STATISTICAL ANALYSIS PLAN

Project 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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3.0	06-Apr-2022	Updated to comply with last Protocol amendment and FDA feedback as well as to clarify some analyses. Statistical lead and CRO changed.	[redacted]
4.0	13-Jan-2025	Updated French rollover study Analysis of SSA Impact Analysis of Covid Impact Forest plot for PFS and OS subgroup analysis	[redacted]

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Abbreviations and Definitions

^{177}Lu-Edo	^{177}Lu-edotreotide, ^{177}Lu-DOTATOC
AD	Absorbed dose
ALT	Alanine transaminase
AP	Alkaline phosphatase
AST	Aspartate transaminase
CgA	Chromogranin A
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CR	Complete response
CT	Computed tomography
DC	Disease control
DCR	Disease control rate
DDC	Duration of disease control
EDC	Electronic data capture
EOS	End of study
FAS	Full analysis set
Gamma-GT	Gamma glutamyl transferase
GE-NET	Gastroenteric NET
GEP-NET	Gastroenteropancreatic NET
GFR	Glomerular filtration rate
Gy	Grey
HRQL	Health related quality of life
ITT	Intent-To-Treat
IMP	Investigational medicinal product
KPS	Karnofsky performance scale
Max	Maximum
MDRD	Modification of diet in renal disease
Min	Minimum
mNET	Metastasised Neuroendocrine Tumours
mOS	Median overall survival

mPFS	Median progression-free survival
MRI	Magnet resonance imaging
NET	Neuro-endocrine Tumours
OR	Overall response
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
P-NET	Pancreatic NET
PP	Per Protocol
PR	Partial response
PRRT	Peptide Receptor Radiotherapy
PT	Preferred term
Q25	25% Quartile
Q75	75% Quartile
RECIST	Response criteria in solid tumours
RMST	Restricted Mean Survival Time
RP	Reference product
RPSFT	Rank preserving structural failure time
SAF	SAFety analysis set
SD	Stable disease
SOC	System organ class
SPECT	Single-photon emission computed tomography
SPSS	Statistical package for social sciences
SRI	Somatostatin receptor imaging
SSA	Somatostatin analogues
SSTR	Somatostatin receptors
TER	Tubular extraction rate
ULN	Upper limit of normal

1 Introduction

1.1 Preface

^{177}Lu-Edo (^{177}Lu-edotreotide, ^{177}Lu-DOTATOC) is an oligopeptide targeting somatostatin receptors (SSTR) which is over-expressed in certain tumour entities. ^{177}Lu-Edo is used for peptide receptor radiotherapy (PRRT) of patients with metastasised Neuroendocrine Tumours (mNET).

The purpose of the present study is to evaluate efficacy and safety of PRRT with 177Lu-edotreotide in patients with metastatic GEP-NET, in comparison to established medical therapy, using a prospective randomised controlled trial design. Everolimus (Afinitor®) was selected as the comparator. It is a drug licensed for the treatment of unresectable or metastatic, well or moderately differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease which, more recently, was also approved 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 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.

Please refer to Section 1 of the current protocol for more details.

1.2 Purpose of the analyses

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-NETs, compared to everolimus.

See Section 2 of the current protocol for further details.

2 Study Objectives and Endpoints

The following study objectives and endpoints are defined. Please also refer to Section 2 of the current protocol.

2.1 Study Objectives

2.1.1 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-NETs, compared to everolimus.

2.1.2 Secondary objectives

Key secondary objectives 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

Other, exploratory secondary objectives 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, 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, Karnofsky Performance Score (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

2.1.3 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

2.2 Endpoints

In the following sections, the study endpoints are described in detail (see protocol section 3.2).

2.2.1 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.

For the purpose of the main confirmatory PFS analysis, central blinded image readings in duplicate, with appropriate adjudication in case of discordance will be used. Local assessments will be presented in sensitivity analysis.

2.2.2 Key secondary endpoints

Key secondary endpoints are

- objective response rates (ORR), defined as the proportion of patients achieving partial response (PR) or complete response (CR) as best outcome

For the purpose of the main confirmatory ORR analysis, central blinded image readings will be used. Local assessments will be presented in sensitivity analysis.

- overall survival (OS) defined as the time from date of randomisation until death

2.2.3 Other secondary/exploratory endpoints

Exploratory analyses will be performed on

- patient and tumour characteristics,
- degree of ^{177}Lu-edotreotide uptake as possible predictors of PRRT efficacy.

2.3 Derived variables

Raw data will be provided in CDISC STDM format, and analysis variables including derived variables will be supplied in CDISC AdaM format following the most recent CDISC Implementation Guides.

3 Study Methods

3.1 General Study Design and Plan

Phase: III, multi-centre

Study configuration and experimental design: confirmatory, prospective, parallel group

Type of control: active drug

Blinding: open-label

Treatment assignment: 300 GEP-NET patients 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).

Duration: Baseline: day -90 to -1

Randomisation: day -28 to -1

Treatment and study procedures: month 0 to 30, or until progression or withdrawal – whichever occurs earlier

EOS: month 30 or at progression or drop-out - whichever occurs earlier

Collection of survival and local disease progression data as well as information on further tumour treatments will be continued after EOS during the long-term follow-up.

Please refer to Section 3.1 of the current protocol for more details.

3.2 General Study 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.

For more details about Inclusion/Exclusion criteria please refer to the current version of the protocol Section 4.2.

3.3 Randomisation and Blinding

Randomisation will be stratified using four independent randomisation lists to control for the two following critical baseline covariates:

A central web-based randomisation system will be used.

Block size: 6 (4 with ^{177}Lu-edotreotide and 2 with everolimus)

System used to generate random lists: BiAS V11.0 (2015)

System used to randomise patients: Clindex EDC (Clindex 4.3.0.132R)

Due to the nature (radioactive vs. non-radioactive) and the administration schemes of investigational and comparator drugs, a blinded design was not possible. However, the RECIST 1.1 evaluation used for the main analysis of the RECIST-based endpoints will be performed centrally and blinded to the treatment arm.

3.4 Study Variables

3.4.1 Primary Variable

Progression-free survival

Progression-free survival will be determined starting from randomisation until the date of an event (PD or death). For the primary analysis, any withdrawal (or drop-out) before EOS visit at month 30 will be censored. Patients who have not shown progression at the end of the study (30 months) will also be censored.

In more details, the following rules will be applied for the main PFS analysis:

Table 1: PFS analysis rules

Situation	Date of Progression or Censoring	Outcome
Tumour progression or death	Earliest date of PD or death	Event (PD or Death)
No tumour progression and not death	Date of last adequate* radiological assessment	Censored
Unless:		
No baseline radiological tumour assessment	Date or randomisation	Censored
No adequate post-baseline radiological assessment and date of death, if any, is after 2 or more scan intervals following randomization**	Date of randomisation	Censored
New anticancer treatment started prior to tumour progression or death (whichever is earlier)	Date of the last adequate radiological assessment prior to start of new anticancer treatment or date of randomization (whichever is later)	Censored
Tumour progression or death documented immediately after 2 or more consecutive missing scan** following last adequate radiological tumour assessment or randomization (whichever is later).	Date of last adequate radiological tumour assessment or date of randomisation (whichever is later).	Censored

Table footnotes:

**Adequate radiological tumour assessment refers to an assessment with one of the following responses: CR, PR, SD, or PD.*

***The interval is higher than 2 times the maximal protocol scheduled RECIST 1.1 assessment interval (i.e. >222 days = 2*(90+21))*

For primary endpoint (PFS) main analysis, post-randomisation tumour assessment based on blinded central review compare to baseline will be used.

Where appropriate, sensitivity analyses will explore the impact of the chosen approaches and data issues observed during the blind review on the study results. These could include but not limit to:

- Blinded central RECIST 1.1 evaluation (main analysis) vs. Local RECIST assessments
- Applied main PFS censoring rules (main analysis, see Table above) vs. different approaches (e.g. next scheduled assessment date instead of date of radiological

assessment showing progression if in between scheduled assessments; events instead of censoring after two consecutive missed radiological assessments, etc.)

- Drop-out pattern influence on study results, including patient's End of Study at 30 months (from Protocol version 4.0 onwards, including re-consenting) vs. 24 months (before version 4.0, not re-consenting)
- Discrepancies in screening/eligibility status (prior to randomisation) between local and central assessments

3.4.2 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 after EOS.

The main analysis of OS must take into consideration new anti-cancer treatment starts and/or treatment switches if a high proportion (i.e. ≥33%) of patients in the control arm started new-anticancer treatment or received subsequent PRRT treatment.

3.4.3 Other Secondary Variables

3.4.3.1 Exploratory Efficacy Parameters

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 response (PR), complete response (CR), and stable disease (SD)

e) Duration of disease control (DDC), will be calculated only in patients who achieve CR, PR or stable disease (SD) as the period from the time point of first establishment of stable disease (or better) until a new diagnosis of morphological progression per RECIST 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 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 (CgA, specific hormones) tumour response, classified as SD, PR, CR, or PD can be investigated, as well as the duration of such response

As an example, in patients with an elevated baseline biomarker, changes in biomarker 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% from nadir or decrease by <50% from baseline; biomarker progressive disease (PD): increase by ≥25% from previous observation nadir.

3.4.3.2 Safety and Tolerability Parameters

a) Tubular extraction rate (TER), percentage depart from baseline value
b) 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)

3.4.3.3 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 randomization to first HRQL deterioration

See HRQL definition details in Section 9.

3.4.3.4 Dosimetry

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

Cumulative absorbed dose (in Gy) of ^{177}Lu-edotreotide to target tumour lesions and kidneys, 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/or hybrid (2D/3D) dosimetry.

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

3.4.3.5 Pharmacokinetics (Sub-Study C)

a) Urine radioactivity in percentage of injected radioactivity (%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

4 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 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).

Based on this historically-assumed treatment effect, a two-sided logrank test with an overall sample size of N= 51 patients (31 events; randomised 1 : 2, N1=17 subjects in the everolimus group and N2=34 subjects in the 177Lu-edotreotide group) would achieve a 80% power at a 5% significance level to detect a hazard ratio (HR) of 0.3667 when the everolimus group median progression free survival time is 11 months and the ^{177}Lu-edotreotide group median progression free survival time is 30 months or above.

The differences in progression free survival amount to 33% (50% vs. 83%) at 11.0 months, which is the mPFS for everolimus, and 30% (32% vs. 62%) at 18.0 months, showing consistency with advancing study time. Based on this, a conservative average difference of at least 25% is assumed, which corresponds to a survival benefit of approximately 11 months for ^{177}Lu-edotreotide over everolimus.

Figure 1 shows the Kaplan Meier estimates of PFS reported for everolimus and ^{177}Lu-edotreotide in NET patients.

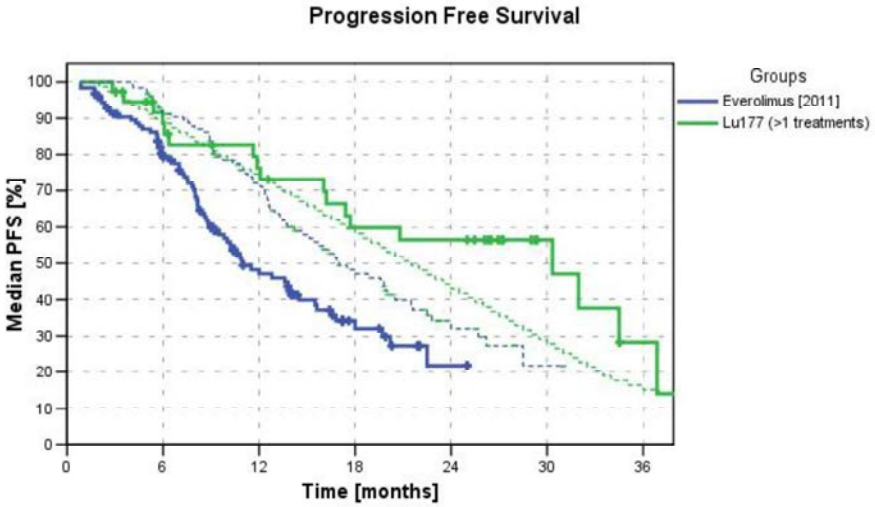


Figure 1: PFS for everolimus and 177Lu-edotreotide in GEP-NET

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

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 visualize, the dotted blue curve 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:

With regard to PFS, a two-sided logrank test with an overall sample size of N=242 subjects (180 events; randomised 1 : 2, N1=80 subjects [68 events] in the everolimus group and N2=162 subjects [112 events] in the ^{177}Lu-edotreotide group) achieves 80% power at a 5% significance level to detect a hazard ratio (HR) of 0.6471 when the everolimus group median survival time is 11 months (i.e., a difference of an additional 6 months in the ^{177}Lu-edotreotide group). 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.

With regard to overall response rates, group sample sizes of 200 in the ^{177}Lu-edotreotide group and 100 in the everolimus group achieve 89% power to detect an odds ratio between the group ORRs of 4.2 (that corresponds to rates of 5% and 18%). The proportion in the ^{177}Lu-edotreotide group is assumed to be 5% 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 (198 events; randomised 1 : 2, N1=100 subjects [76 events] in the everolimus group and N2=200 subjects [122 events] in the ^{177}Lu-edotreotide group) achieves 80% power at a 5% significance level to detect a hazard ratio (HR) of 0.660 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 after EOS for all patients. The study duration was planned to last 48 months during which patient recruitment would take place in the first 24 months. The post-study follow-up period will then continue for another 5 years (60 months).

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 31 events) and minimal clinically relevant PFS difference (which would need 180 events).

In case a difference of 11 months in median PFS is observed (m1=11 months versus m2=22 months) the sample size also allows confirmation of PFS improvement for ^{177}Lu-edotreotide relative to reference treatment. This would need a total number of:

- 205 events (E1=84 events in the everolimus group and E2=121 events in the ^{177}Lu-edotreotide group) with a power of about 99% and a two-sided level of significance of 1%
- or 156 events with a power of about 99% and a two-sided level of significance of 5%.
- or 67 events with a power of about 80% and two-sided level of significance of 5%.

In conclusion, the trial sample size of 300 randomized patients associated with the interim analysis plan at 90, 135 and 180 events (See Section 5.7) will allow to cover all the possible treatment effect assumptions at an overall two-sided alpha of 0.05 and with acceptable power (i.e. ≥80%; see Table 2).

Table 2: summary of PFS primary endpoint sample size assumptions

	Minimal clinically relevant difference	Historical treatment effect	Expected treatment effect		
Median PFS IMP	17	30	22		
Median PFS control	11	11	11		
Number of PFS events needed	180	31	67	156	205
Sample size (2:1)	242 (300 with dropout rate)	51	300		
Power	80%	80%	80%	99%	99%
Alpha two sided	0.05	0.05	0.05	0.05	0.01

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

5 General Considerations

5.1 Timing of Analyses

Statistical analysis will be performed after the last patient has completed the study primary endpoint according to the interim and final analysis plan (see Section 5.7) after the database was checked, cleaned and appropriately locked.

5.2 Analysis Populations

5.2.1 Full Analysis Population (Full Analysis Set)

The Full Analysis Set (FAS) set 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. FAS patients who have inadequate data post-baseline to assess efficacy according to the criteria for response or who dropped out before 30 months follow up (without appropriate PD or death event) will be considered censored for analysis of PFS on the date of the last adequate tumour assessment prior to withdrawal (See Section 3.4.1 for more details).

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

5.2.2 Per Protocol Population

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).

The PPS set is defined as:

- All patients with no serious protocol deviation determined before statistical analysis plan finalisation

Serious protocol deviations are defined as those that could impact the efficacy or safety evaluations, as well as data integrity and will be specified in section 6.2, Protocol Section 9.3.3.2 and protocol deviation plan.

5.2.3 Safety Population

Safety Analysis set (SAF)

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

5.2.4 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 sub-study variables will only be analysed based on the population of patients who actually participated in the corresponding sub-study.

5.3 General Statistical Methods

Statistical analyses will be performed after the data base was appropriately locked.

All data from the CRF and other study and measurement documents will be analysed. Continuous parameters will be summarised using descriptive statistics (number, mean, standard deviation, minimum, median, maximum) and categorical parameters 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 5.7).

Exploratory statistical hypothesis tests will be used at a significance level of 0.05 (two-sided) 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 Section 5.5). 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 results based on the complete data set, differences will be discussed.

5.4 Covariates and Subgroups

To enable a meaningful subgroup analysis randomisation will be stratified for primary tumour origin with a sufficient number of

- GE-NETs and
- P-NETs

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.

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

In this trial patients with histologically and clinically confirmed diagnosis of well-differentiated neuro-endocrine tumour of

- non-functional gastroenteric origin (GE-NET) or
- 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. 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.

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

In the present trial both,

- treatment naive (1st line), and
- patients having 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 2nd line patients will be differentiated into chemotherapy, SSA, targeted therapy (e.g. sunitinib), and others.

5.4.3 Tumour grade (G1 vs. G2), KI-67 and KPS/ECOG

Tumour grade, KI-67, and baseline clinical status, determined using the KPS/ECOG are suspected to be further relevant baseline co-variates, which should be investigated at the time of analysis.

5.4.4 Other Characteristics

Summary tables and/or listings will be provided for demographics and other baseline characteristics, including the above-mentioned variables and:

- 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
- HRQL scores at baseline (QLQ C30 and GI.NET21 questionnaires)
- Change of inclusion criteria (protocol version 2.2 amendment 2) based on record in CRF.

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 the analysis will be investigated including with stratified methods if appropriate.

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

Cox proportional hazard model will be used for PFS and OS to explore treatment effect within each subgroup. And forest plots (including p-value and 95 % confidence interval) of hazard ratios for PFS and OS will be presented. The pre-specified subgroups are:

- primary tumour origin (GE-NET vs. P-NET),
- prior medical treatment (1st line vs. 2nd line),
- tumour grade (G1 vs. G2) based on local assessment for baseline
- baseline KPS (70, 80, 90 and 100)
- Received SSA prior to baseline or not
- Received SSA prior to baseline and did not stop prior baseline
- Change of inclusion criteria (protocol version 2.2 amendment 2) based on record in CRF.

5.5 Missing Data

In general, missing values will be treated as such, no imputation will be performed. The number of missing values will be reported.

Missing information about tumour response at EOS will be censored on the day of the last available adequate assessment or at randomisation (See Section 3.4.1 for full censoring rule details).

Missing HRQL data will be handled according to the QoL questionnaire manuals.

Regarding partial dates, imputation was done as follows by the data management team directly in the clinical database according to the data management plan (version 2.0):

Partial dates were only imputed in the clinical database for the following dates where at least the year was provided:

- Medical history (MH) and Surgical history (SH) start and stop dates
- Previous Therapy/Post study Follow up treatment
- Tumour Histology
- AE start and resolution dates
- Concomitant Medication
- Somatostatin analogues medication

Incomplete dates in other fields resulted in a query being raised. The imputations derived for the above-mentioned dates were conducted as follows:

- Missing days defaulted to the first of the month for start dates and the last day of the month for stop dates.

- Missing months defaulted to the first month (January) for start dates and to the last month (December) for stop dates.
- There was no default for a missing year field.

Incomplete or incorrect times resulted in a query being raised. The imputations derived for confirmed unknown times were as follows: Unknown times defaulted to 00:00.

5.6 Baseline Definition

Unless stated otherwise:

- for demographic parameters, tumour assessment, QoL, biomarkers and in general all efficacy related variables, baseline is defined as the last non-missing measurement on or prior to randomisation date.
- for lab, vital signs and in general all safety related variables, baseline is defined as the last non-missing measurement prior to first dosing of study treatment.

5.7 Interim Analyses and Multiple Testing

Per the Protocol, a three-stage group sequential design, including two interim analyses to assess the primary efficacy endpoint (Progression Free Survival: PFS) after 90 and 135 PFS events have occurred will be performed, using an O'Brien Fleming alpha spending approach.

To take multiple testing into account, i.e. to keep the overall alpha level of 5%, the primary and key secondary endpoints will be tested in a strictly hierarchical procedure:

The primary endpoint (PFS) will be tested using O'Brien-Fleming type boundaries applied on the information time point as presented in the table below first.

Table 3: PFS interim analysis information time points and significant thresholds

	First PFS Interim Analysis	Second PFS Interim Analysis	Final PFS Analysis
Conducted after	90 PFS events occurred	135 PFS events occurred	180 PFS events occurred*
Two-sided Local Significance Level according to O'Brien Fleming alpha spending	0.0031	0.0183	0.044
Upper critical boundary according to O'Brien Fleming alpha spending	2.963	2.359	2.014

** Or all randomized patients reach EOS*

Note: Calculations were made using the "rpact" R package developed according to the methods described in the monograph by Wassmer and Brannath (2016).

If the PFS test results in a significant p-value (i.e. p< x.xxx, see the table above for significance levels at each interim analyses), a confirmatory test for the ORR will be performed with a similar approach using O'Brien-Fleming type boundaries calculated extemporaneously based on the number of evaluable patients at the time of the interim analysis compared to the 300 patients to be randomised (see examples of different possible scenarios at the first PFS interim analysis in Table 4 below). Otherwise the test for ORR is considered exploratory.

Table 4: Examples of O'Brien-Fleming type boundaries calculated for the first interim analysis time point of the ORR

Number of Randomised patients evaluable in the ORR analysis at the first significant PFS interim analysis	100	150	180	200	220	230	240	250	280	300
Information time point (basis: 300 randomised patients)	33.3%	50.0%	60.0%	66.7%	73.3%	76.7%	80.0%	83.3%	93.3%	100.0%
Two-sided Local Significance Level according to O'Brien Fleming alpha spending	0.0002	0.0031	0.0076	0.0121	0.0177	0.0209	0.0244	0.0282	0.0407	0.05
Upper critical boundary according to O'Brien Fleming alpha spending	3.711	2.963	2.669	2.509	2.371	2.309	2.250	2.195	2.047	1.96

Note: The actual critical boundaries for ORR will be calculated at the time of the interim analysis according to the number of randomised patients evaluable for ORR over an estimated total 300 patients to be randomised. Calculations were made using the "rpact" R package developed according to the methods described in the monograph by Wassmer and Brannath (2016).

A confirmatory test for OS will only be performed if both previous tests (i.e. PFS and ORR) resulted in significant p-values. The actual O'Brien-Fleming type critical boundaries for OS will be calculated at the time of interim according to the number of OS events actually observed over an estimated total of 198 death events (See examples of different scenarios in the table below). Otherwise, the test for OS is considered exploratory.

Table 5: Examples of O'Brien-Fleming type boundaries calculated for the first interim analysis time point of OS

Number of OS events observed at the first significant PFS and ORR interim analysis	20	30	35	40	45	50	60	70	80	90
Information time point (Basis: 198 OS events)	10.1%	15.2%	17.7%	20.2%	22.7%	25.3%	30.3%	35.4%	40.4%	45.5%
Two-sided Local Significance Level according to O'Brien Fleming alpha spending	<1E-07	<1E-07	1.96E-07	1.23E-06	5.16E-06	1.64E-05	9.33E-05	0.0003	0.0008	0.0018
Upper critical boundary according to O'Brien Fleming alpha spending	6.956	5.640	5.203	4.851	4.558	4.310	3.907	3.593	3.338	3.126

Note: The actual critical boundaries for OS will be calculated at the time of the interim analysis according to the number of OS events observed over an estimated total 198 deaths. Calculations were made using the "rpact" R package developed according to the methods described in the monograph by Wassmer and Brannath (2016).

The tests on variables other than PFS, ORR, and OS will only be considered exploratory and performed on 5% significance levels.

The interim results sharing policy and procedure is described in the Interim Analysis Result Sharing Plan attached to this SAP.

5.8 Multi-centre Studies

Individual centre results will not be summarised. In doubt of underlying centre effects, they may be explored where deemed appropriate or necessary.

6 Summary of Study Data

Progression-free survival (PFS), overall survival (OS), and other time-to-event data will be analysed using the Kaplan-Meier method, the Cox's proportional Hazard model (for hazard ratio computation) and the Log-rank test (stratified for the main analysis, non-stratified on randomization factors where needed for sensitivity analysis).

For OS, the main analysis will take into consideration new anti-cancer treatment starts and/or treatment switches if a high proportion (≥33%) of patients in the control arm started new anti-cancer treatment or received subsequent PRRT treatment. In this case the main OS analysis would be conducted treating treatment as time-dependent variable and sensitivity analyses

would include Rank preserving structural failure time (RPSFT), Intent To Treat and censoring at time of switch.

Cox proportional hazard regression will also be used when adjusting for the co-variates

- primary tumour origin (GE-NET vs. P-NET),
- prior medical treatment (1st line vs. 2nd line),
- tumour grade (G1 vs. G2)
- baseline KPS (70, 80, 90 and 100),

The same covariates can be used for subgroup analyses as deemed appropriate and necessary. Other baseline characteristics such as but not limited to:

- Age (continuous or <65 vs. ≥65 or <75 vs. ≥75)
- Gender (M vs. F)
- Ethnic origin (White/Caucasian vs. others)
- ECOG (recalculated: 1=KPS 70 or 80 vs. 0=KPS 90 or 100)
- Time from primary diagnosis (continuous in months)
- Time from diagnosis of progression (continuous in months)
- Chromogranin A at baseline (continuous or >2*ULN vs. ≤2*ULN)
- Alkaline Phosphatase at baseline (continuous or >ULN vs. ≤ULN)
- BMI (continuous or ≤21 vs. 22 to 27 vs. >27)
- P-NET functioning status
- site of metastases (e.g. extra-hepatic vs. no extra-hepatic)
- Received SSA prior to baseline
- Received SSA prior to baseline and continue during treatment period

etc.

can also be used for subgroup analysis and/or Cox proportional Hazard regression with stepwise approach as deemed appropriate.

For time-to-event endpoint (PFS, OS), the proportional hazard assumption will be examined using appropriate method(s) including graphical diagnostics and/or statistical tests where needed.

In case of unequivocal non-proportional hazards (e.g. crossing survival curves), the main time-to-event analysis can be rather based on Restricted Mean Survival Time (RMST) approach in addition to Log-rank and Cox model. Alternatively, this approach can be used as sensitivity analysis to further investigate the results patterns where deemed appropriate.

The unstratified RMST analysis will be used if there is at least one strata with either:

1) too few participants to comparatively analyse;
2) no participant followed up for long enough to make a proper comparison

Continuous parameters:

Will be summarized using standard summary statistics as appropriate (n, mean, standard deviation, minimum, 25th percentile, median, 75th percentile and maximum). Corresponding 95% CIs may be presented where meaningful.

Ordinal and categorical variables:

Summary statistics will include

- frequency counts and percentages.
- corresponding 95% confidence interval may be presented where meaningful.

Non-parametric methods will be used for comparison between study groups or subgroups (Mann-Whitney U test), changes within groups (Wilcoxon test) or percentages (Chi^2 test/Fisher's exact test).

Statistical tests will be stratified for the main analyses (e.g. stratified log-rank test for time to event comparisons, Mantel Haenszel test for percentage comparisons) but appropriate corresponding non-stratified tests can be used where deemed necessary for sensitivity analysis purposes.

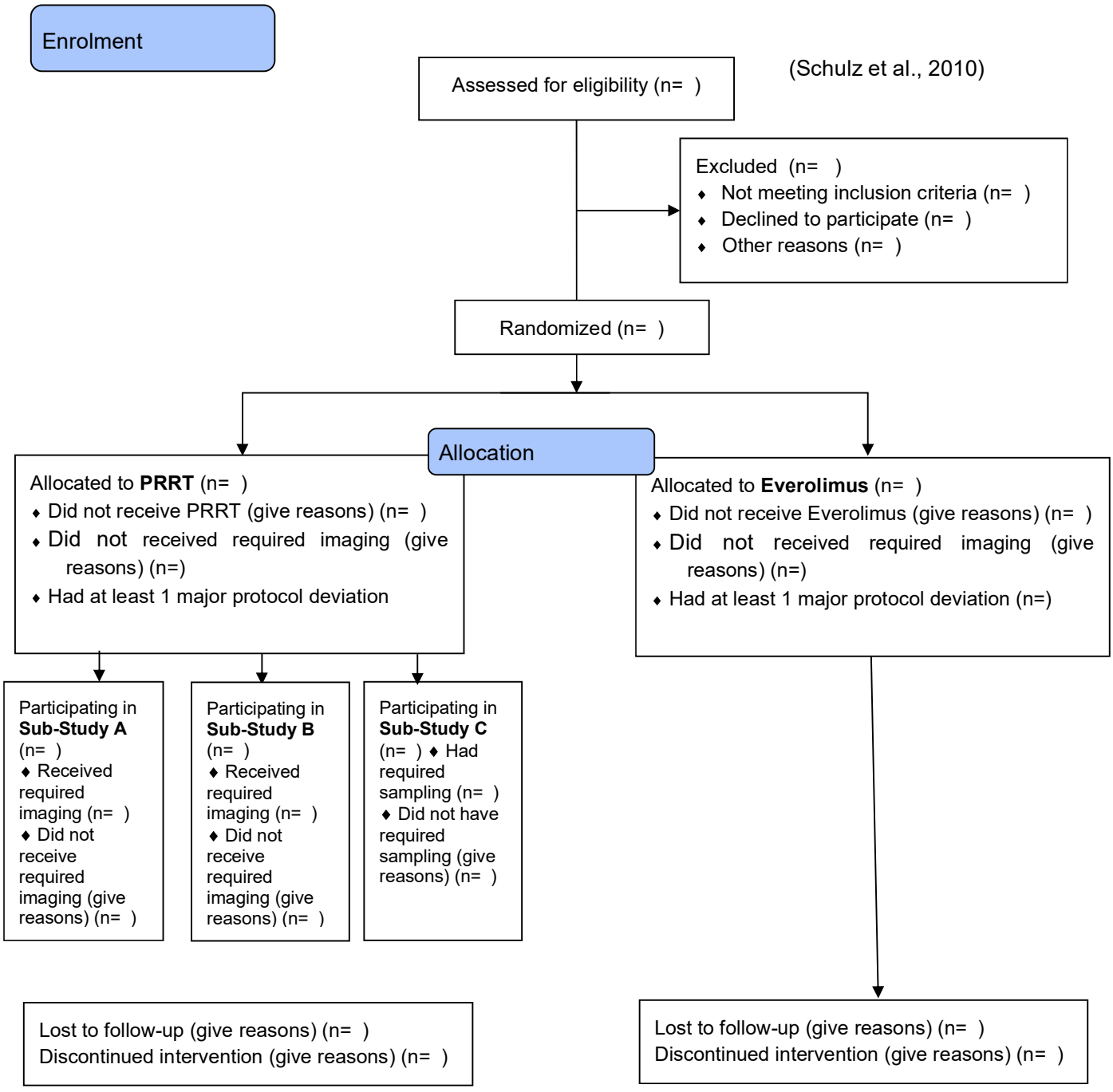
Other variables will be analysed descriptively or by means of frequency tables.

All data of the clinical database will be listed, summaries will be provided for at least the primary and secondary efficacy endpoints and for the safety endpoints.

6.1 Subject Disposition

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

Flow Diagram according to CONSORT 2010



6.2 Protocol Deviations

As per current protocol (see Protocol Section 9.3.2), for the study arms at least the following protocol deviations are defined as major protocol deviations which should lead to PP set exclusion

- ^{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 doses 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 protocol Section 5.4.2).

Decisions on all Serious Protocol deviations which lead to PP set exclusion will be taken on an ongoing basis according to the Protocol Deviation Plan, confirmed at the blind data review meetings and finalised before analysis. Protocol deviations and the resulting exclusions from the PP set will be summarised and listed in a frequency distribution table.

6.3 Demographic and Baseline Variables

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

- Primary tumour origin
- Prior medical treatment
- Tumour grade, KI-67 and KPS/ECOG (reclassified: ECOG 1=KPS 70 or 80 and ECOG 0=KPS 90 or 100)
- 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
- Histological entity, functional state
- HRQL scores at baseline (QLQ C30 and GI.NET21 questionnaires)

For all variables of the population characteristics, p values will be derived by using non-parametric statistical tests to compare both treatments at baseline on a purely descriptive level (“homogeneity tests”; except for detailed physical exam, medical/surgical history and prior/concomitant medication).

6.4 Concomitant Diseases and Medical Conditions

MedDRA coding for this study will be started with version 19.1 or 20.0, based on the time of the first AE, and updated with every MedDRA release. The following data will be coded:

- Adverse Events
- Medical History
- Surgical History

These data will be summarised in tables and listings as described in section 11.

The Preferred Term (PT) and System Organ Class (SOC) for each coded item will be populated in the clinical database, but entire term hierarchy will be included in the exported data to the Biostatistician unless otherwise requested.

6.5 Prior and Concomitant Medication

ATC Hierarchy will be used for coding of the following data:

- Concomitant medication
- Previous Therapy
- Somatostatin Analogues Medication
- Post Study Follow-up Treatment Received

Prior medication is defined as medication taken up to 4 weeks prior to the screening visit.

Concomitant medication is defined as medication taken from baseline until EOS (including herbal products).

6.6 Treatment Compliance and Extent of Exposure

The following variables will be analysed:

- ^{177}Lu-edotreotide arm:
  - ^{177}Lu-edotreotide infusion, amount of activity injected compared to per protocol
  - Injection schedule (number of doses, mean treatment duration and mean dose interval for each of the 3 dose intervals: D1 to D2, D2 to D3 and D3 to D4), compared to per protocol schedule.
  - DMTs and treatment discontinuation: count and reasons
- Everolimus arm:
  - Average daily dose until EOS visit (continuous with descriptive stats and ≥10mg, [5,10[, < 5mg)
  - Mean (and SD) treatment duration
  - DMTs and treatment discontinuation: count and reasons
- By treatment arm and by therapies as:

- Total duration of treatment in month.
- Number of subjects who received SSA as prior and/or concomitant medications
- Subjects with SSA will be also listed

Major protocol deviations with regard to treatment compliance are defined in section 6.2.

6.7 Impact of COVID Infection

In general, any missing visit/assessment window due to COVID will be documented as protocol deviations. Once a subject misses a visit, the subject's impact on the study conduct will be assessed to help distinguish between data "affected" and "unaffected" by COVID. Specific reasons for COVID-related protocol deviations should be provided as detail as possible, including, but not limited to, confirmed/suspected COVID-19 infection, movement restricted due to COVID or social distancing guidelines, drugs shipping delayed/blocked due to COVID, sponsor/site action due to COVID. A listing will be provided to present the COVID-related protocol deviations.

7 Efficacy Analyses

Parameters	Method	Details
Continuous	Summary statistics	number of observations (N), number of missing observations (Nmiss), mean, standard deviation, minimum, 25th percentile, median, 75th percentile, maximum, lower bound 95% confidence interval, upper bound 95% confidence interval
Ordinal and categorical	Frequency counts and percentages	95% confidence interval
Comparison between groups	Van Elteren test (stratified main analysis) and Wilcoxon test (non-stratified sensitivity analysis)	rank-sum
Changes within groups	Wilcoxon test	signed rank
Comparison of percentages	Mantel Haenszel (stratified main analysis) and Fisher's exact test (non-stratified sensitivity analysis)	contingency table

Influence of censored data	Kaplan-Meier analysis and log-rank test (stratified for main analysis and non-stratified for sensitivity analysis)	as appropriate
	Cox proportional hazard regression	for hazard ratio (HR) computation and when adjusting for covariates
	RMST	in case of unequivocal non-proportional hazards or as sensitivity analysis where deemed appropriate
	treating treatment as time-dependent variable and/or RPSFT and/or censoring at time of switch	to account for new anti-cancer treatment starts and treatment switches in the two arms where necessary

All p-values less than 0.05 will be considered "statistically significant" on a descriptive level. p-values resulting from a main confirmatory test for primary and key secondary endpoints will be considered "statistically significant" according to the interim analysis and multiple testing plan (see Section 5.7).

7.1 Primary Efficacy Analysis

Variable	Method	Details
PFS	Kaplan-Meier methods incl median estimates and Log-rank tests (stratified for the main analysis and non-stratified for sensitivity analysis); Cox proportional hazard (for all hazard ratios and multivariate sensitivity analyses)	Take into account the impact of censored observations* For the main analyses, in addition to the 95%CI, the Hazard Ratio Confidence Interval will also be presented adjusted on the analysis level**

*See Section 3.4.1 for more details

** At the first interim analysis the 99.7% CI will be also reported for the HR, at the second interim analysis the 98.2%CI and at the final analysis the 95.6%CI (see Section 5.7 for more details)

In case of unequivocal non-proportional hazards, RMST approach will be used (see Section 6 for more details).

7.2 Key Secondary Efficacy Analysis

Variable	Method	Details
objective response rates (ORR),	Mantel Haenszel test (stratified main analysis) and Fisher's exact test (non-stratified sensitivity analysis)	defined as the proportion of patients achieving partial response (PR) or complete response (CR) as best outcome
Overall survival (OS)	Kaplan-Meier method, Cox models and Log-rank tests as appropriate* (stratified main analysis and non-stratified for sensitivity analysis)	Take into account the impact of censored observations

* In case of a high number of patients in the control arm starting new anticancer treatment or switching to PRRT treatment, appropriate methods to account for new anti-cancer treatment starts and switches in the two arms must be used for the main analysis of OS (see Sections 3.4.2 and 6 for more details).

7.3 Other Secondary Efficacy Analyses

Variable	Method	Details
Percentage of patients progression-free at 2 years after randomisation in either treatment arm (% 2y-PFS)	Estimates based on PFS Kaplan Meier curve	With 95% CI
Disease control rate (DCR)	Mantel Haenszel test (stratified main analysis) and Fisher's exact test (non-stratified sensitivity analysis)	defined as the proportion of patients achieving stable disease (SD), partial response (PR) or complete response (CR) as best outcome
duration of disease control (DDC)	Kaplan-Meier methods incl. log-rank test and median estimates	measured from the time of initial diagnosis of stable disease or better response (SD, PR or CR) until diagnosis of progression
Duration of response (DoR)	Kaplan-Meier methods incl. log-rank test and median estimates	measured from the time of initial diagnosis of response (PR or CR) until diagnosis of progression
Biomarkers and response (see section 3.4.3.1)	Descriptively: subgroups by levels, correlations if relevant, graphs as appropriate	By treatment group

8 Safety Analyses

8.1 Adverse Events

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

The number of event episode as well as the count and percentage of patients with at least one event will be determined by treatment arm. The analysis will be presented overall and by maximal severity grades.

This analysis will be tabulated for treatment emergent AEs (TEAEs), Adverse reactions (ARs = AEs at least possibly related to the study drug), Serious TEAEs (TESAEs), Serious ARs (SARs), SARs by possible cause of event, TEAEs by action taken on the study drug (change or discontinuation), TEAEs that led to premature study termination, and Fatal TEAEs.

AEs will also be tabulated according to the primary system organ class (SOC), preferred term (PT) and maximal severity. Patient-based count and percentages will be given by treatment arm for SOC followed by those for PT in descending order of the IMP arm.

In this analysis a patient with several events with identical SOC and PT will be counted only once at the maximal severity.

This analysis will be tabulated for TEAEs, ARs, SAEs, SARs, TEAEs by action taken on the study drug (change or discontinuation), TEAEs that led to premature study termination, and fatal TEAEs.

A summary will also be presented by SOC and PT such as mentioned above by treatment arm for all pooled severity grades and pooled grades 3 or 4 TEAEs and ARs.

If deemed appropriate other analysis, table and summaries can be presented to further explore the pattern of adverse events.

All AEs will be listed.

8.2 Deaths, Serious Adverse Events and other Significant Adverse Events

All deaths, AEs and other significant AEs will be listed.

8.3 Pregnancies

Pregnancy will not be classified as SAE except in cases where it can be shown that the effectiveness of the contraception was affected by the IMP/RP. All pregnancy cases 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 a SAE.

8.4 Clinical Laboratory Evaluations

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

Tumour markers: Chromogranin-A, further markers

All lab parameters will be summarised by visit and treatment arms as continuous data (raw and change from baseline) or category data where appropriate (e.g. urine test with category units).

The following parameters will also be presented as boxplot graphs by visit and treatment arm: WBC, RBC, HB, Neutrophils, Lymphocytes, Platelets, alkaline phosphatase, bilirubin, AST, ALT, albumin, potassium, sodium, calcium, and tumour markers.

For the following parameters the percentage of patients experiencing CTCAE toxicity will also be summarised by worst CTCAE grades (all grades pooled and Grades 3 and 4 pooled) and by treatment arm for baseline and post first IMP dosing parts of the study:

Table 6: List of laboratory parameters to be analysed according to CTCAE guidelines

Lab parameter	CTCAE term:
Lymphocytes	Lymphocyte count increased
	Lymphocyte count decreased
Hb	Anaemia
Leukocytes	Leukocytosis
	White blood cell decreased
Platelets	Platelet count decreased
PNN	Neutrophil count decreased
Creatinine	Creatinine increased
Fasting blood glucose	Hypoglycaemia
	Hyperglycaemia
Calcium	Hypocalcaemia
	Hypercalcaemia
Potassium	Hypokalaemia
	Hyperkalaemia
Sodium	Hyponatremia
	Hypernatremia
GGT	GGT increased
Alkaline Phosphatase	Alkaline Phosphatase increased
AST	AST increased
ALT	ALT increased
Total bilirubin	Blood bilirubin increased
Albumin	Hypoalbuminemia

8.5 Other Safety Measures

- Tubular extraction rate (TER):

Relative change from baseline by treatment arm and by visit.

Box plot of raw data by visit and by treatment arm.

- Glomerular filtration rate (GFR)

GFR will be calculated based on the CKD-EPI equation (2021):

$GFR = 142 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.200} * 0.9938^{Age} * [1.012 \text{ if female}]$

Scr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.241 for females and -0.302 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Relative change from baseline by treatment arm and by visit.

Box plot of raw data by visit and by treatment arm.

- Renal volume (V_{kidney})

Relative change from baseline by treatment arm and by visit.

Box plot of raw data by visit and by treatment arm.

- Frequency of occurrence and severity of abnormal findings in safety investigations:
    - vital signs:

Vital signs include heart rate, temperature, systolic and diastolic blood pressures and weight measurement.

The BMI will derived from the collected vital signs using the following formula: BMI = weight / height^2

In addition to summary table for continuous data (change from baseline), box plots by visits will be generated for all vital signs as well as for variables derived from vital signs (e.g. BMI) by treatment arm.

    - 12-lead ECG

ECG parameters will be presented by visit and treatment arm as continuous data (change from baseline) and also classified as follows:

QTc Absolute count

Post-administration value > 500 ms when not present at baseline (new onset)

Post-administration value of > 480 and ≤ 500 ms when not present at baseline (new onset)

Post administration value of > 450 and ≤ 480 ms when not present at baseline (new onset)

Other

QTc Change from baseline:

Change in QTc from baseline of > 30 and ≤ 60 ms

Change in QTc from baseline > 60 ms

Other

PR

PR relative change from baseline of more than 25% increase leading to PR > 200 ms

Other

QRS

QRS relative change from baseline of more than 25% increase leading to QRS > 120 ms

Other

HR

HR relative change from baseline of more than 25% increase leading to HR > 100 bpm

HR relative change from baseline of more than 25% decrease leading to HR < 50 bpm

Other

9 Health related Quality of Life (HRQL)

Health Related Quality of Life (HRQL) will be assessed by EORTC QLQ-C30 and GI.NET21 questionnaires.

Questionnaires scoring including missing data management will be conducted as per EORTC QLQ scoring manuals.

The QLQ C30 and derivatives will be interpreted based on the validated dimensions (15 for the QLQ C30, 9 multi-item scales and 6 single-item measures; 5 multi-item scales for the QLQ GINET21).

For each HRQL dimension, box plots of raw scores by visit and treatment arm will be presented.

Maximum HRQL improvement (total scores relative to baseline) will be summarized by HRQL dimension and treatment arm.

It is also to be noted that the interpretation of an increase or decrease dimension score can have different meaning depending on the nature of the dimension scale itself (e.g. an increase in a positive scale such as global quality of life corresponds to an improvement in the patient status whereas an increase in a negative scale such as symptoms corresponds to a worsening in the patient status).

For QLQ tools the positive scales (increased score represents a improved quality of life or functioning) are global health status and function scales:

- Global health status/QoL
- Physical functioning
- Role functioning
- Emotional functioning
- Cognitive functioning
- Social functioning

Whereas the negative scales (increased score represents a deterioration of symptomatology / problems) are symptom scales, single item domains and all GI-NET domains:

- Fatigue
- Nausea and vomiting
- Pain (SS)
- Dyspnea
- Insomnia
- Appetite loss
- Constipation
- Diarrhoea
- Financial difficulties
- Endocrine scale
- G.I. scale
- Treatment scale
- Social functioning scale
- Disease related worries scale
- Muscle /bone pain symptom
- Sexual function
- Information/communication function
- Body Image

Proportion of patients with stable score or improvement in score of ≥ 10 compared to baseline or deterioration in score of ≥ 10 points compared to baseline score will be tabulated by treatment arm and by visit and overall (best HRQL response) along with the median time to improvement (defined as the time from randomisation until first improvement) and median duration of improvement (defined as the time from first improvement to subsequent deterioration) for the patients with at least 1 HRQL improvement.

Time to HRQL deterioration will be calculated as the time from randomization to the first deterioration for the same domain. Patients with no deterioration are censored at the last adequate HRQL assessment date. Patients with no baseline and/or no follow-up are censored at randomization.

For each domain, a Kaplan-Meier plot will be produced showing time to event by treatment arm and used to generate a point estimate of the median time to event with corresponding 95% confidence interval (CI).

The stratified log-rank test will be used to compare the time to event in the two groups. The hazard ratios (HR) and corresponding 95% CIs will be estimated from a Cox proportional hazards mode including randomized treatment as a factor.

For sensitivity analysis purposes, the p-value using a log-rank test not stratified on randomization stratification factors will also be computed as well as the corresponding hazard ratio (Cox model adjusting for the same factors).

Subgroup and/or multivariate Cox model analyses can be performed as deemed appropriate to explore the impact of co-variates on the HRQL results.

10 Dosimetry

Time activity curves of target organs and tumour lesions will be presented.

Descriptive statistics of target organ and tumour lesions absorbed doses in Gy/GBq will be tabulated by cycle (D1 for all patients, D2-4 for sub-study A patients). A summary of the mean absorbed dose and SD (in Gy/GBq and in Gy for 7.5 GBq) will also be presented by target organs and by cycle. The estimated extrapolation of the cumulative absorbed dose to target organs and tumour lesions will be summarised for a theorical full course 4 doses of 7.5GBq (i.e. 30GBq).

The association between absorbed dose of ^{177}Lu-edotreotide in the tumours and RECIST 1.1 response will be explored, as well as the association between bone marrow absorbed dose and highest CTCAE haematological toxicities (AEs and labs) or kidney absorbed dose and highest CTCAE kidney toxicities (AEs and labs). Association between baseline kidney function impairment and organ dosimetry will also be explored based on baseline eGFR (i.e. classified as <15, [15,30[, [30,45[, [45,60[, [60,90[≥90 or less categories in case of too low sub-group sample sizes).

Sub-study A and B:

To verify the accuracy of cumulative absorbed dose (AD) estimations to tumours and kidneys from PRRT cycles D1-D4, 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 (sub-study A).

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

The following Dosimetry information will be summarised (mean and SD, in Gy) for tumour lesion absorbed dose and kidney absorbed dose:

Table 7: Dosimetry information to be summarised for sub-studies A and B

Dosimetry	C1	C2-C4
Planar	Measured (All patients, Sub-A, Sub-B)	Extrapolated vs. measured (Sub-A, Sub-B) (Sub-A)
	Vs.	Vs.
Hybrid	Measured (All patients, Sub-A, Sub-B)	Extrapolated vs. measured (Sub-A, Sub-B) (Sub-A)
	Vs.	
3D	Measured (Sub-B)	Extrapolated (Sub-B)

Sub-study C:

Blood radioactivity will be measured in sub-study C patients at different time points during and after administration. Blood radioactivity (time activity curves) will be used to calculate the bone marrow absorbed dose.

Descriptive statistics of blood derived bone marrow absorbed dose will be tabulated. A summary of the mean absorbed dose and SD (in Gy/GBq, Gy for 7.5 GBq and Gy for 30GBq) will also be presented.

11 Pharmacokinetics

To investigate pharmacokinetics (PK), blood and urine samples will be collected from 20 patients who received their first dose of ^{177}Lu-edotreotide. Blood and urine radioactivity will be measured. Blood radioactivity will be used to calculate a surrogate bone marrow dose (see Section 0). Urine radioactivity will be used to measure rate of excretion. In addition, urine samples will be analysed for drug metabolites with HPLC. As no comparisons are performed, 20 subjects are considered sufficient for this PK analysis. The following PK variables will be analysed:

a) Urine radioactivity in % 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 post-injection to assess clearance pattern

c) Radiochemical purity assessed through HPLC of urine samples collected within 48 hours post-injection

12 Other Analyses

Not applicable.

13 Tables, Figures and Listings

Tables, Figures and Listings specifications including mock-ups will be prepared in a separate TFL tracker attached to this SAP.

14 Reporting Conventions

P-values ≥0.0001 will be reported to 4 decimal places; p-values less than 0.0001 will be reported as “<0.0001”. The mean, standard deviation, and any other statistics as median or quartiles, will be reported to one decimal place greater than the original data. Minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant digits. Confidence limits will be presented using the same number of decimal places than the centre point of the CI.

Percentages will be rounded off to 1 decimal place. Rounding errors in the sum in table listings will not be aligned to 100%.

15 Technical Details

All statistical evaluations, including graphical data summaries, will be performed using appropriate software (preferably SAS® statistical analysis software (version 9.2 or higher, SAS Institute Inc., Cary, NC, USA or R, R Foundation for Statistical Computing, Vienna, Austria).

16 Supplementary Analyses

In case additional analyses are considered necessary, amendments to the protocol and to the SAP are to be produced describing the needed analysis in detail. Otherwise such additional analysis will be considered “post-hoc” analyses.

17 Open-label Rollover Post-treatment Extension in France

This section provides a description of the strategy and methodology to be used to perform the analysis of the data generated in Appendix 6 of the Study Protocol (Version 8.3) Amendment 11 (France Only): Open-label Rollover Post-treatment Extension to Enable Access to 177Lu-edotreotide PRRT in Patients Treated with Everolimus who Discontinued Due to Tumour Progression.

The open-label rollover post-treatment extension is to enable patients who received everolimus in the main study and who discontinued treatment due to tumour progression, to receive 177Lu-edotreotide PRRT in France. This section only contains the rollover patients, please refer to Appendix 6 of the protocol for more details.

17.1 Study Objectives Rollover Post-Treatment Extension Study

The objective of the rollover post-treatment extension analysis is to assess the safety, tolerability, and efficacy of ^{177}Lu-edotreotide PRRT in patients who received everolimus in the main study and discontinued treatment due to tumour progression.

17.2 Study Endpoints of Rollover Post-treatment Extension Analysis

17.2.1 Efficacy Endpoint

The efficacy endpoints in rollover study include Rollover Progression-free survival (Rollover PFS), Rollover overall survival (Rollover OS), Rollover Objective Response Rate (Rollover ORR), Rollover Disease control rate (Rollover DCR), Rollover Disease control rate (Rollover DCR), Rollover Duration of Response (Rollover DoR) and Rollover Duration of Disease Control (Rollover DDC).

Imaging for the assessment of PFS (using RECIST 1.1) will be performed and evaluated at the study centre according to local standards. RECIST 1.1 baseline must be reset at rollover post treatment extension entrance.

17.2.2 Safety and Tolerability Endpoint

General safety parameters include frequency of occurrence and severity of abnormal findings in safety investigations (physical examination, vital signs, ECG, ^{99}mTc-MAG3 renal scintigraphy, clinical laboratory tests), AEs, and concomitant medication.

17.3 Study Design of Rollover Post-treatment Extension Study

17.3.1 Enrolled Population

All patients participating in the main study in France who meet the eligibility criteria for the rollover extension are planned to be enrolled. Enrollment into the rollover extension will occur within 3 months of a patient's discontinuation from everolimus treatment in the main study. Patients who enroll in the rollover extension may have their early withdrawal visit procedures from the main study and rollover extension visit procedures done on the same day.

17.3.2 Study Duration of Rollover Post-treatment Extension Study

Patients in the rollover extension may receive up to a maximum of 4 cycles of ^{177}Lu-edotreotide. Each cycle will be administered as an IV infusion given 90 (±14) days apart. The investigator will decide whether to continue treatment after each cycle based on the patient's state of health, and safety and efficacy assessments performed at the study centre.

Rollover EOS: The end of the rollover extension is defined as the last visit of the last patient. The end of study for the rollover extension for each individual patient will be their last rollover EOS, or death, whichever occurs earlier. At 90 (±14) days after the last treatment cycle, patients will return to the study centre for the rollover EOS (see Table 10 of the current protocol. for assessments to be performed).

17.3.3 Rollover Study Visits and Time-Points

Safety and efficacy assessments will be performed as shown on Table 10 in the protocol. Study visit consists of screening/baseline, treatment cycle (pre-dose, PRRT, post-dose) and follow-up. The assessments will be conducted at the study centre according to local standards. 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 standards. However, the physical examination, vital signs, and 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. Assessments will be recorded in the eCRF. Patients enrolled in the rollover extension will simultaneously participate in the post-study follow-up for the main study (i.e. every 6 months for 5 years).

17.4 Handling of Missing Data

In general, unless otherwise specified, the handling strategy for all intercurrent events will be based on a treatment policy approach based on ICH E9 (R1). If possible, subjects will be followed up continuously and measurements will be collected continuously after the occurrence of the intercurrent event, until the subject either completes the study or withdraws from the study before completion. All subjects and measurements will be included in analysis.

Missing values will be treated as such, no imputation will be performed. The number of missing values will be reported. Missing information about tumour response at EOS will be censored on the day of the last available adequate assessment (See Section 17.8.2 for full censoring rule details for the rollover study).

17.5 Analysis Sets of Rollover Post-treatment Extension Study

As this is an open-label rollover extension without comparisons and with a very low number of patients, only descriptive statistics will be performed. All variables will be listed and summarised descriptively in tabular format. Analysis sets will include:

- Rollover FAS: The full analysis set of the rollover study will consist of all patients who have had at least 1 dose of everolimus in the core study and were included in the rollover extension. All eligible patients who signed the informed consent document for the rollover extension and have had at least 1 dose of everolimus in the core study will be included.

- Rollover SAF: The safety analysis set will consist of all patients who have had at least 1 dose of everolimus in the core study and are included in the rollover extension and have received at least 1 dose of 177Lu-edotreotide.

Protocol deviation is described in Section 3.5 of the protocol for details on protocol adherence. Major protocol deviations with regard to treatment compliance are defined in Section 6.2 of the SAP.

17.6 Baseline of Rollover Post-treatment Extension Study

Rollover Date: Rollover Date will be defined the date that patients signed the informed consent document for the rollover extension study.

17.6.1 Rollover Baseline Characteristics

Rollover Baseline Values: Rollover baseline values of rollover post-treatment extension study will be defined as last non-missing value collected within 30 days prior to rollover date but not yet received the first dose of ^{177}Lu-edotreotide PRRT, including unscheduled visits. Screening examinations/assessments of rollover study are considered identical to baseline and pre-dose values if performed within 7 days pre-dose. Refer to Section 8.3.1 of the protocol for details about assessing and recording baseline findings, as applicable to treatment with ^{177}Lu-edotreotide PRRT during the rollover extension. Data from core study will be used, if these values are not collected on the rollover CRF.

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

- Primary tumour origin
- Prior medical treatment
- KPS/ECOG (reclassified rule in Appendix 3 in the protocol)
- Age, ethnic origin, sex, weight, height, BMI, physical exam
- Prior and concomitant medication prior to or at rollover baseline
- Time from the randomization date in the main study

17.6.2 Prior and Concomitant Therapy

Prior and concomitant medications/therapies will be recorded throughout the rollover extension until the rollover EOS.

Prior therapy is defined as any condition/medication/procedure/therapy that occurred only before the first administration of ^{177}Lu-edotreotide PRRT.

Concomitant therapy is defined as any condition/medication/procedure/therapy that occurred at or after the first administration of ^{177}Lu-edotreotide PRRT.

Prior and concomitant condition/medication/procedure/therapy as per this definition will be listed and tabulated separately.

Any condition/medication/procedure/therapy which started before signature of the rollover informed consent and for which new or worsening symptoms or further therapy are present between signature of the rollover informed consent and first administration of 177Lu-edotreotide PRRT are recorded as baseline and prior findings.

If a therapy end date is before the first administration of ^{177}Lu-edotreotide PRRT, then the therapy will be summarized as a prior therapy regardless of whether the therapy start date is missing or not. If a therapy start date is at or after the administration of ^{177}Lu-edotreotide PRRT, then a therapy will be summarized as concomitant therapy regardless of whether the therapy

end date is missing or not. If a therapy that is started prior to the administration of ^{177}Lu-edotreotide PRRT and continued after the administration of ^{177}Lu-edotreotide PRRT will be summarized as the prior therapy and separately as the concomitant therapy.

Medical/surgical history will be coded using the latest version of MedDRA dictionary and summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT) with count and percentage of patients by treatment. Patients with medical history findings in more than one category of SOC or PT will be counted only once within each category.

All prior and concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHODrug). Prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) Level 2 and Preferred Term (PT)/ATC Level 4.

Current version of MedDRA and WHODrug dictionaries will be updated and stated in the tables and listings (in title or footnote).

Refer to Section 6.1 of the protocol for details on the recording and use of prior and concomitant medications, Section 6.1 of the protocol for prohibited medications (with the exception of those related to patients taking everolimus), and ^{177}Lu-edotreotide precautions (Section 6.1.5.1 of the protocol).

17.6.3 Rollover Treatment Compliance and Treatment Exposure

Treatment of exposure to ^{177}Lu-edotreotide is summarized as the same as in the main study except that the calculation will be based on the rollover baseline date. Time from the rollover baseline date to the first dosing date of ^{177}Lu-edotreotide PRRT during the rollover period and time intervals between cycles will be summarized as continuous variables.

Number (%) of patients treated, number (%) of cycles completed (all treated patients) will be summarized as categorical variables. Average drug exposure by cycle in GBq and duration of treatment in months will be summarized as continuous variables. Details are described in Section 6.1 and Section 6.6 of the SAP.

Average drug exposure by cycle in GBq = Cumulative dose in Gbq/Total number of doses

Duration of treatment in months = (End date of treatment – Start date of treatment +1)/30.4375

17.7 Data Analysis of Rollover Post-treatment Extension Study

17.7.1 General Considerations in Statistics

Statistical analyses will be performed after the database was appropriately locked. All data from the CRF and other study and measurement documents will be analysed. Continuous variables will be summarised using descriptive statistics (number, mean, standard deviation, minimum, median, maximum) and categorical variables using frequency tables. Corresponding 95% confidence intervals will be presented additionally, if meaningful. Time to event data will be summarized using Kaplan-Meier estimator, if applicable. Estimated median and/or 25% (75%) of time to event will be presented, if applicable.

Withdrawals and protocol deviations in the rollover study will be listed. Missing data that cannot be obtained will not be substituted or imputed, unless stated otherwise.

17.7.2 Analysis of Efficacy Endpoint

No formal hypothesis will be generated and tested. The following efficacy endpoints will be summarized using descriptive statistics. Imaging for the assessment (using RECIST 1.1) will be performed and evaluated at the study centre according to local standards. RECIST 1.1 baseline must be reset at rollover post treatment extension entrance.

Rollover Progression-free survival (Rollover PFS):

Progression-free survival will be determined starting from the first dosing administration date of ^{177}Lu-edotreotide PRRT during the rollover period until the date of an event (PD or death). For those patients who are part of the rollover FAS but have not received any dose of 177-Lu-edotreotide, the rollover ICF date will be used as start date instead.

For the analysis, any withdrawal (or drop-out) before the last rollover EOS visit will be censored. Patients who have not shown progression at the end of the rollover EOS study will also be censored (Table 8).

Table 8: Rollover PFS analysis rules

Situation	Date of Progression or Censoring	Outcome
Tumour progression or death	Earliest date of PD or death	Event (PD or Death)
No tumour progression and not death	Date of last adequate* radiological assessment	Censored
Unless:		
No baseline radiological tumour assessment	Date or the first dosing administration of ^{177}Lu-edotreotide PRRT	Censored
No adequate post-baseline radiological assessment and date of death, if any, is after 2 or more scan intervals following the first dosing administration date of ^{177}Lu-edotreotide PRRT **	Date of the first dosing administration of ^{177}Lu-edotreotide PRRT	Censored
New anticancer treatment started prior to tumour progression or death (whichever is earlier)	Date of the last adequate radiological assessment prior to start of new anticancer treatment or date of the first dosing administration of ^{177}Lu-edotreotide PRRT (whichever is later)	Censored
Tumour progression or death documented immediately after 2 or more consecutive missing scan** following last adequate radiological tumour assessment or the first dosing administration date of ^{177}Lu-edotreotide PRRT (whichever is later).	Date of last adequate radiological tumour assessment or date of the first dosing administration of ^{177}Lu-edotreotide PRRT (whichever is later).	Censored

Table footnotes:

*Adequate radiological tumour assessment refers to an assessment with one of the following responses: CR, PR, SD, or PD.

**The interval is higher than 2 times the maximal protocol scheduled RECIST 1.1 assessment interval (i.e. >222 days = 2*(90+21)).

Rollover overall survival (Rollover OS):

Rollover OS will be calculated starting from the rollover baseline date 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 after EOS of the main study.

A supplementary analysis of overall survival (OS) will be calculated starting from the randomisation date until the date of death for subjects in rollover FAS, described in Section 3.4.2.

Rollover Objective Response Rate (ORR):

Rollover ORR is defined as the percentage of patients, achieving (based on RECIST 1.1) a partial response (PR) or complete response (CR) as best outcome given baseline be reset at rollover post treatment extension entrance (rollover baseline date).

Rollover Disease control rate (Rollover DCR):

Rollover DCR considers the percentage of patients, achieving partial response (PR), complete response (CR), and stable disease (SD) after the rollover baseline date.

Rollover Duration of Response (Rollover DoR):

Rollover 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 morphological progression per RECIST 1.1 criteria during the rollover period.

Rollover Duration of Disease Control (Rollover DDC):

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

17.7.3 Analysis of Safety and Tolerability Endpoints

Safety parameters include frequency of occurrence and severity of abnormal findings in safety investigations (physical examination, vital signs, ECG, ^{99}mTc-MAG3 renal scintigraphy, clinical laboratory tests), AEs, and concomitant medication. Conditions (e.g., abnormal physical examination findings, symptoms, diseases, laboratory, ECG) present before the first administration of the first administration of ^{177}Lu-edotreotide PRRT will be documented as baseline findings. Conditions which started or deteriorated after the first administration of the first administration of ^{177}Lu-edotreotide PRRT will be documented as adverse events.

17.7.3.1 Adverse Events

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. By definition, all AEs in the rollover period are regarded as 'treatment emergent', i.e., not seen before the first administration of ^{177}Lu-edotreotide PRRT or, if already present before treatment, worsened after start of treatment.

Events/Conditions prior to the first dosing administration of ^{177}Lu-edotreotide PRRT will be captured for all rollover patients and reported separately from treatment emergent AEs (TEAEs), as rollover baseline findings.

If the rollover baseline finding is "continuing" into the rollover period, no AE is to be recorded if, after start of dosing administration of ^{177}Lu-edotreotide PRRT, 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 onset date of an AE is not recorded and if the onset date of an AE occurring after the first drug administration cannot be excluded, then, the AE is considered as TEAE. An AE, having been absent pretreatment, or worsens relative to the pretreatment state is also considered as TEAE.

Refer to Section 8.3.2 of the protocol for details on assessing and reporting AEs, as applicable to treatment with ^{177}Lu-edotreotide PRRT during the rollover extension.

All deaths, AEs and other significant AEs will be listed.

17.7.3.2 Pregnancies

Pregnancy will not be classified as SAE except in cases where it can be shown that the effectiveness of the contraception was affected by ^{177}Lu-edotreotide PRRT. Available pregnancy test results from the main study are accepted for the screening/baseline visit. SAE reporting/pregnancy reporting and pregnancy monitoring and follow-up will be performed as described in Section 8.3.1.1 and Section 8.3.6 of the protocol and summarized as in Section 8.3 of the SAP.

17.7.3.3 Clinical Laboratory Evaluations

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.

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: specific gravity, pH, protein, glucose, blood, leukocytes, ketones, nitrite, albumin, creatinine.

All lab parameters will be summarised by visit as continuous data (raw and change from baseline) or category data where appropriate (e.g. urine test with category units).

The following parameters will also be presented as boxplot graphs by visit and treatment arm: WBC, RBC, HB, Neutrophils, Lymphocytes, Platelets, alkaline phosphatase, bilirubin, AST, ALT, albumin, potassium, sodium, calcium, and tumour markers.

For the following parameters the percentage of patients experiencing CTCAE toxicity will also be summarised by worst CTCAE grades (all grades pooled and Grades 3 and 4 pooled) for the rollover baseline and post first dosing administration of ^{177}Lu-edotreotide PRRT during the rollover period.

For clinical laboratory tests (haematology, clinical chemistry, and clotting parameters) and urinalysis (dipstick), refer to Section 8.3.5 of the main study in the protocol and Section 8.4 and Table 6 of the SAP.

17.7.3.4 Other Safety Measures

Kidney function: ^{99}mTc-MAG3 renal scintigraphy will be performed to assess the TER of the kidneys and evaluate the kidney functionality from renogram and sequence images. ^{99}mTc-MAG3 renogram to be performed at screening/baseline; within 7 days prior to administering the Cycle 3 dose. Raw value, relative change from baseline and box plot of raw data will be summarized by visit for parameters of kidney function as described in Section 8.5 of the SAP, including tubular extraction rate (TER), glomerular filtration rate (GFR) and renal volume (Vkidney).

Vital signs and 12-lead ECG: Data will be summarized as described in Section 8.5.

17.8 Technical Details

Tables, Figures and Listings specifications including mock-ups will be prepared in a separate TFL tracker attached to this rollover study of the SAP. Reporting conventions are described in Section 14 of the SAP, All statistical evaluations, including graphical data summaries, will be performed using appropriate software (preferably SAS® statistical analysis software (version 9.4 or higher, SAS Institute Inc., Cary, NC, USA or R, R Foundation for Statistical Computing, Vienna, Austria). The coding system is summarized in the following table.

Domain	Coding System	Reporting Terms
Medical history	MedDRA (the latest version before DBL)	SOC = MedDRA SOC Preferred term = MedDRA Preferred term
Prior and concomitant medication	WHO Drug Dictionary (the latest version before DBL)	ATC Code Medication Group = ATC Level 2 and ATC Level 4 term
Adverse events	MedDRA (the latest version before DBL)	SOC = MedDRA SOC Preferred term = MedDRA Preferred term

18 References

See clinical study protocol and:

- PASS version 13

- PASS Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.
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