Pregnancy Form, once the investigator or other study site personnel are aware of the pregnancy.

The Sponsor is obliged to report SAEs and SUSARs to the respective authority within the statutory reporting period. The reporting is delegated by the sponsor to the Pharmacovigilance representative (see page 5).

8.3.2.6 Additional Provisions due to the Nature of the Underlying Disease

Progression-free interval is the primary endpoint of this study. Tumour progression will be considered **not** to be an SAE within the scope of this study. However, death or other serious adverse events linked to disease progression/tumour progression will be considered as SAEs. If these serious

adverse events are linked to the disease progression/tumour progression, a diligent evaluation of the IMP/RP impact (see Section 8.3.2.2) through the reporter is necessary before the relatedness is classified as “unlikely” or “not related”.

The SAE cases where the relatedness was classified as either “not related” or “unlikely” will be treated by the sponsor as not related to the IMP/RP and thus will not underlie the provisions of the expedited reporting of SUSARs (the latter does not affect the local provisions to submit local fatal SAEs if required and applicable).

The SAE cases where no relationship to the IMP/RP was stated will be treated as “possible” and a follow-up with the reporter will be initiated.

The SAE cases where the relationship was stated as “not assessable” will be treated as “unlikely” and a follow-up with the reporter will be initiated.

8.3.3 Physical Examination

A physical examination will be performed at each study visit from baseline visit(s) until end of study. It consists of general appearance, orientation to time, space and person, cardio-pulmonary auscultation, manual abdominal examination, and further investigation of any abnormal system, as appropriate.

Physical examination will be performed prior to dosing of study medication.

All pertinent findings will be recorded in the subject’s study records and transcribed to the appropriate pages of the CRF.

8.3.4 Vital Signs

Body temperature, supine blood pressure and heart rate will be measured at baseline visit(s) and at each study visit.

Body temperature: The same location as for first measurement will be used throughout the entire study.

Supine blood pressure and heart rate: Both parameters will be measured on the non-dominant arm after 5 minutes of supine rest.

Vital signs will be measured for all subjects at the points of time given in Table 1 and Table 2.

Subjects randomised into the ^{177}Lu-edotreotide group will have additional vital signs collected prior to ^{177}Lu-edotreotide infusion, immediately after end of infusion (approx. 0.5 h) and at 6, 24, 48, 72-96 hours post start of infusion.

Locations of measurements and results will be recorded in the patient's file.

8.3.5 Clinical Laboratory Tests

Blood and urine samples for clinical laboratory parameters will be collected for all subjects at the points of time given in Table 1 and Table 2.

Laboratory assessments will be performed by the institutional or local laboratories. Because of the potential for radioactivity in some blood and urine samples, the local laboratory must adhere to their SOPs and/or any guidance and regulations for handling radioactive substances.

^{177}Lu-edotreotide arm ONLY: at study site wherever possible. If not logistically feasible, inter-visit lab samples can be taken by a medical general practitioner (GP) in the vicinity of the patient's home.

Samples will be tested for the following parameters:

Haematology: haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), white blood cell count (total and differential: leukocytes, neutrophils, eosinophils, basophils, lymphocytes, monocytes), red blood cells, platelets.

Biochemistry: sodium, potassium, chloride, calcium, glucose, creatinine, urea, albumin, total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (AP), gamma-glutamyl transferase (GGT), lipase, amylase, total protein.

Clotting parameters: prothrombin time (quick), reagent-independent prothrombin ratio (international normalised ratio; INR), activated partial thromboplastin time (aPTT).

Urinalysis (dipstick accepted): specific gravity, pH, protein, glucose, blood, leukocytes, ketones, nitrite, albumin, creatinine. Alpha-1-microglobulin will also be tested in urine but only in centres with adequate technical equipment and an established test method.

Tumour marker: Chromogranin-A, further markers (see Section 8.2.1.3).

The investigator will sign each laboratory printout and assess clinical significance. Clinically significant values have to be highlighted as "c.s." (clinically significant). The printouts will be included in the patient's file.

8.3.6 Pregnancy Tests

A serum or urine β-HCG pregnancy test will be performed for all female patients of childbearing potential at baseline, within 28 days prior to first study treatment.

Post-menopausal status (for female patients <60 years of age) must be proven by one of the following:

- History of hysterectomy
- Last spontaneous bleeding at least 1 year prior to informed consent and negative β-HCG
- Serum estradiol <20 pg/mL and FSH >40 IU/L

During the course of the study, pregnancy tests will be repeated monthly until end of study in female patients of childbearing potential. At the first dosing visit (D0), a pregnancy test does not need to be

performed if the baseline pregnancy test result is not older than 14 days. Since after month 12 and during the 2nd year (months 12-27), visits are performed in three monthly intervals, female patients of childbearing potential will be provided with pregnancy test strips for the performance of pregnancy tests at home during months: 13, 14, 16, 17, 19, 20, 22, 23, 25, and 26. The study sites/Investigators will collect and register information on the outcome of the tests via telephone contacts.

A female patient who becomes pregnant during the treatment phase of the study must be discontinued from study treatment. SAE reporting/pregnancy reporting and pregnancy monitoring and follow-up will be performed as described in Sections 8.3.1.1 – pregnancy – and 8.3.2.5.

8.3.7 12-Lead ECG

A 12-Lead ECG will be recorded after 5 minutes supine rest at the following points of time:

- At baseline, within 28 days prior to first study treatment
- Study visits of treatment phase (months 0 - 11): at 0, 3, 6, 9 months
- Study visits of 2nd year (months 12 - 24): at 12, 18, and 24 months
- At EOS visit

Subjects randomised into the ^{177}Lu-edotreotide group will have additional ECGs at 72 h after each dose administration.

Rhythm, RR-, HR-, PR-, QT-, QTc- and QRS-intervals will be assessed at each point of time that a 12-lead ECG is recorded. The ECG printout will be included in the patient's file, and the investigator will comment on whether the results are normal, abnormal (not clinically significant) or abnormal (clinically significant).

8.3.8 Renal Scintigraphy (^{99m}Tc-MAG3)

Within 28 days prior to randomisation, each subject will undergo ^{99m}Tc-MAG3 (^{99m}Tc-mercapto-acetyltri-glycine) renal scintigraphy, to assess the baseline tubular extraction rate (TER) of the kidneys and evaluate the kidney functionality from renogram and sequence images. Follow-up ^{99m}Tc-MAG3 renal scintigraphy will be performed in 6-monthly intervals in both groups: at month 6, 12, 18, 24, and 30. For the ^{177}Lu-edotreotide arm, the month 6 ^{99m}Tc-MAG3 renal scintigraphy has to be performed within 7 days before administration of the cycle D3 dose of study drug. In case an additional ^{99m}Tc-MAG3 renal scintigraphy is prescribed to allow dosing up to 29 Gy to the kidney, it also has to be performed before dosing of study drug (see Section 3.1).

The renal scintigraphy will be performed as clinically established, but in accordance with the details defined in the Clinical Imaging Manual (CIM).

8.3.9 Kidney Function and GFR

Kidney function will be monitored assessing

- Quantitative TER (see Section 8.3.8) determined at baseline, and thereafter in 6-monthly intervals

- GFR calculated from serum creatinine, determined at baseline, thereafter in 3-monthly intervals.
- The calculated GFR will be determined centrally for consistency. Body weight, and height, as well as sex and age will be recorded in the CRF.
- Kidney volume (abdominal MRI/CT, baseline, 3-monthly interval).
- GFR will be calculated using the recommended CKD-EPI formula (Levey et al., 2009)

8.4 Pharmacogenomics

Not applicable.

8.5 Total Volume of Blood

Blood volumes drawn for safety evaluations correspond to those used in clinical routine for patients with GEP-NET. In addition, blood for tumour marker analyses will be drawn.

Total volume of samples will not exceed 50 mL / month. They are summarised in Table 7.

Patients in Sub-study C will also have a total of 11 mL of blood taken for dosimetry within 7 days.

Table 7: Total Volume of Blood

Sample	Volume per Sample [mL]	Number of Samples	Total Volume [mL]
Haematology			
Screening	3	1	3
Months 0-11	3	20 x 1	60
2nd year, EOS	3	7 x 1	21
Biochemistry [A]			
Screening	7.5	1	7.5
Months 0-11	7.5	20 x 1	150
2nd year, EOS	7.5	7 x 1	52.5
Clotting parameters			
Screening	3	1	3
Months 0-11	3	12 x 1	36
2nd year, EOS	3	7 x 1	21
TER by ^{99m}Tc-MAG3 renal scintigraphy			
Screening	7.5	1	7.5
Month 6 (*optional M 9*)	7.5	1 (*x1*)	7.5 (*7.5*)
Months 12, 18, 24	7.5	1 x 3	22.5
EOS	7.5	1	7.5
Overall TOTAL		83	399.0 (*406.5*)
[A] *including tumour markers; including pregnancy test (if not performed from urine)*			

8.6 Sample Shipment

8.6.1 Tumour Histology Samples

For central histological investigations, mounted tissue specimens will be shipped to the following Central Pathology Laboratory (CPL) in ambient temperature with a sample shipment log:

Address	University Bern Institute of Pathology Murtenstrasse 31 CH-3010 Bern, Switzerland
Contact Person	Prof. [redacted]
Telephone	[redacted]
Fax	[redacted]
E-Mail	[redacted]

The samples will be examined for quality and completeness, and receipt will be documented.

8.6.2 Electronic File Transfer

Where possible, all image data are transferred using ABX-DIRECT® software as described in the Clinical Imaging Manual. If ABX-DIRECT® is not available, image data will be transferred via DVD by pick up postal service.

8.6.3 Other Samples

Samples for analysis of chromogranin A (and other tumour marker samples, if applicable; see Section 8.2.1.3), pregnancy status and clinical laboratory will be analysed in the institutional laboratories of each site according to local specifications.

8.7 Image Analyses

Image acquisition, processing, analysis, and format of reporting will follow standardised procedures that are defined in separate documents (Clinical Imaging Manual, Image Review Charter).

Primary image analysis (e.g. determination of target lesion dimensions of individual time points), as well as secondary image analysis (e.g. RECIST 1.1 classification, considering earlier reference time points) will be performed by a central ICL whose readers are blind to the treatment group.

Reading of morphological imaging (MRI/CT) for determination of progression-free survival (PFS, primary endpoint) will be in duplicate, with adjudication in case of discordance.

All secondary image analyses will be made by a single reader at the central ICL, only.

Results of image analysis will be transferred in a suitable alphanumeric format to the Study Data Management in batches.

8.8 Appropriateness of Procedures / Measurements

The purpose of this study is the evaluation of efficacy and safety of ^{177}Lu-edotreotide in the treatment of inoperable, progressive, somatostatin receptor-positive GEP-NET in comparison to everolimus, the only medication currently licensed in the target indication advanced low- and intermediate-grade NET of pancreatic or gastroenteric origin. Comprehensive characterisation of survival endpoints (progression-free survival and overall survival), taking into consideration objective response (RECIST 1.1), biomarker response (tumour markers), and symptomatic response (HRQL questionnaires), corresponds to current standards in oncological efficacy evaluation.

Standard safety evaluations (laboratory, ECG) as well as treatment-specific evaluations (^{99m}Tc-MAG3 renal scintigraphy) are included.

Serial planar scintigraphic imaging (2D) is considered the traditional standard method for the evaluation of radiation dosimetry, expected by regulatory agencies. Hybrid dosimetry (2D/3D), based on serial planar and single time point SPECT/CT imaging, is the emerging clinical standard, allowing to investigate absorbed doses to kidneys (safety) and tumour (efficacy) more accurately, due to a higher spatial resolution and more precise delineation of organ-bound activity, compared to 2D dosimetry (see Section 8.2.2).

This approach is considered to be adequate for verifying the therapeutic index of ^{177}Lu-edotreotide PRRT in greater detail.

9 Statistical Methods and Determination of Sample Size

9.1 Randomisation

Randomisation will be stratified using four independent randomisation lists to control for primary tumour origin (GE-NET vs. P-NET) and for prior medical therapy (1st line vs. 2nd line) as critical baseline co-variates (see Section 9.2.3). A central web-based randomisation system will be used.

9.2 List of Variables and Population Characteristics

For the main analyses of variables based on tumour response, centrally assessed RECIST 1.1 will be used. Local RECIST 1.1 assessment can be used for sensitivity analyses, if deemed relevant.

9.2.1 Primary Variable

Progression-free survival

Progression-free survival will be determined starting from randomisation until the date of an event (PD by RECIST 1.1 or death). For the primary analysis, any withdrawal (or drop-out) before EOS visit will be censored. Patients who have not shown progression at the end of the study will also be censored.

9.2.2 Secondary Variable(s)

9.2.2.1 Key Secondary Variables

a) Objective response rate (ORR), defined as the percentage of patients, achieving (based on RECIST 1.1) a partial response (PR) or complete response (CR) as best outcome

b) Overall survival (OS), will be calculated starting from the date of randomisation until the date of death. OS will be determined based on all available evidence, including study visits, follow-up telephone calls, subsequent medical reports, or the report of death, as appropriate. OS will be followed up for 5 years (60 months) after EOS.

9.2.2.2 Exploratory Efficacy Variables

c) Percentage of patients progression-free at 2 years after randomisation in either treatment arm (% 2y-PFS)

d) Disease control rate (DCR), considers – in contrast to the ORR – the percentage of patients, achieving partial reponse (PR), complete response (CR), and stable disease (SD) as best outcome

e) Duration of disease control (DDC), will be calculated only in patients who achieve CR, PR or SD as the period from the time point of first establishment of SD (or better) until a new diagnosis of morphological progression per RECIST 1.1 criteria

f) Similarly, duration of response (DoR), will be calculated only in patients who achieve CR or PR as the period from the time point of first establishment of PR (or better) until a new diagnosis of morphological progression per RECIST 1.1 criteria

g) Association between RECIST 1.1 tumour response and CgA and/or specific hormone levels will be explored. If relevant, percentage of patients experiencing a biomarker tumour response (CgA, specific hormones), classified as SD, PR, CR, and PD, can be investigated, as well as the duration of such response

9.2.2.3 Safety and Tolerability Parameters

a) Measured tubular extraction rate (TER), percentage depart from baseline value
b) Calculated glomerular filtration rate (GFR), percentage depart from baseline value
c) Renal volume (V_{kidney}), percentage depart from baseline value
d) Frequency of occurrence and severity of abnormal findings in safety investigations (vital signs, 12-lead ECG, clinical laboratory, adverse events)

9.2.2.4 Health-Related Quality of Life (HRQL)

a) Maximum HRQL improvement (EORTC QLQ-C30 and GI.NET21 questionnaires) total scores, relative to baseline
b) Duration of maximum HRQL improvement
c) Time to HRQL deterioration, defined as the time from randomisation to first HRQL deterioration

9.2.2.5 Dosimetry

Full dosimetry assessments of target organs and tumour lesions will be reported including time to activity curves.

Cumulative absorbed dose (in Gy) of ^{177}Lu-edotreotide to target tumour lesions and kidneys, will be estimated from dosimetry after first ^{177}Lu-edotreotide cycle (D1) considering prospective total ^{177}Lu-edotreotide dose prescriptions from D1 – D4 (assuming dose linearity).

In Sub-study A patients, the cumulative absorbed dose to kidneys and to tumour lesions extrapolated from absorbed dose estimated at D1 will be compared with the cumulative absorbed dose measured at the different administration times (i.e. D1 to D4).

In Sub-study B patients, absorbed dose (in Gy) determined by 3D dosimetry, will be analysed in comparison to absorbed dose values obtained by planar (2D) and hybrid (2D/3D) dosimetry.

In Sub-study C patients, bone marrow absorbed dose (in Gy) will be extrapolated from blood radioactivity.

9.2.2.6 Pharmacokinetics (Sub-Study C)

a) Urine radioactivity in percentage of injected activity (%IA) at pre-defined intervals within 48 hours post-injection to assess excretion pattern
b) Blood radioactivity in %IA at pre-defined time points within 7 days post-injection to assess clearance pattern
c) Radiochemical purity assessed through HPLC of urine samples collected within 48 hours post-injection

9.2.3 Population Characteristics

9.2.3.1 Primary Tumour Origin (GE-NET vs. P-NET)

In this trial patients with histologically confirmed diagnosis of well-differentiated neuro-endocrine tumour of non-functional gastroenteric origin (GE-NET) or both functional or non-functional pancreatic origin (P-NET) will be eligible. Therefore, stratified randomisation will be used to ensure a balanced frequency of GE-NET and P-NET patients in both treatment arms. To enable an optimal subgroup analysis, ideally equal numbers of GE-NET and P-NET should be recruited.

9.2.3.2 Prior Medical Treatment (1st line vs. 2nd line)

In the present trial both, treatment-naive (1st line), and patients who have progressed under prior medical therapy (2nd line) will be eligible. Since prior medical treatment status is expected to be a relevant baseline co-variate, stratified randomisation will be used, to ensure a balanced frequency of 1st line and 2nd line subjects in both treatment arms.

In addition, the evaluation of prior medical treatment in patients receiving second line therapy will be differentiated into chemotherapy, SSA, targeted therapy (e.g. sunitinib), and others.

9.2.3.3 Tumour Grade (G1 vs. G2), Ki-67, and KPS

Tumour grade, Ki-67, and baseline clinical status, determined using the Karnofsky Performance Score (KPS) are suspected to be further relevant baseline co-variates, which should be investigated at the time of analysis.

9.2.3.4 Other Characteristics

Summary tables and/or listings will be provided for demographics and other baseline characteristics, including:

- Age, ethnic origin, sex, physical exam
- Medical/surgical history at baseline,
- Prior and concomitant medication
- Time from primary diagnosis, time from diagnosis of progression, number and type of prior therapies for condition, site(s) of metastases
- Histological entity, functional state

All variables of population characteristics will be confirmed by non-parametric statistical testing for both treatment groups to check their comparability at baseline (except for detailed physical examination, medications, and medical/surgical history). If there should be major differences between the treatment groups, their impact on analysis will be investigated including with stratified methods, if deemed appropriate.

In addition, appropriate methods (stratification, multivariate analyses, subgroup analyses) will be used to assess the impact of patient and tumour characteristics and tumour histology on tumour response as foreseen in the exploratory study objectives.

9.3 Statistical and Analytical Plans

9.3.1 General Considerations

The primary objective of this trial is to demonstrate the efficacy of PRRT with ^{177}Lu-edotreotide to prolong progression-free survival (PFS) in patients with inoperable, progressive, SSTR+ GEP-NET, compared to everolimus.

The primary variable progression-free survival (PFS) will be analysed using confirmatory statistics. All survival data will be analysed using the Kaplan-Meier method, which takes into account the impact of censored observations and the Log-rank test. Likewise, the secondary variable overall survival (OS) and PFS, adjusted for the co-variates primary tumour origin, prior medical treatment, tumour grade and baseline KPS, will be compared using exploratory statistics. Further statistical stratified tests will not be made. Instead, the influence of other baseline and/or intercurrent factors such as, but not limited to, concomitant SSA treatment and treatment switch will be investigated by sensitivity analyses.

The main analysis of OS may take into consideration treatment switches if a high proportion (e.g. >33%) of patients in the everolimus arm received subsequent PRRT treatment.

All secondary variables will be analysed descriptively by treatment group. All continuous and ordinal parameters will be summarised using standard summary statistics as appropriate (n, mean, standard deviation, median, minimum, maximum, 25th percentile, and 75th percentile). Summary statistics for ordinal and categorical variables will include frequency counts and percentages. 95% confidence interval will be calculated where relevant. Non-parametric methods will be used for comparison between study groups or subgroups (Mann-Whitney U test), changes within groups (Wilcoxon test) or percentages (Fisher's exact test or Chi^2 test). The influence of censored data will be evaluated by using Kaplan-Meier, log-rank test and Cox model analysis when appropriate.

A statistical power of at least $P = 0.8$, and a significance level of $p < 0.05$ (two-sided) are envisaged. All data will be listed and summarised.

Adverse events prior to the first treatment will be captured for all enrolled patients and reported separately from treatment emergent AEs, as baseline findings.

Patient assignment to the analysis sets, specified in Section 9.3.3, will be performed and listed prior to any analysis taking place.

9.3.2 Interim Analysis and Multiple Testing

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

9.3.3 Analysis Sets

9.3.3.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will be used for all efficacy analyses and is defined as all patients who are randomised to treatment; patients in this population will be analysed according to the treatment to which they were randomised. All available data for PFS and survival will be collected and analysed for these patients. For FAS patients who have inadequate data post-baseline to assess efficacy according to the criteria for response or who dropped out before EOS, follow-up will be censored for

analysis of PFS on the date of the last adequate tumour assessment prior to withdrawal (see the Statistical Analysis Plan [SAP] for more details).

The confirmatory analysis of the primary and the 2 key secondary endpoints will be based on the FAS.

9.3.3.2 Per Protocol set (PP)

In order to determine if any bias results from including untreated patients or patients lost to follow-up in the primary FAS analysis, an additional analysis will be conducted on patients who are protocol-compliant: the Per Protocol set (PPS). Patients with major protocol violations determined before statistical analysis will be excluded from this population. Major protocol violations are defined as those that could impact the efficacy or safety evaluations and will be specified in the SAP. For the study arms the following deviations are defined as major protocol deviations, leading to exclusion from the PPS:

- ^{177}Lu-edotreotide arm:
  - Subjects with incomplete ^{177}Lu-edotreotide infusion, in which less than 50% of the total pre-scribed activity (GBq) based on initially dosimetry assessment was injected.
  - Subjects missing more than two scheduled doses, or in whom dose were administered more than 30 days outside the date, specified per protocol.
- Everolimus arm:
  - Subjects missing more than 14 doses, within a visit interval of 30 days (with exception of treatment interruptions due to toxicity (see Section 5.4.3.1).

9.3.3.3 Safety Analysis Set (SAF)

All patients who received at least one dose of any study treatment will be included in the Safety Analysis Set (SAF). Patients will be analysed according to the treatment they actually received. Analyses of safety parameters will be based on the SAF.

9.3.3.4 Other Populations

In case of specific assessments in specific groups of patients, analyses will only be conducted in the appropriate group of patients where relevant. As an example, the analysis of substudy variables will only be analysed based on the population of patients who actually participated in the corresponding substudy.

9.3.4 Statistical Analyses

The detailed procedures for data analysis are described in the Statistical Analysis Plan (SAP), which will be defined before start of statistical evaluation. Any changes in the original statistical methodology will be documented in the SAP.

Statistical analyses will be performed after the data base has been appropriately locked (See Section 9.3.2).

All data from the CRF and other study documents will be reported in listings. Continuous parameters will be summarised using descriptive statistics (number, mean, standard deviation, minimum, median, maximum) and categorical parameters will be summarised using frequency tables. Corresponding 95% confidence intervals will be presented additionally where meaningful.

Statistical hypothesis testing of the primary variable and the key secondary variables will be performed maintaining an overall Type I Error (alpha) of 5% (two-sided).

Multiplicity will be accounted for by adhering strictly to the described interim analysis and hierarchy testing plan with regard to the primary and the key secondary endpoints (see Section 9.3.2).

Exploratory statistical hypothesis tests will be used at a significance level of 0.05 (two-sided), and considered at a purely descriptive level.

Withdrawals and protocol deviations will be listed. Missing data that cannot be obtained will not be substituted, unless stated otherwise (see SAP for more details). A given data set entry is presumed to be an outlier if the value is evidently contrary to generally accepted data. Such occurrences will be recorded. Results from analyses excluding outliers may be explored by comparing to results based on the complete data set; differences will be discussed.

All statistical evaluations, including graphical data summaries, will be performed using appropriate software.

9.4 Determination of Sample Size

Considering that everolimus will be used as comparator in the planned study, a sample size estimation was conducted, based on a median PFS of 11.0 months reported for everolimus (Yao et al., 2011, 2016). and a median PFS of 32 months in NET patients (34.5 in GEP-NET patients), as determined for ^{177}Lu-edotreotide in subjects treated with ≥2 PRRT cycles in the retrospective study (van Echteld 2015, Baum et al., 2016).

[redacted]

[redacted]

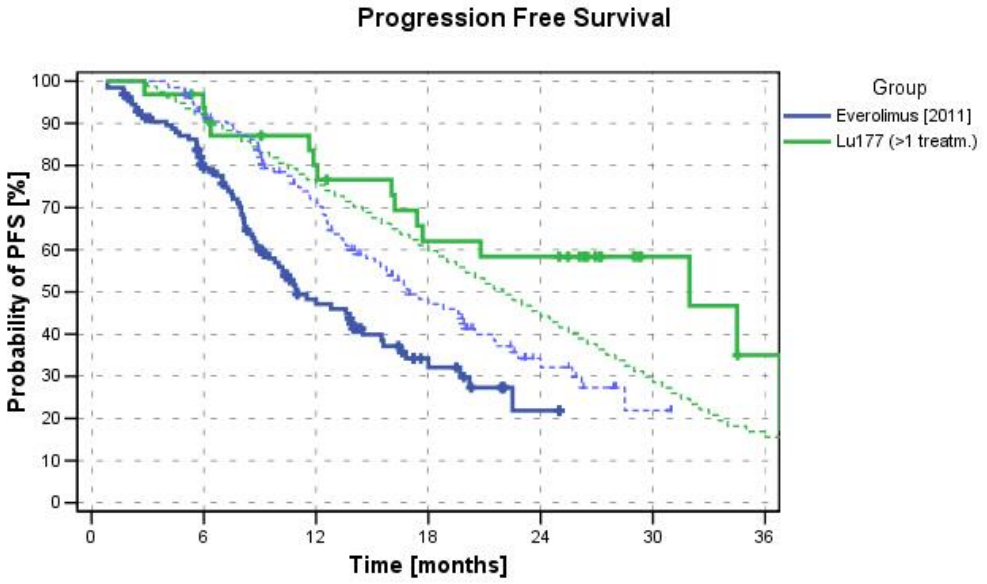

Figure 4: PFS for everolimus and ^{177}Lu-edotreotide in NET

Kaplan Meier estimates of PFS, reported for everolimus (blue), and ^{177}Lu-edotreotide (≥ 2 cycles; green), in patients with NET (N=32)

Figure 4 shows the Kaplan Meier estimates of PFS reported for everolimus (Yao et al., 2011) and ^{177}Lu-edotreotide (van Echteld et al., 2015; Baum et al., 2016) in NET patients.

A prolongation of mPFS by ≥6 months, compared to comparator is already considered a relevant clinical benefit, constituting superiority over existing treatments in patients with advanced GEP-NET. To visualise, the dotted blue curve in Figure 4 is a simulated curve representing this mPFS benefit of 6 months, which shows a difference of 25% in PFS at 11 months.

For the sample size calculations, i.e. estimating the sample size, the power and/or the effect size, the following considerations were taken into account:

[redacted]. Study duration per patient will be 30 months. The accrual across time is uniform. Of note, the trial sample size was not revised (i.e. decreased) after the protocol amendment that extended the patient follow-up from 24 months to 30 months.

Based on this HR a total sample size of 300 will compensate for a dropout rate (censored data) of 15% for primary endpoint analysis. Switching from the one group to the other is not allowed in this study and therefore not considered in the sample size calculation.

With regard to overall response rates, group sample sizes of 200 in the ^{177}Lu-edotreotide group and 100 in the everolimus group achieve [redacted]% power to detect an odds ratio between the group ORRs of [redacted] (that corresponds to rates of [redacted]% and [redacted]%). The proportion in the ^{177}Lu-edotreotide group is assumed to be [redacted]% under the null hypothesis and 18% under the alternative hypothesis. The proportion in the everolimus group is assumed to be 5% according to results of the RADIANT-3 study (Yao et al., 2011). The test statistic used is the two-sided Fisher's Exact Test. The significance level of the test is 5%. A dropout rate of 15% is included in this calculation using PASS software.

With regard to overall survival, a two-sided logrank test with an overall sample size of N=300 subjects ([redacted] events; [redacted], N1=100 subjects [redacted]] in the everolimus group and N2=200 subjects [[redacted] events] in the ^{177}Lu-edotreotide group) achieves [redacted] power at a [redacted] significance level to detect a hazard ratio (HR) of [redacted] when the everolimus group median overall survival time is 44 months as in the RADIANT-3 study (Yao et al., 2016) (i.e., a difference of an additional 23 months in the ^{177}Lu-edotreotide group). The observation time for overall survival will be 5 years (60 months) after EOS for all patients.

The sample size of 300 patients was chosen as the primary endpoint and the 2 key secondary endpoints are to be tested in a confirmatory manner. This sample size allows to address historically assumed PFS treatment effect (which would require [redacted] events) and minimal clinically relevant PFS difference (which would need [redacted] events).

[redacted]

- [redacted]
- [redacted]
- [redacted]

In conclusion, the trial sample size of 300 randomized patients associated with the interim analysis plan will allow to cover all the possible treatment effect assumptions (minimal, expected and historical) at an overall two-sided level of significance of 0.05 and with acceptable power (i.e. [redacted]).

The sample size estimation was performed using SAS, PASS Power Analysis and Sample Size Software (version 13).

10 Data Handling and Quality Assurance

10.1 Data Recording

10.1.1 Case Report Form (CRF)

For this study patient data will be entered into a sponsor defined eCRF, transmitted electronically to the sponsor or designee and combined with data provided from other sources in a validated data system. The case report form will be supplied for recording all study data from each patient. It is the responsibility of the investigator to ensure that the CRFs are completed in full. All data therein must be supported by source documentation at the study centre. The completion of study page of the CRF must be signed by the principal investigator at the end of the study confirming that he/she is satisfied with its completion and accuracy. A CRF must be completed for every patient who signed an informed consent. The eCRFs must be kept up-to-date so that they always reflect the latest observations on the patient.

Study monitors must never write in the CRF (except to write queries).

In all cases, subject initials or personal data will not be collected by or transmitted to the sponsor or the coordinating CRO.

10.1.2 Missing Data

If any information is not available, and it is considered by the investigator that it will never be available (e.g. the weight on a particular visit was not recorded), the investigator will explain in the eCRF, why the investigation was missed out (e.g. the patient was not well enough to undergo the procedure).

10.1.3 Storage

It will be the responsibility of the investigator to guarantee adequate storage for all study records, including the hospital notes during the study (and for a minimum of 25 years following the end of the study). If he/she leaves the employ of the hospital he/she will inform the sponsor and nominate a contact person who will have access to the study documents.

The investigator should take measures to prevent accidental or premature destruction of these documents. Essential documents shall be stored in such a way that ensures that they are readily available upon authorities' request.

Archiving is described in Section 10.6.

10.2 Monitoring

This study will be monitored at all stages of its development by the clinical research personnel designated by the sponsor. Monitoring will include personal visits and telephone communication to ensure that the investigation is conducted according to the protocol and in order to comply with guidelines of GCP and applicable regulatory requirements. On-site and remote (according to local regulations) review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each patient.

During monitoring visits, the data recorded in the CRFs, source documents, and other study-related records will be compared against each other in order to ensure accurate, authentic and complete data that reflects the actual experience of the patient in the study, i.e. source data verification. In addition, monitoring must ensure that the safety and rights of subjects are being protected. The investigator must ensure that the hospital notes will be available for direct verification of source data. The sponsor will not keep any records of patient's full identity.

To this end, the investigator agrees to allow regular visits by the study monitors and ensures direct access to study documents. He/she also agrees to allocate their time and the time of their staff to discuss findings and any issues with the monitor.

Medical monitors and CRAs or assistants may request to witness patient evaluations occurring as part of this protocol. The investigator and appropriate personnel will be periodically requested to attend meetings or trainings organised by the sponsor to ensure acceptable protocol execution.

The study may be audited or inspected by the sponsor (or a designated CRO), regulatory or health authorities or IEC/IRB. If such an audit or inspection occurs, the investigator must agree to allow access to the study site, required patient records and study documents. If notified of audits/inspections by bodies other than the sponsor, the investigator is to notify the sponsor of any such inspection immediately. By signing this protocol, the investigator grants permission to personnel from the sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in the CRF generation, where clinically appropriate. The investigator agrees to allocate his/her time and the time of the study team to accompany the audit and to discuss the findings with the auditor. The investigator will be informed about the outcome of the audit.

The following activities will be undertaken to ensure the quality of trial-related activities:

- Adherence to the trial site SOPs to maintain accurate and consistent practices and procedures
- Conduct of a site initiation visit to ensure the investigator and all personnel involved in the trial understand the protocol, including the study procedures and their responsibilities
- Completion of a standard CRF in accordance with GCP requirements to ensure accurate and reliable data
- Periodic monitoring to ensure the trial data are accurate, complete and verifiable from source documents, and that the protocol is being followed

Quality control procedures regarding data entry and statistical analysis will be documented in the SAP.

10.3 Data Processing

The CRO will be responsible for the processing and quality control of data. Data management will be carried out as described in the CRO's SOPs for clinical studies to ensure the integrity of the data, e.g. removing errors and inconsistencies of the data. Data entry and correction will be tracked by a validated audit trail. All systems are validated and compliant to FDA's ordinance 21 CFR part 11.

The FDA-validated medical dictionary MedDRA (current version) will be used for data coding (e.g. AEs, baseline findings, medication, medical/surgical history). The processes used for coding will be specified in the SAP.

10.4 Data Confidentiality

10.4.1 Documentation of Patients' Participation

For all patients who give informed consent, regardless of whether they receive any study medication, the investigator must record patient identification data in the "Patient Identification List" (full name, initials, date of birth, patient identification code). The patient identification list must allow for the definite identification of any patient that takes part in the study. In addition, study participation must be documented in the patient's regular medical records. For details about patient identification, see Section 4.5.

10.4.2 Data Protection

To protect the patient's identity, a unique patient identification code will be assigned by the investigator to each trial patient and used in lieu of the patient's name when the investigator reports adverse events and/or other trial related data (see Section 4.5). Thus, this number, rather than the patient's name, will appear on all documents and will be cross-referenced by the patient's date of birth. Personal information will be treated as confidential, but may need to be reviewed by the PIs, the ethics committee and regulatory authorities.

In order to be compliant with any country-specific laws, all relevant submissions to the respective authorities will be done and the corresponding approvals will be obtained before collection of any data considered to be sensitive, such as: ethnic origin, race, full date of birth etc.

10.5 Auditing

A member of the sponsor's (or a designated clinical research organisation, e.g. a CRO) quality assurance unit may arrange to visit the investigator in order to audit the performance of the study at

the study site and the study documents originating there. The auditor(s) will usually be accompanied by a CRA or the study team lead. The investigator will be informed about the outcome of the audit.

In addition, inspections by health authority representatives – including foreign authorities – and IEC(s) / IRB(s) are possible at any time. The investigator is to notify the sponsor of any such inspection immediately.

10.6 Archiving

The sponsor and the investigator / medical institution shall, in every case, retain the essential documents relating to this study for at least 25 years after its completion. They shall retain the documents for a longer period if required by other applicable regulatory requirements or by a separate agreement between the sponsor and the investigator. Essential documents shall be archived in such a way that ensures that they are readily available upon authorities' request.

Electronic CRFs (including queries and audit trails) will be retained by the sponsor, and copies will be sent to the investigator to maintain as the investigator copy.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The ISF is not to be destroyed without the sponsor's approval. The investigator's contract will contain all regulations relevant for the study centre.

Storage is described in Section 10.1.3.

11 Premature Termination of the Study

At the discretion of the PI, the patients' treatment may be interrupted for medical reasons. In addition, the sponsor retains the right to end the study for medical-scientific or GCP-relevant reasons. In case of premature termination, the investigators, IRB / IECs and regulatory authorities will be informed by the study manager. As required by local law, current safety-relevant information will be provided to the IEC / IRB and the regulatory authorities by the sponsor. The sponsor will also inform all investigators about relevant safety events according to the applicable regulations. Stopping criteria are described in Section 11.1.

If the trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the trial subjects and should assure appropriate therapy and follow-up. Should the study be terminated and/or the site closed for whatever reason, all documentation will be stored at the institution for the legally required period. Access will be granted to the coordinating CRO during this period. All study medication pertaining to the study must be returned to the sponsor or its representative in compliance with the applicable local regulations.

11.1 Stopping Criteria

11.1.1 Stopping Criteria for the Entire Trial

The entire study must be stopped if there is evidence of serious safety issues. An independent data safety monitoring board (IDSMB, see Section 11.2) will review safety data at regular intervals and may suggest terminating the trial.

To identify any possible safety issues in due time, all SAEs, deaths, instances of DMT (see Section 5.4.3.2), any instances of premature treatment discontinuation, as well as other AEs of interest (e.g. creatinine values) will be reviewed by the IDSMB on an ongoing basis during treatment of the first 36 PRRT patients who have actually received a ^{177}Lu-edotreotide dose. Written safety assessments with conclusions and recommendations will be initially issued by the IDSMB for every 12 PRRT patients (i.e. after patient 1 - 12, 13 - 24, and 25 - 36), thereafter in 6-monthly intervals (see Section 11.2). The IDSMB will take into consideration the observed safety data, the safety profile of comparable PRRT agents, the safety profile of other licensed treatments for neuroendocrine tumours, and the natural history of the disease when making a recommendation to stop the trial.

The IDSMB may recommend to stop the trial for any serious safety issue of concern.

Only patients who have actually received at least one PRRT cycle will be considered for these stopping criteria.

Statistical stopping criteria are not planned.

The study may also be stopped by the sponsor for medical-scientific or GCP-relevant reasons.

11.1.2 Stopping Criteria for Individual Patients

Study participation for an individual patient *must* be stopped

- In case of tumour progression (see Section 8.2.4)
- In case of excessive toxicity defined as an AE considered by the Investigator to necessitate permanent discontinuation of ^{177}Lu-edotreotide, e.g., serious, treatment-related adverse events (see Section 8.3.2.5)
- If the patient decides to withdraw from the trial (see Section 13.2)

Study participation for an individual patient *may* be discontinued (see Section 4.4.1):

- For medical reasons at the discretion of the Investigator
- Due to non-compliance
- Following a protocol deviation
- Due to pregnancy
- If the patient is lost to follow-up.

Study treatment for an individual patient *must* be discontinued in the case of pregnancy (see Section 4.4.1). See Section 8.3.1.1 for follow-up procedures in the case of pregnancy.

^{177}Lu-edotreotide treatment for an individual patient *must* be discontinued in the case of hypersensitivity or anaphylactic reaction, or TLS or CRS development (see Section 8.3.2.4).

11.2 Independent Data Safety Monitoring Board

An independent data safety monitoring board (IDSMB) will review safety data at regular intervals throughout the study. If there are any signs of safety issues, the IDSMB may suggest terminating the trial.

Corresponding to the previously described toxicity pattern for PRRT agents (IAEA PRRNT monograph 2013), the IDSMB will put special emphasis on identifying possible acute and delayed radiotoxic effects which are predominantly expected for bone marrow and kidneys.

To identify relevant safety issues in a timely fashion, the IDSMB will perform an ongoing review of SAE notifications, deaths, instances of DMT (see Section 5.4.3.2), instances of patients not meeting the pre-defined eligibility criteria for continued administration of ^{177}Lu-edotreotide after cycle 1 (see Section 5.4.1.2), or other toxicities requiring discontinuation of ^{177}Lu-edotreotide treatment in the opinion of the investigator, as well as other AEs of interest (e.g. creatinine values). The IDSMB will prepare summary reports with safety assessments and recommendations. For the first 36 PRRT patients, the IDSMB will review 3 consecutive cohorts of 12 PRRT patients who have reached the day 90 (±14) day evaluation (i.e. baseline for cycle 2), allowing to characterise a representative safety profile at the end of this treatment cycle, but will also consider any available additional data from patients who have already advanced beyond cycle 1 at the time of review. After the first 36 PRRT patients, the IDSMB will convene in 6-monthly intervals. Details will be described in the IDSMB charter.

Results of previous trials have shown that ^{177}Lu-edotreotide has the potential to perform considerably better than current standard therapy (Baum et al., 2016). Therefore, termination for futility was not considered. Patients who experience progression under everolimus may switch to treatment with ^{177}Lu-edotreotide off-study at the discretion of the Investigator (see Section 7.4.2).

12 Investigator's Obligations and Regulatory Aspects

12.1 Investigator's Commitment

By signing this protocol, the investigator accepts to carry out all procedures related to this study according to the laws and guidelines of their respective countries related to the conduct of clinical research. All investigators must allow access to all documents pertinent to the study. In particular, the investigator must comply with ICH harmonised tripartite guidelines for Good Clinical Practice

(finalised, July 1996). The investigator's responsibilities as detailed in these guidelines are available upon request.

The study may be subject to inspection or audit by regulatory authorities and will be monitored by authorised company personnel to ensure adherence to these guidelines.

The protocol must be read thoroughly and the instructions herein must be followed exactly. Any deviations should be agreed between the sponsor and the investigator, with appropriate written protocol amendments made to reflect the changes agreed upon. Substantial amendments to the protocol will not be implemented until after approval by the appropriate EC / IRB / regulatory authority according to national legislation (see Section 3.5). Where the deviation occurs for the well-being of the patient, the monitor must be informed and a course of action agreed. Subsequently all such deviations, including the reasons thereof, will be submitted to the sponsor and the IEC(s) / IRB(s) as well as the relevant Competent Regulatory Agencies/Authorities if applicable and according to national regulations.

If an investigator moves, withdraws from the study or retires, the responsibility for conducting the study and maintaining the records may be transferred to another investigator at the same centre who will accept responsibility for taking over the study. Notice of transfer must be made to, and agreed by the sponsor.

12.2 Documentation

12.2.1 Approvals and Agreements

The following documents must be made available to the sponsor prior to enrolling patients into the study:

- Signed final protocol investigator's agreement page.
- Completed and signed investigator agreement, where applicable.
- *Curriculum Vitae* and *Financial disclosure* of the principal investigator together with investigators at his/her centre, where appropriate. Each should be up-to-date, signed and dated, confirming their accuracy.
- Copy of the ethics committee/investigational review board's approval.
- List of members of the ethics committee/investigational review board and their affiliations.
- Sample of the consent form and patient information leaflet to be used (if different from the ones provided by the sponsor).

12.2.2 Hospital Case Notes

The investigator should maintain individual patient records, usually hospital notes. The records should include patient visit dates, records of vital signs, medical history, examinations, any adverse event, and other notes as appropriate. Source documents containing key data relevant to the patient's

condition, procedures and outcome must be kept by the investigator and will be reviewed by the study monitor. All entries in the eCRF must be backed up by source data.

13 Ethical and Legal Aspects

13.1 Ethical and Legal Conduct of the Study

The planning and conduct of this clinical study are subject to national laws. Only when all of the requirements of the appropriate regulatory authority have been fulfilled will the study begin. The guidelines of the World Medical Association Declaration of Helsinki, the Guidelines of GCP (CPMP/ICH/135/95) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

The investigator is responsible for ensuring that no patient is subject to any study-related examination or activity before that patient has given informed consent. The patient must give written consent prior to any study-related activity and after the receipt of detailed information. The verbal explanation will cover all the elements specified in the written information provided for the patient.

The investigator will inform the patient of the aims, methods, anticipated benefits and potential hazards of the study including any discomfort it may entail. The investigator will inform patients that in providing informed consent, they are giving permission for representatives of the study centre PIs, ethics committees, or regulatory authorities to inspect their medical records to verify the collected information. Patients will be informed that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The patient must be given every opportunity to clarify any points he/she does not understand and if necessary, ask for more information. At the end of the interview the patient may be given time to reflect if this is required, or if the patient requests more time. Patients will be required to sign and date the informed consent form. After completion, the consent forms will be kept and archived by the investigator in the investigator's study file.

It should be emphasised that the patient has the liberty to withdraw his/her consent to participate at any time, without penalty or loss of benefits to which the patient is otherwise entitled. Patients who refuse to give or withdraw written informed consent may not be included or continued in the study.

13.2 Patient Information and Consent

All relevant information on the study will be summarised in an integrated patient information and consent sheet provided by the sponsor. A sample patient information and informed consent form is provided as a document separate to this protocol.

Based on this patient information sheet, the investigator will explain all relevant aspects of the study to each patient before his/her entry into the study (i.e., before examinations and procedures associated with selection for the study are performed).

The investigator will also mention that written approval of the IRB / IEC has been obtained.

Each patient will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Following this informative discussion, the patient will be asked if he/she is willing to sign and personally date a statement of informed consent, which includes consenting to the processing of his/her data as explained in the patient information sheet. Only if the patient voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator will personally sign and date the form, too. The patient will receive a duplicate of the signed and dated form.

The signed informed consent statement is to remain in the ISF or, if locally required, in the patient's note / file of the medical institution. In addition, the consent process will be documented in the source documents with an independent entry.

The investigator will document on the CRF the time and date of obtaining informed consent. In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or patient's clinical record must clearly show that informed consent was obtained prior to these procedures.

If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness. The informed consent form and any other written information provided to patients will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol which necessitates a change to the content of the patient information and/or the written informed consent form. The investigator will inform the patient of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IRB / IEC's approval / favourable opinion in advance of use.

13.3 Financial Disclosure

Each investigator (including principal and/or any other investigators; who is directly involved in the treatment or evaluation of research subjects) has to provide a financial disclosure (also on behalf of spouses and dependent children) according to all applicable legal requirements. All relevant documentation will be filed in the TMF and/or ISF, as appropriate.

13.4 Publication Policy

The sponsor is interested in the publication of the results of every study it performs. As some of the information concerning the study drug and the sponsor's development activities may be strictly confidential, any publication manuscript (including conference contributions, etc.) must first be reviewed by the sponsor before its submission or presentation.

Publication of subgroup data and single centre data shall not be performed until the complete study has been published.

All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator / institution.

The sponsor has committed to the global industry position on disclosure of information about clinical trials. The information regarding the study protocol is made publicly available on the internet at www.clinicaltrials.gov. This derives from the standards that international medical journal editors have established requiring protocol registration at the outset of the study as a prerequisite of consideration for publication.

13.5 Compensation for Health Damage of Patients / Insurance

Where required by the laws and regulations of the country in which the study is performed, insurance of patients against health impairment occurring as a result of participation in the study will be set up in accordance with said laws and regulations. All relevant documentation regarding such insurance will be filed in the TMF and/or ISF, as appropriate.

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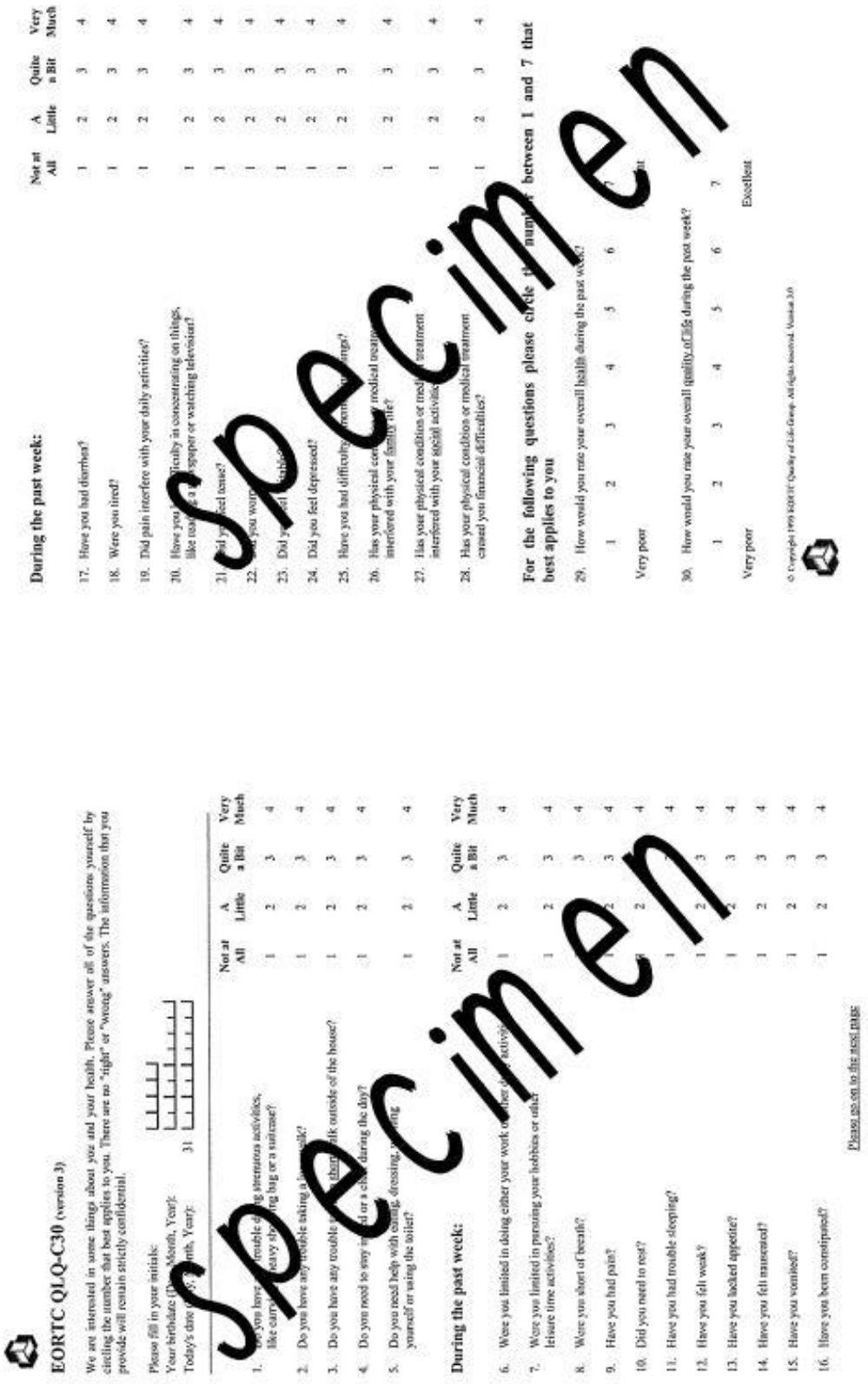
Appendix 1: EORTC QLQ-C30



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you found it difficult to concentrate on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 2: EORTC QLQ-GI.NET21

ENGLISH

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31. Did you have hot flushes?		1	2	3	4
32. Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
33. Did you have night sweats?		1	2	3	4
34. Did you have abdominal discomfort?		1	2	3	4
35. Did you have a bloated feeling in your abdomen?		1	2	3	4
36. Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
37. Have you had acid indigestion or heartburn?		1	2	3	4
38. Have you had difficulties with eating?		1	2	3	4
39. Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
40. Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
41. Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
42. Were you concerned about disruption of home life?		1	2	3	4
43. Have you worried about your health in the future?		1	2	3	4
44. How distressing has your illness or treatment been to those close to you?		1	2	3	4
45. Has weight loss been a problem for you?		1	2	3	4
46. Has weight gain been a problem for you?		1	2	3	4
47. Have you been worried about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
48. Have you had aches or pains in your muscles or bones?		1	2	3	4
49. Did you have any limitations in your ability to travel?		1	2	3	4
During the past four weeks:					
50. Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
51. Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4

Appendix 3: Karnofsky Performance Status (KPS) Scale

The performance status is an attempt to quantify cancer patients' general well-being and activities of daily life. This study uses the performance status scale according to Karnofsky and Burchenal, 1949. Table 8 shows definition of scales in relation to ECOG score.

Table 8: Karnofsky Performance Status (KPS) Scale

KPS scale [%]	ECOG score	Definition
100	0	Normal; no complaints; no evidence of disease.
90	0	Able to carry on normal activity; minor signs or symptoms of disease.
80	1	Normal activity with effort; some signs or symptoms of disease.
70	1	Cares for self; unable to carry on normal activity or to do active work.
60	2	Requires occasional assistance, but is able to care for most of his personal needs.
50	2	Requires considerable assistance and frequent medical care.
40	3	Disabled; requires special care and assistance.
30	3	Severely disabled; hospital admission is indicated although death not imminent.
20	4	Very sick; hospital admission necessary; active supportive treatment necessary.
10	4	Moribund; fatal processes progressing rapidly.
0	5	Dead

Appendix 4: Afinitor Dose Adjustment Recommendations

(see Afinitor®, current version of local product information for the countries participating in this study)

Table 9: Afinitor Dose Adjustment Recommendations

Adverse reaction	Severity1	Afinitor dose adjustment
Non-infectious pneumonitis	Grade 2	Consider interruption of therapy until symptoms improve to Grade ≤1. Re-initiate treatment at 5 mg daily. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3	Interrupt treatment until symptoms resolve to Grade ≤1. Consider re-initiating treatment at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment.
Stomatitis	Grade 2	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate treatment at 5 mg daily.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at 5 mg daily.
	Grade 4	Discontinue treatment.
Other non-haematological toxicities (excluding metabolic events)	Grade 2	If toxicity is tolerable, no dose adjustment required. If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at same dose. If toxicity recurs at Grade 2, interrupt treatment until recovery to Grade ≤1. Re-initiate treatment at 5 mg daily.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Consider re-initiating treatment at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment.
Metabolic events (e.g. hyperglycaemia, dyslipidaemia)	Grade 2	No dose adjustment required.
	Grade 3	Temporary dose interruption. Re-initiate treatment at 5 mg daily.
	Grade 4	Discontinue treatment.
Thrombocytopenia	Grade 2 (<75, ≥50x109/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x109/l). Re-initiate treatment at same dose.
	Grade 3 & 4 (<50x109/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x109/l). Re-initiate treatment at 5 mg daily.
Neutropenia	Grade 2 (≥1x109/l)	No dose adjustment required.
	Grade 3 (<1, ≥0.5x109/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x109/l). Re-initiate treatment at same dose.
	Grade 4 (<0.5x109/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x109/l). Re-initiate treatment at 5 mg daily.
Febrile neutropenia	Grade 3	Temporary dose interruption until recovery to Grade ≤2 (≥1.25x109/l) and no fever. Re-initiate treatment at 5 mg daily.
	Grade 4	Discontinue treatment.
1 Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03		

Special populations:

Elderly patients (≥65 years)

- - No dose adjustment is required (see Section 5.2 of the original document),

Renal impairment

- No dose adjustment is required (See Section 5.2 of the original document)

Hepatic impairment

- Mild hepatic impairment (Child-Pugh A) – the recommended dose is 7.5 mg daily.
- Moderate hepatic impairment (Child-Pugh B) – the recommended dose is 5 mg daily.
- Severe hepatic impairment (Child-Pugh C) – Afinitor is only recommended if the desired benefit outweighs the risk. In this case, a dose of 2.5 mg daily must not be exceeded.

Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment (see also Sections 4.4 and 5.2 of the original document).

Appendix 5: Tumour Scoring

SSTR positive is defined as: “lesions need to show adequate tracer uptake, defined as being clearly differentiable from background” (SSTR positive)”

Examples for ^{111}In-pentetreotide (OctreoScan®) for clearly differentiable from background are given in Figure 5. All lesions show increased uptake compared to surrounding tissue and will be considered SSTR positive. In Figure 6, liver lesions identified with III and IV are considered SSTR positive. Lesion defined with II would be SSTR negative.

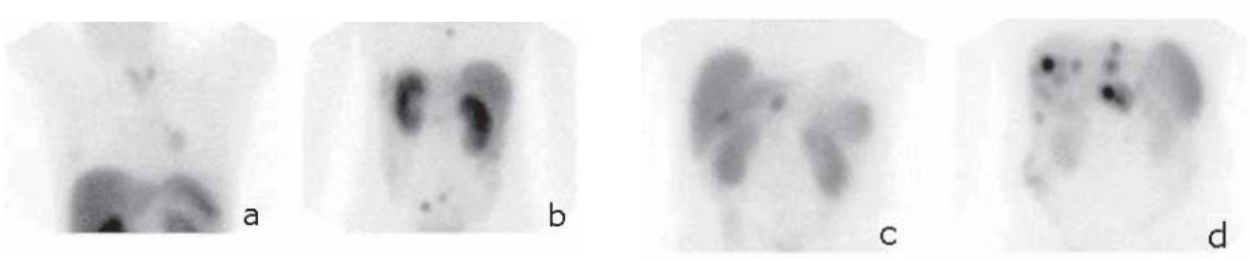


Figure 5: ^{111}In-pentetreotide-positive lesions

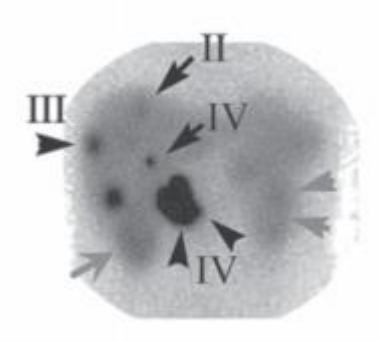


Figure 6: ^{111}In-pentetreotide example of Liver Lesions

The same approach applies for ^{68}Ga-Dotatate, and other ^{68}Ga-labelled PET imaging agents as well as ^{64}Cu-Dotatate: the lesions are identified by increased uptake compared to surrounding tissue. This evaluation should first be performed on ^{68}Ga-Dotatate MIP image data (Figure 7), and axial views can be looked at for further details.

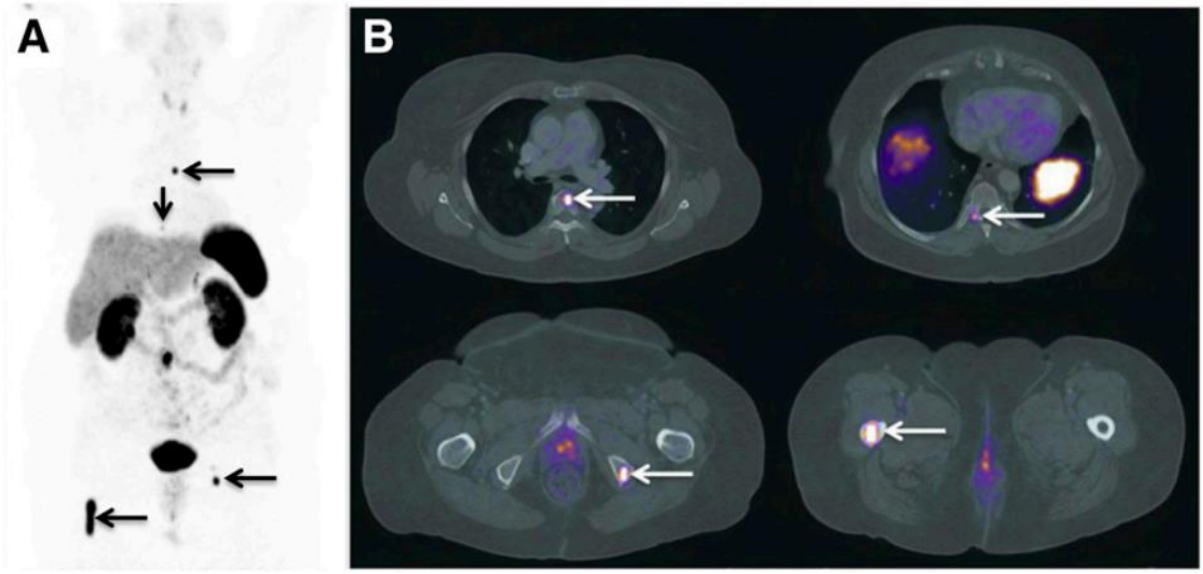


Figure 7: ^{68}Ga-Dotatate MIP

Examples can be found in Figure 7 (arrows indicate SSTR positive lesions) and Figure 8 (A: no lesion uptake; to be classified as SSTR negative, B and C: increased uptake; to be classified as SSTR positive).

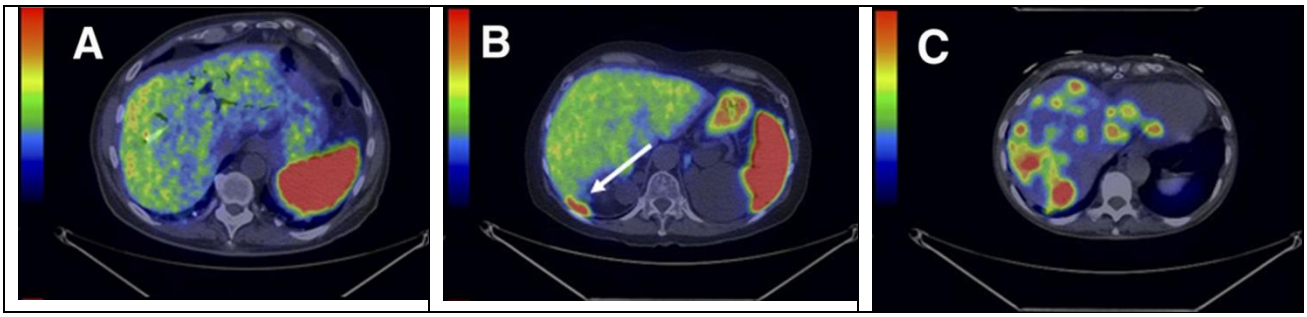


Figure 8: ^{68}Ga-Dotatate examples. A) negative, B) and C) positive

For ^{64}Cu-Dotatate, an example can be found in Figure 9 showing multiple small liver metastases (>10), peritoneal solitary tumour mass, and 3 lymph node metastases shown on ^{64}Cu-DOTATATE PET/CT in patient with pancreatic NET. All findings on PET were confirmed to be true-positive (Pfeiffer et al., 2015). Figure 10 shows an example of patient with intestinal NET and multiple metastases (Johnbeck et al., 2017).

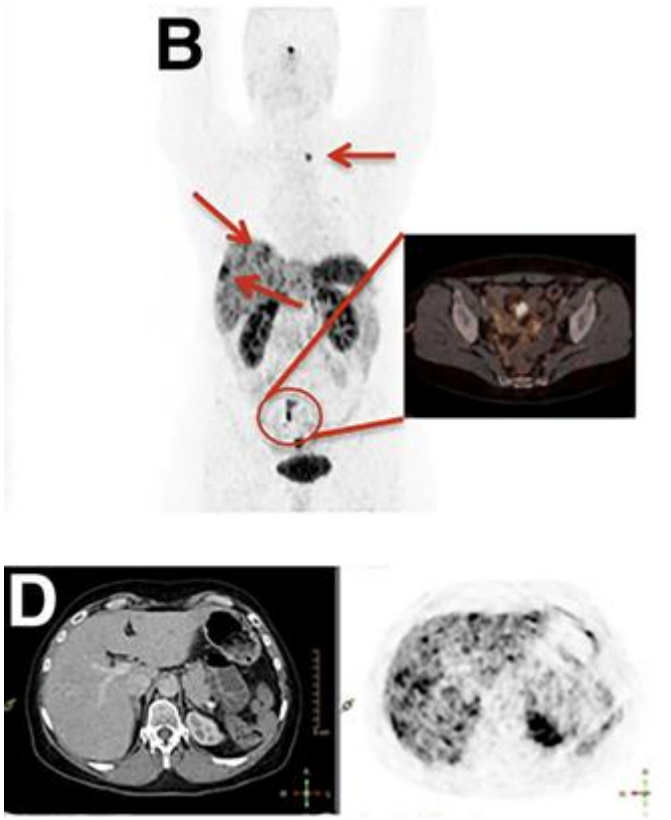


Figure 9: ^{64}Cu-Dotatate examples (B) ^{64}Cu-DOTATATE maximum-intensity-projection image with arrows pointing at liver and lymph node metastases. Insert is fused PET/CT of peritoneal solitary tumour mass. (D) Axial CT and PET of liver revealing several small liver metastases.

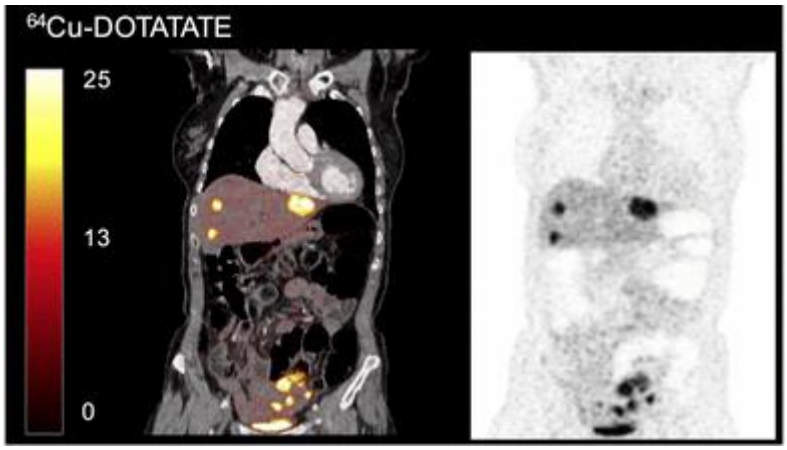


Figure 10: ^{64}Cu-Dotatate example PET/CT (left) and PET (right) scans of patient with intestinal NET and multiple metastases.

Detailed descriptions of the evaluation will be included in the Subject Imaging Manual.

Figure 5 and Figure 6 reference: IAEA 2013 - Includes bibliographical references. 1. Nuclear medicine. 2. Neuroendocrine tumors. 3. Radioisotopes -Therapeutic use. I. International Atomic Energy Agency. II. Series.

Figure 7 reference: Bodei et al., 2017

Figure 8 reference: Velikyan et al., 2014

Figure 9 reference: Pfeiffer et al., 2015

Figure 10 reference: Johnbeck et al., 2017