FINAL STUDY REPORT

Full title of the trial:	^{177}Lu-octreotate treatment outcome prediction using Multimodality imaging in refractory neuroEndocrine tumours
Short title of the trial:	LuMEn
EudraCT Number:	2012-003666-41
Sponsor protocol number:	LuMEn
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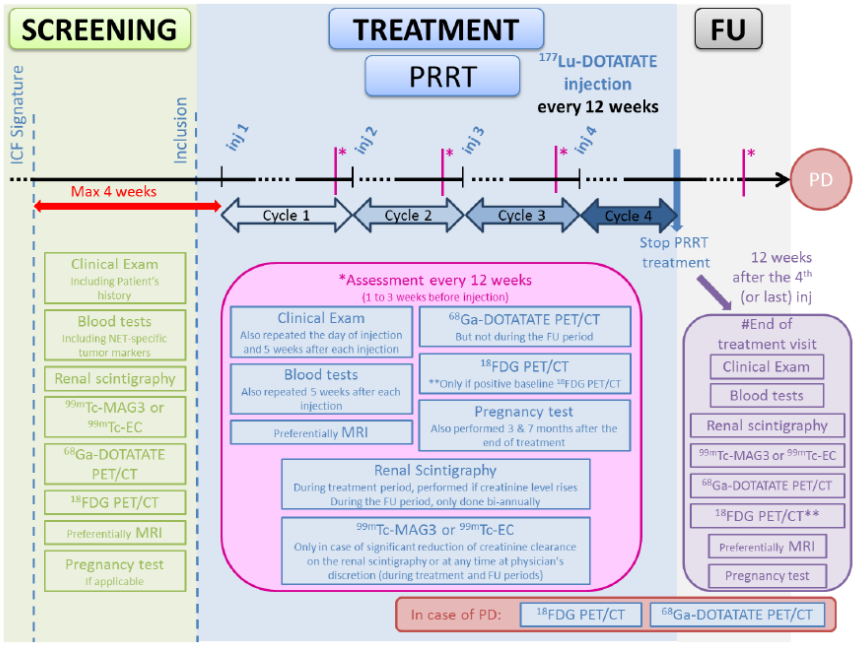
1 TRIAL INFORMATION

PHASE	Phase II
TRIAL DESIGN	This study is a single arm, non-randomized, clinical-imaging study. Subjects with refractory gastroenteropancreatic neuroendocrine tumours were included and treated with ^{177}Lu-octreotate. This treatment consisted of ^{177}Lu-octreotate injections (4 cycles) in fixed activities of 7,4GBq (200 mCi) (±5%) each, given 12 weeks (±1week) apart, injected intravenously, simultaneously with nephroprotective perfusion of an amino acid solution.  The end of treatment visit took place 12 weeks (± 1 week) after the 4th (or last) ^{177}Lu-octreotate injection. After the 4 (or last) ^{177}Lu-octreotate injection, follow-up visits will be planned every 12 weeks (±1 week) from the end of treatment visit and until disease progression.
RATIONALE	Peptide receptor radionuclide therapy (PRRT) has been trialled for more than 20 years as an effective and safe therapeutic imaging-based modality for advanced progressive NETs. Patient eligibility is primarily based on tumour lesion SSTR expression, visualized with ^{68}Ga-labeled somatostatin analog PET/CTs, however there are currently no widely available, well-validated biomarkers to predict the outcome of patients receiving PRRT.
OBJECTIVES	**Primary objective**: For each lesion: To assess the value of the following parameters (obtained through functional and molecular imaging) for predicting the lesion-by-lesion PRRT treatment outcome: • ^{18}FDG uptake on ^{18}FDG PET/CT, • ^{68}Ga-octreotate uptake on ^{68}Ga-octreotate PET/CT • Apparent Diffusion Coefficient on Diffusion Weighted-MRI,

	[for these three parameters, absolute values at baseline will be assessed]
	• Tumour dosimetry on post-^{177}Lu-octreotate SPECT/CT after the first cycle.
	
	Secondary objective:
	To generate a patient-based response model based on the previously defined parameters.
	
	Exploratory objectives:
	• For each lesion: to assess the value of the parameters mentioned in primary objective for predicting the lesion-by-lesion PRRT treatment outcome:
	  ○ absolute values of the three imaging parameters and their relative changes after each cycle;
	  ○ serial tumour dosimetry on post-^{177}Lu-octreotate SPECT/CT after each cycle.
	• To assess safety parameters, especially in relation with the absorbed dose to bone marrow and kidneys.

ENDPOINTS	**Primary endpoint:** The time to progression (TTP) for each target lesion assessed on MRI (or on CT scan if MRI is not applicable). TTP is defined as the time between treatment initiation and objective tumour progression with censoring of patients who die as a result of any cause. **Secondary endpoints:** • Best morphological response according to RECIST 1.1, • Progression Free Survival (PFS). PFS is defined as the time between treatment initiation and the first of the following events: disease progression (clinical or radiological) or death resulting from any cause. • Biochemical response (evolution of NET-specific tumour markers, as for inclusion). **Exploratory endpoints:** • The time to progression (TTP) for each target lesion assessed on MRI (or on CT scan if MRI is not applicable). • Adverse events according to NCI-CTCAE v4.03.

INCLUSION CRITERIA	1. Age above or equal to 18 years.
	2. Histology-proven advanced GEP-NETs.
	3. Disease progression defined as follows (at least one of the following):
	  - Radiological disease progression (according to RECIST 1.1) on an MRI or CT over the last 12 months
	  Or
	  - Disease progression on a somatostatin receptor-imaging, PET/CT or SPECT/CT over the last 12 months [apparition of new lesion(s) or increase in the transaxial plane diameter of more than 30% on the same imaging modality]
	  Or
	  - Both of the following criteria (a+b):
	  a. clinical progression:

	○ sustained (for more than 2 weeks) increase of NET-specific hormonal hypersecretion related symptom frequency by 50% or, ○ sustained (for more than 2 weeks) increase of severity by 1 grade (according to NCI-CTCAE version 4.03). b. biochemical progression: by increase of NET-specific tumour markers (plasma Chromogranin A, plasma NSE or urine 5-HIAA) in two successive measurements. 4. Disease refractory to SSAs and/or standard systemic therapy available in Belgium at the time of inclusion criteria 5. Long-acting SSAs should be discontinued at least 4 weeks before study treatment start date and, if needed, switched to short-acting analogues which should be stopped 48h before the treatment date 6. Adequate renal function with GFR ≥ 50 mL/min/1.73m2 (evaluated by renal scintigraphy test). 7. Adequate bone marrow function with hemoglobin ≥ 9 g/dL; neutrophil ≥ $1.5 \cdot 10^3$/µL; platelet count ≥ $100 \cdot 10^3$/µL. 8. Adequate liver function with total bilirubin ≤ 2 x ULN and transaminases ≤ 5 x ULN, serum albumin > 3 g/dL with normal prothrombin time (> 70%). 9. ECOG Performance Status ≤ 1. 10. Women of childbearing potential and men with partners of childbearing potential must agree to use a highly-effective form of contraception for the duration of study participation and up to six months after the end of the treatment. A pregnancy test (serum) must be performed within 4 weeks prior to inclusion for every female patient of childbearing potential and it must be negative. 11. Subject's written informed consent obtained prior to any study procedure. 12. All necessary baseline procedures should be performed within 4 weeks prior to first 177Lu-octreotate injection (D0). **<u>Lesion-based</u>** 13. The subject must have at least one target lesion fulfilling all of the below criteria: - On the ^{68}Ga-octreotate PET/CT: tumour uptake higher than the physiological liver uptake (grade III or IV of the Rotterdam visual score30) in a lesion with longest transaxial plane diameter ≥ 20mm (measured on the CT, part of the PET/CT or on the dedicated diagnostic CT or MRI); - At least one of these lesions morphologically measurable according to RECIST 1.1 and progressive on the MRI (or CT if MRI is not applicable); - Target lesion shall not have been previously irradiated.
EXCLUSION CRITERIA	1. Resectable tumour with curative intent. 2. Any major surgery within the last 6 weeks prior to inclusion in the study 3. Radiotherapy, chemotherapy, embolization, mammalian target of rapamycin (mTOR)-inhibitors, receptor tyrosine-kinase inhibitors, interferon, or other investigational therapy within the last 12 weeks prior to inclusion in the study.

	4. Diffuse bone marrow infiltration on the baseline ^{68}Ga-octreotate PET/CT confirmed by MRI. 5. Prior external beam radiotherapy on kidneys or on more than 25% of bone marrow. 6. Patients with known uncontrolled brain metastases. 7. Patients with a significant medical, neuro-psychiatric, or surgical condition, currently uncontrolled by treatment, which, in the investigator's opinion, may interfere with completion of the study. 8. Pregnant or lactating patients. 9. Women of childbearing potential and men with partners of childbearing potential refusing an adequate contraception.
PARTICIPATING COUNTRY	Belgium
START DATE OF THE TRIAL	27/05/2013
PARTICIPATING SITES NUMBER	1
LENGTH OF THE STUDY	• Actual start date of recruitment to the protocol: 25/07/2013 • Actual date stop date of recruitment to the protocol: 14/01/2020 • Long term follow-up planned? Yes for safety, efficacy.
INDEPENDENT DATA MONITORING COMMITTEE	No
PROTECTION OF TRIAL SUBJECTS	A nephroprotective perfusion of an amino acid solution was simultaneously administered with the ^{177}Lu-octreotate injection. This nephroprotective perfusion was preceded by the administration of an anti-emetic regiment to prevent nausea or vomiting from the amino acids.
ANALYSIS STAGE & DATE	Final Date of final analysis: 24/08/2023
PRIMARY COMPLETION DATA	• Is this the analysis of the primary completion data? Yes • Primary completion date: 20/05/2022
GLOBAL END OF TRIAL DATE	• Global end of trial reached? Yes • Global end of trial date: 16/09/2022
PREMATURE END OF TRIAL	No

2 SUBJECT INFORMATION

In the LuMEn trial, 50 subjects were included (i.e. ICF signature). The age group breakdown for the whole trial is provided in the table hereunder.

Age of subjects	Number of subjects
In utero	-
Preterm newborn - gestational age <37 wk	-
Newborns (0-27 days)	-
Infants and toddlers (28 days - 23 months)	-
Children (2-11 years)	-
Adolescents (12-17 years)	-
Adults (between 18 and 64 years)	21
From 65 to 84 years	29
85 years and over	-

The median of subjects' age is 64.5 years (full range 45 - 81).

Amongst the 50 subjects included (24 females and 26 males), 37 subjects were enrolled and exposed to ^{177}Lu-octreotate with 28 subjects who completed the trial. In total, 22 subjects did not complete the trial. The reasons why some subjects did not complete the trial with the corresponding subject's number are specified in the below table.

Non-completion reasons	Number of subjects
Screen failure	13
Consent withdrawn by subject	3
Loss of follow-up	1
Second primary malignancy	2
Disease progression	2
Death	1

3 STATISTICAL ANALYSIS

3.1 Subjects and treatment data

Between July 2013 and January 2020, 37 consecutive subjects with advanced GEP-NETs were included in the study. Subject demographics and tumour characteristics are detailed in Table 1. All subjects had proven disease progression before inclusion in the study: radiological (n=34) and/or progression on SSTR imaging (n=16) and/or clinical progression (n=18). Approximately one-third (n=12) did not present any symptoms at the time of study inclusion. All subjects underwent at least one line of previous loco-regional or systemic treatment (median: 2; range: 1-10). Four subjects had prior splenectomies.

Overall, 140 ^{177}Lu-DOTATATE cycles were administered in all 37 subjects with a mean cumulated administered activity of 27.9GBq (range: 7.5-36.9). The average time between treatment cycles was 12.9 weeks. Most subjects (28/37) received four cycles of PRRT with a mean administered activity of 7.5GBq (±0.65%) per cycle. Five cycles of 7.4GBq (±5%) were administered in two subjects, reaching a cumulative administered activity of 36.8GBq and 36.9GBq, respectively. In one subject, due to the development of grade 2 nephrotoxicity after the first PRRT cycle, the following injection was administered with reduced activity of 3.8GBq. He was given a fifth cycle with reduced activity (3.8GBq). The remaining six subjects received less than four cycles of PRRT due to: myelotoxicity (n=2 and n=1 subject receiving three and two cycles, respectively), development of ascites (n=1 patient receiving two cycles), subject withdrawal (n=1 patient receiving two cycles) and subject lost to follow-up (n=1 subject receiving one PRRT cycle).

3.2 Lesion and patient outcomes

3.2.1 Lesion Time to Progression

A nuclear medicine physician and a radiologist selected 116 target lesions. The most common tumour location was the liver (n=78), followed by lymph nodes (n=17), peritoneum and mesentery (n=13), pancreas (n=8) and adrenal glands (n=2). After excluding lesions which were treated with other than four cycles of PRRT (n=29 in nine subjects) and lesions for which morphological response assessment was not available (n=3 in one subject), 84 out of 116 were considered evaluable. Twenty-two (26%) lesions in 13 subjects, mostly hepatic (15/22), showed partial response and were categorised as responding. There were no target lesions with complete response. Fifty target lesions (60%) were stable, and 12 (14%) progressed morphologically (only five of which progressed three months after the fourth PRRT injection). The median follow-up time for all subjects (data analysis in July 2022) was 57 months (95%CI: 50-71), during which the median lesion-based TTP was not reached.

3.2.2 Objective response rate (ORR) and Progression-free survival

The ORR was 30% (n=11 subjects with PR and no subjects had CR). The median PFS for the whole cohort was 27.8 months. The association between PFS and potential prognostic factors is presented in Table 2. Subjects with pancreatic NETs had significantly shorter median PFS compared to intestinal (i.e. small-intestinal and colorectal) NETs: 19.4 months vs 29.5 months [p=0.01, HR (95%CI): 2.96 (1.25-7.02)]. A trend towards improved PFS was shown in subjects receiving only one systemic treatment before PRRT (including SSAs) compared to subjects receiving more than one systemic therapy (including targeted therapy and chemotherapy). However, this difference was not statistically significant (p=0.08).

3.3 Imaging parameters and association with lesion outcome

3.3.1 ^{68}Ga-DOTATATE PET/CT imaging

At baseline, ^{68}Ga-DOTATATE PET parameters were available in 110 (97 for tumour-to-spleen ratio) out of the 116 target lesions (n=6) excluded due to PET/CT artefacts and n=13 belonging to subjects with prior splenectomy). Association with outcome was tested in 80 out of 84 morphologically evaluable target lesions. Baseline SUVmax, SUVmean, tumour-to-blood ratio, SSTR-TV and total lesion SSTR expression were not associated with the lesion morphological outcome (Table 3). Baseline tumour-to-spleen ratio was significantly lower in the responding lesions compared to the non-responding (p=0.03), however no correlation was found in a lesion-by-lesion analysis, with Spearman rank coefficient of 0.04 (p=0.73; 95%CI: -0.20 to 0.27), as detailed in Table 3.

The change of the volumetric 68Ga-DOTATATE PET-parameters after one PRRT course was significantly associated with the lesion morphological outcome: a higher decrease was observed in the responding compared to the non-responding lesions for SSTR-TV (p=0.05) and total lesion SSTR expression (p=0.01) (Figure 1). A statistically significant correlation was also found in the lesion-by-lesion analysis, with Spearman rank coefficient of 0.27 (95%CI: 0.05-0.47, p=0.01) and 0.32 (95%CI: 0.11-0.51, p=0.004) for both the SSTR-TV and total lesion SSTR expression, respectively (Table 4). Uptake 68Ga-DOTATATE PET-parameters, i.e. SUVmax, SUVmean, tumour-to-spleen and tumour-to-blood ratio showed significant "early" decrease in all lesions, while on the subsequent pre-cycle evaluations and at end-of-treatment, their values remained globally stable compared to pre-cycle 2 (Supplementary Figure S1); their "early" decrease however, was not associated with the lesion morphological outcome (Table 4).

3.3.2 ^{18}FDG PET/CT imaging

At baseline, 21 target lesions, found in 12 subjects, were ^{18}FDG-positive. The quantification of ^{18}FDG-PET parameters was performed in 18 lesions (n=3 excluded due to image artefacts), of which 15 were morphologically evaluable. Median (IQR) baseline values of SUVmax, SUVmean, MATV and TLG in all lesions were 5.7 (5.1-8.3), 4.2 (3.8-4.8), 4.0 (2.2-15.9) and 17.9 (9.1-49.4), respectively. No significant association with the lesion morphological outcome was observed for the 18FDG PET baseline parameters.

Minor "early" decrease of SUVmax was observed between baseline and pre-cycle 2 in all lesions (median: -10%; IQR: -20% to -8%) (p=0.03). However, this was not associated with the lesion morphological outcome. SUVmean showed a higher "early" decrease in the non-responding lesions (median: -12.2%, IQR: -38.6 to -5.8) compared to the responding lesions (median: 5.9%, IQR: 4.2 to 7.7) (p=0.03). No significant change between treatment cycles or association with lesion outcome was found for MATV (p=0.82) and TLG (p = 0.60).

3.3.3 dwMR imaging (diffusion-weighted MRI)

Baseline ADC values (ADC = apparent diffusion coefficient) were available for 86 of the 116 target lesions (n=6 excluded due to MR image artefacts; n=24 belonged to eight subjects followed by CT). The Median (IQR) baseline ADC in all lesions was 859 (718-1002). In 62 morphologically evaluable lesions, no association was found between baseline ADC and lesion outcome (p=0.58).

A significant "early" increase of ADC from baseline was observed in all evaluable lesions (median of 12%; IQR: 2% to 27%) (p < 0.001), while in the subsequent pre-cycle evaluations and at end-of-treatment, ADC remained stable compared to pre-cycle 2. No association was found between the "early" ADC increase and morphological lesion outcome (p=0.71).

3.4 Imaging parameters and association with patient outcome

3.4.1 ^{68}Ga-DOTATATE PET/CT imaging

On a subject level, the "early" change of SSTR-TV and total lesion SSTR expression (average value per patient) were tested for association with PFS. An optimal cut-off of -10% was identified for both parameters. The "early" decrease of SSTR-TV of more than 10% discriminated subjects with significantly longer median PFS of 51.3 months, compared to median PFS of 22.8 months in subjects in which SSTR-TV increased or decreased less than 10% at the pre-cycle 2 evaluation (p=0.003; HR:0.35, 95%CI:0.16-0.75) (Figure 2). "Early" decrease of the total lesion SSTR expression of more than 10% discriminated subjects with a median PFS of 32.2 months compared to 26.2 months (p=0.05; HR:0.42, 95%CI:0.17-1.0).

The "early" change of SSTR-TV and total lesion SSTR expression remained significantly associated with the subject's best objective response according to RECIST1.1. Both parameters were significantly lower in responding subjects with a median of -9% (IQR: -36% to 9%; p=0.04) and -34% (IQR: -52% to -10%; p=0.008) for SSTR-TV and total lesion SSTR expression, respectively, compared to a median of 8% (IQR: 3% to 30%) and -3% (IQR: -19% to 10%) in the non-responding subjects.

As the baseline tumour-to-spleen ratio was significant in a lesion-based analysis, the average values per subject were tested for association with PFS and best objective response. An optimal cut-off of 1.25 demonstrated no statistical significance in association with PFS (p=0.20). Furthermore, no association was found between this parameter and the best objective response (p=0.11).

3.4.2 ^{18}FDG PET/CT imaging

Out of the twelve subjects with ^{18}FDG-positive target lesions, quantification of baseline ^{18}FDG PET/CT was available only in 10 (in n=2 subjects baseline timepoint was excluded because of image artefacts). Due to the low number of subjects and events, no statistical analysis for association with PFS or best objective response was performed for the 18FDG PET/CT imaging parameters.

3.4.3 dwMR imaging

In the 29 subjects followed by MR, no significant association was found between the best objective response and baseline ADC and its "early" increase (p=0.31 and p=0.79, respectively). Similarly, no statistical evidence for association with PFS was found as well.

3.5 Tumour dosimetry

3.5.1 Absorbed dose over treatment cycles

Complete three-timepoints SPECT/CT tumour dosimetry was performed in 83 target lesions in 35 subjects (33 target lesions were excluded, Supplementary Figure S2). The mean (±SD) cumulative absorbed dose in all lesions was 116.4Gy (±59.9) and ranged from a minimum of 20.9Gy to a maximum of 286Gy. The median absorbed dose declined from the first to the last treatment cycle with a median (IQR) C1 dose of 32.6Gy (21.8-50.2), C2 dose of 30.3Gy (19.2-44.2), C3 dose of 26.5Gy (17.3-38.7) and C4 dose of 21.8Gy (13.6-33.9), reaching significance between C1 and C4 (p=0.001), and C2 and C4 (p=0.03) as presented in Figure 3.

3.5.2 Tumour dose and lesion outcome

In 69 target lesions treated with four or more cycles of PRRT, no correlation was found between C1 dose and the lesion morphological outcome. In the subgroup analyses, a significant correlation with Spearman rank coefficient -0.89 (95%CI: -0.97 to -0.60; p<0.001) was found between C1 dose and

morphological outcome in lesions from the colorectal primary NET origin (n=10). When combining primary colorectal NET origin and size of at least 22mm at baseline (n=8), the Spearman rank coefficient was -0.92 (95%CI: -0.99 to -0.61; p<0.001). Complete results are presented in Table 5.

3.5.3 Tumour dose and progression-free survival

On a subject level, median (IQR) values for minC1 dose, maxC1 dose and meanC1 dose were 26.7Gy (17.7-26.9), 41.9Gy (26.7-62.5) and 36.6Gy (24.6-45.9), respectively.

For the minC1 dose, an optimal cut-off of 35Gy was identified. Nine subjects in whom all target lesions received at least 35Gy C1 dose had significantly longer PFS (median: 48.1 months), compared to a median PFS of 26.2 months in 26 subjects in whom at least one target lesion was treated with <35Gy in the C1 of PRRT (p=0.02; HR: 0.37, 95%CI: 0.17-0.82) (Figure 4). No association with PFS was found for the maxC1 and meanC1 doses.

Twenty-one out of the 26 (81%) subjects who had minC1 dose <35Gy, did not show sufficient "early" decrease of SSTR-TV. Combining these two parameters, a stronger association with PFS was demonstrated. Namely, all 21 patients with minC1dose <35Gy and SSTR-TV "early" increase or decrease of less than 10% showed significantly shorter PFS (median: 22.8 months) compared to the 13 subjects in whom minC1 dose was at least 35Gy or had an "early" SSTR-TV decrease more than 10% (median: 51.3 months, p<0.001; HR: 0.32, 95%CI: 0.14-0.71), as presented in Figure 5.

3.6 Hematological toxicities and organs-at-risk (OARs) dosimetry

The most common AEs (any grade) were anaemia (65% of the patients), lymphopenia (65%) and thrombocytopenia (51%). The most common grade ≥3 AEs were lymphopenia (43%), gamma-glutamyltransferase increased (14%) and aspartate aminotransferase increased (11%). One in three subjects has an SAE. A higher cumulative Biologically Effective Dose (BED) in the bone marrow was seen in subjects with anaemia (mean 0.83 vs 0.64 in those without anemia, p-value 0.01) and thrombocytopenia (mean 0.85 vs 0.67 in those without thrombocytopenia, p-value 0.01). The cumulative Absorbed Dose (AD) in the spleen seems to be unrelated to the occurrence of anaemia, lymphopenia or thrombocytopenia (respective p-value 0.53, 0.25, and 0.37).

There seems to be a decrease in the GFR from screening till EOT: 11% decrease, p-value 0.03, but this decrease was unrelated to the cumulative BED in the kidneys (spearman correlation 0.07, p-value 0.71).

Figures and tables

Table 1. Subject demographics and tumour characteristic. n = number, SD = standard deviation, IQR = interquartile range.

Characteristics	Subjects (n = 37)
Gender, n (%)	
male	19 (51)
female	18 (49)
Mean age (SD) at diagnosis, y	61 ± 10
Mean age (SD) at inclusion, y	66 ± 8.1
Median (IQR) time since diagnosis, y	3.4 (1.7-7.7)
Primary tumour site, n (%)	
small intestinal	23 (62)
pancreatic	10 (27)
colorectal	4 (11)
Tumour grade, n (%)	
grade 1	12 (32)
grade 2	22 (59)
grade 3	3 (8)
Site of metastasis, n (%)	
liver	32 (86)
lymph nodes	31 (84)
bone	22 (59)
peritoneum	12 (32)
pancreas	3 (8)
lung	2 (5)
other*	6 (16)
Symptoms, n (%)	
diarrhoea	16 (43)
pain	15 (41)
fatigue	11 (30)
flushes	9 (24)
no symptoms	12 (32)
Positive ^{18}FDG PET/CT at baseline, n (%)	15 (41)
Previous treatments, n (%)	
surgery (including primary tumour resection)	27 (73)
SSAs	36 (97)
targeted therapy**	11 (30)
chemotherapy	8 (22)
liver targeted therapy***	8 (22)
radiotherapy (external beam radiation)	4 (11)
interferon	1 (3)

*pleural, adrenal, ovarium, mesentery/pelvic
** including everolumus and sunitinib
*** including chemo-embolisation, radio-embolisation and radiofrequency ablation

Table 2. Association between PFS and potential prognostic factors. n = number, HR = hazard ratio, CI = confidence interval, PFS = progression-free survival

Prognostic factor	n sujects	n events	PFS (months)	*p* value	HR (95%CI)
Primary tumour origin					
pancreatic	10	8	19.4	**0.01**	**2.96 (1.25-7.02)**
SI and colorectal	27	19	29.5		
Tumour grade					
grade 1	12	7	22.8	0.35[§]	0.66 (0.27-1.60) [§]
grade 2	22	17	29.5		
grade 3	3	3	21.7		
Age at diagnosis					
<61	16	10	27.8	0.64	0.82 (0.37-1.86)
≥61	21	17	28.6		
Age at inclusion					
<67	18	12	28.1	0.82	1.09 (0.50-2.38)
≥67	19	15	26.2		
Gender					
male	19	16	28.6	0.67	1.19 (0.54-2.63)
female	18	11	27.6		
Symptoms before PRRT					
yes	25	17	27.6	0.89	0.95 (0.42-2.11)
no	12	10	28.6		
Previous systemic treatment					
1	21	16	29.5	0.08	0.49 (0.22-1.10)
>1	16	11	21.7		
Positive ^{18}FDG PET/CT at baseline					
yes	15	13	28.2	0.90	1.05 (0.48-2.30)
no	22	14	27.6		
Liver metastases					
yes	32	24	27.8	0.74	1.23 (0.36-4.19)
no	5	3	31.6		
Bone metastases					
yes	22	17	26.2	0.13	1.95 (0.83-4.59)
no	15	10	31.6		

p values: Cox proportional hazards regression.
[§]*p* value and HR (95%CI) for tumour grade 2/3 versus grade 1

Table 3. Association of *baseline* ^{68}Ga-DOTATATE PET/CT parameters and morphological tumour response. TV = tumour volume, R = responding lesion, NR = non-responding lesion, n = number of lesions, IQR = interquartile range, CI = confidence interval.

Baseline ^{68}Ga-DOTATATE PET/CT parameters							
	Response	n	Median	IQR	*p* value	Spearman ρ (95% CI)	*p* value
SUVmax	R	21	18.7	(14.7 to 24.2)	0.71		
	NR	59	18.6	(14.8 to 25.4)			
SUVmean	R	21	11.4	(9.7 to 13.1)	0.99		
	NR	59	11.0	(9.1 to 13.7)			
Tumour-to-spleen ratio	R	16	1.3	(0.8 to 1.9)	**0.03**	0.04 (-0.20-0.27)	0.73
	NR	54	1.8	(1.3 to 2.7)			
Tumour-to-blood ratio	R	21	59.8	(51.1 to 82.1)	0.37		
	NR	59	54.6	(39.6 to 80.8)			
SSTR-TV	R	21	8.4	(2.4 to 26.5)	0.81		
	NR	59	7.6	(3.9 to 20.9)			
Total lesion SSTR expression	R	21	86	(45 to 227)	0.81		
	NR	59	108	(39 to 247)			

Table 4. Association of "early" (*pre-cycle 2*) %change of ^{68}Ga-DOTATATE PET/CT parameters and morphological tumour response. TV = tumour volume, R = responding lesion, NR = non-responding lesion, n = number of lesions, IQR = interquartile range, CI = confidence interval.

Early change of ^{68}Ga-DOTATATE PET/CT parameters							
	Response	n	Median	IQR	*p* value	Spearman ρ (95% CI)	*p* value
SUVmax	R	19	-23%	(-33% to 0%)	0.48		
	NR	59	-16%	(-33% to 0%)			
SUVmean	R	19	-21%	(-39% to 3%)	0.29		
	NR	59	-15%	(-29% to 5%)			
Tumour-to-spleen ratio	R	14	-32%	(-41% to -8%)	0.91		
	NR	54	-30%	(-50% to -12%)			
Tumour-to-blood ratio	R	19	-18%	(-35% to 3%)	0.44		
	NR	59	-16%	(-31% to 19%)			
SSTR-TV	R	19	-9%	(-36% to 20%)	**0.05**	0.27 (0.05-0.47)	**0.01**
	NR	59	11%	(-8% to 27%)			
Total lesion SSTR expression	R	19	-27%	(-46% to -3%)	**0.01**	0.32 (0.11-0.51)	**0.004**
	NR	59	-6%	(-24% to 11%)			

Table 5. Correlation between tumour absorbed dose in first PRRT cycle (C1 dose) and lesion morphological outcome in all lesions and in subgroup of lesions based on size (i.e. longest axial diameter on baseline MR or CT), primary NET origin (i.e. pancreatic, small-intestinal and colorectal) and their combination. n = number of lesions.

Correlation between C1 absorbed dose and morphological outcome				
Lesions		n	Spearman ρ (95% CI)	*p* value
All		69	-0.13 (-0.36 to 0.11)	0.28
Size < 22mm		31	0.02 (-0.34 to 0.37)	0.92
Size ≥ 22mm		38	-0.29 (-0.56 to 0.03)	0.07
Pancreatic primary NET		20	-0.35 (-0.69 to 0.11)	0.12
Small-intestinal primary NET		39	0.26 (-0.06 to 0.53)	0.10
Colorectal primary NET		10	-0.89 (-0.97 to -0.60)	**<0.001**
Size < 22mm	Pancreatic primary NET	10	-0.58 (-0.89 to 0.08)	0.06
	Small-intestinal primary NET	19	0.41 (-0.06 to 0.73)	0.07
	Colorectal primary NET	2*	/	/
Size ≥ 22mm	Pancreatic primary NET	10	-0.13 (-0.70 to 0.54)	0.71
	Small-intestinal primary NET	20	0.12 (-0.33 to 0.54)	0.60
	Colorectal primary NET	8	-0.92 (-0.99 to -0.61)	**<0.001**

*Number of lesions too small for analysis

Figure 1. Scatter diagram with loess smoother and 95% confidence area of SSTR-TV and Total lesion (TL) SSTR expression at *baseline* ^{68}Ga-DOTATATE PET/CT and during subsequent treatment cycles in morphologically responding lesions showing partial or complete response (left) and morphologically non-responding target lesions: stable and progressive lesions (right). PR = partial response, CR = complete response, SD = stable disease, PD = progressive disease.

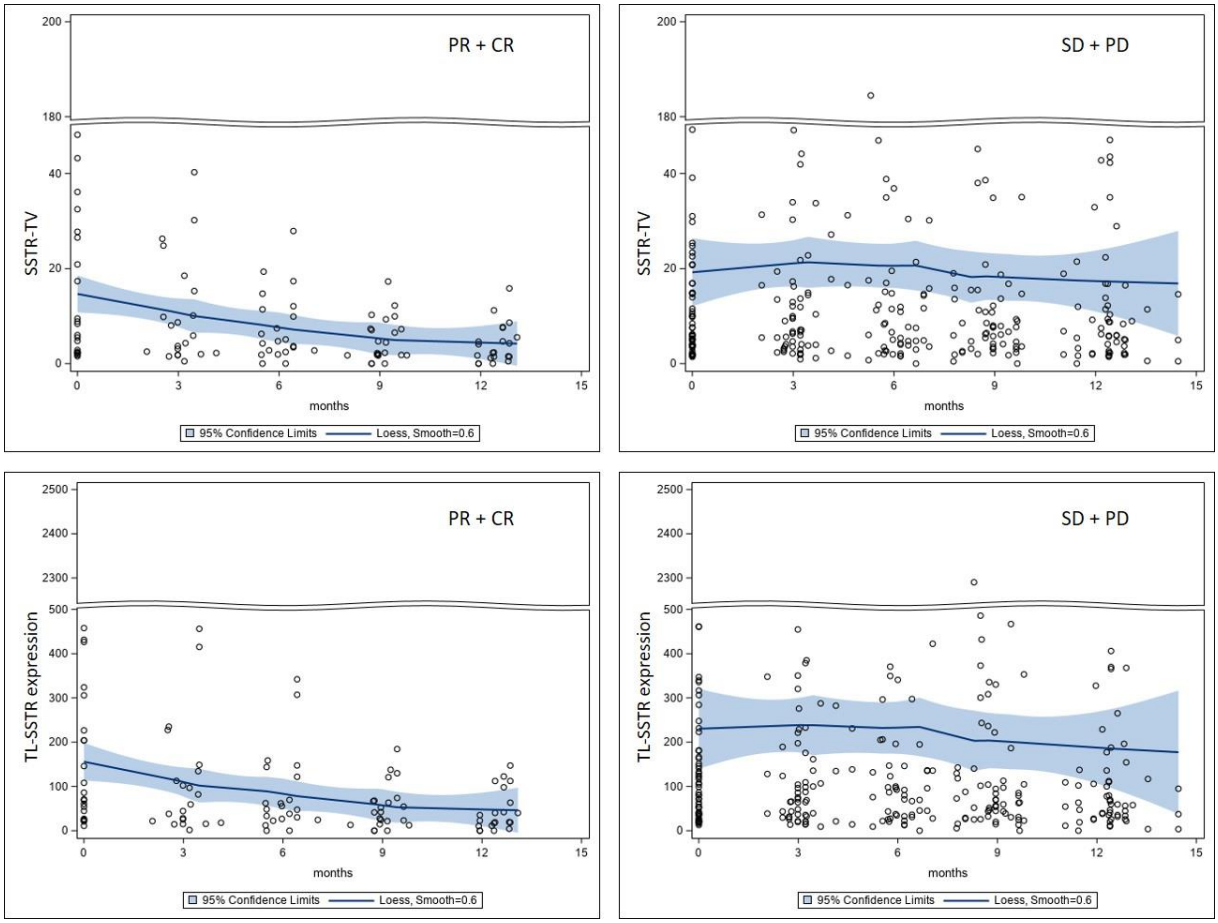


Figure 2. Kaplan-Meier analysis for "early" (*pre-cycle 2*) change of SSTR-TV.

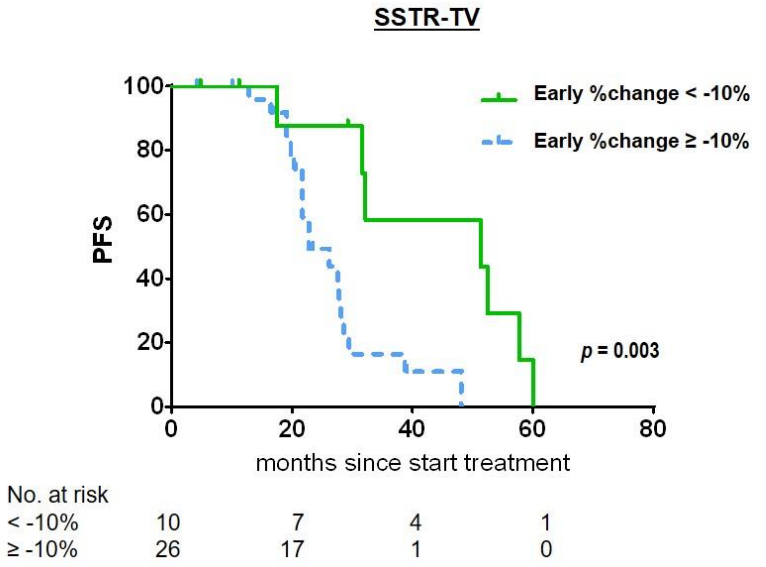


Figure 3. Tumour absorbed dose at each PRRT cycle for all target lesions (n=83), continually decreasing during the course of treatment, and significantly between cycle 1 (C1) and C4, and between C2 and C4.

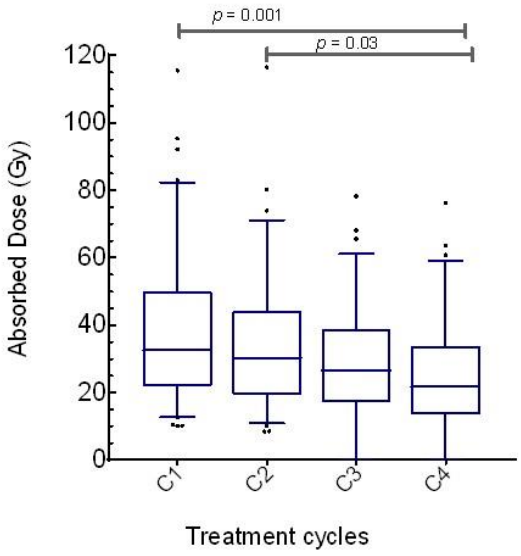


Figure 4. Kaplan-Meier analysis for the minimal absorbed dose per target lesion received in the first PRRT cycle (minC1 dose).

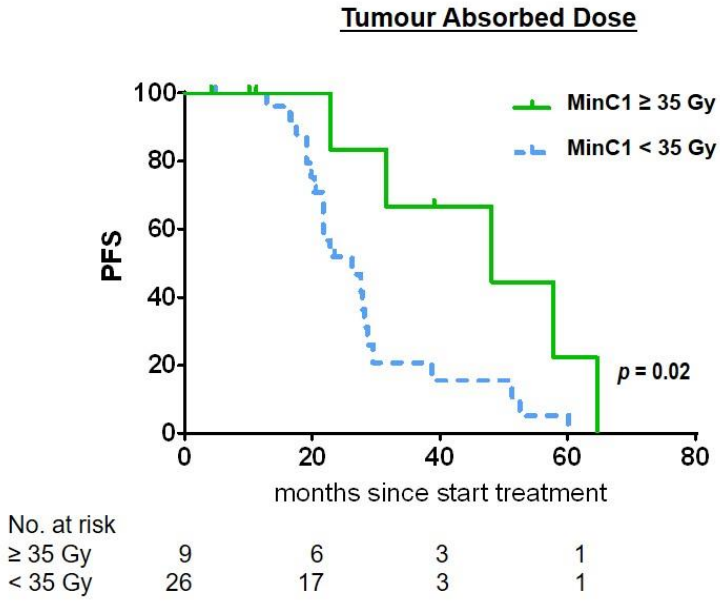
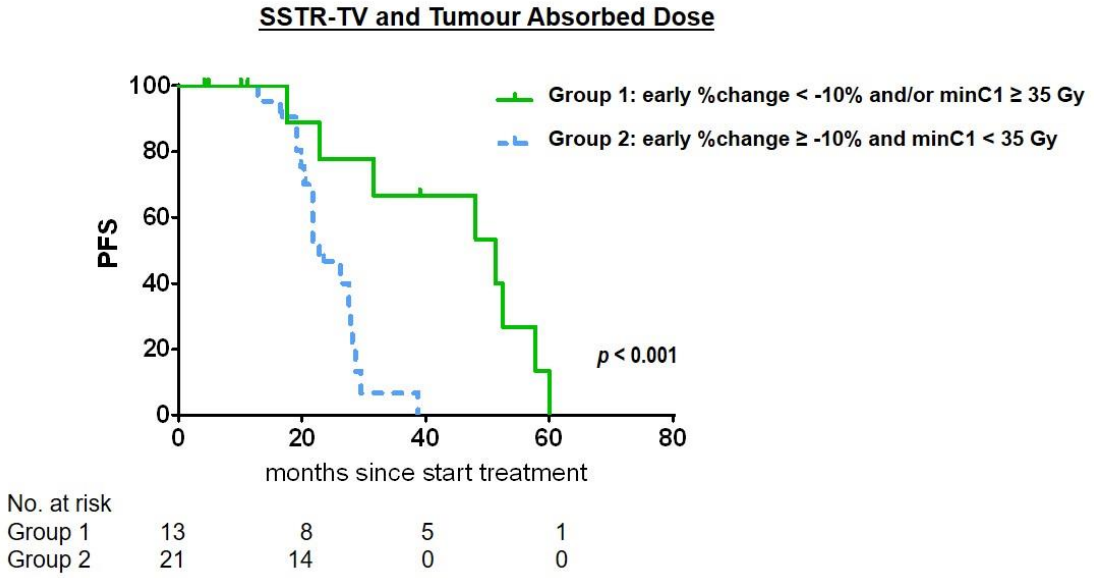


Figure 5. Kaplan-Meier analysis for the combination of "early" (*pre-cycle 2*) change of SSTR-TV and minimal absorbed dose per target lesion received in the first PRRT cycle (minC1 dose).



4 ADVERSE EVENTS

4.1 Adverse events information

Serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the first administration of ^{177}Lu-octreotate until 12 weeks after the last dose of ^{177}Lu-octreotate.

37 subjects were exposed to ^{177}Lu-octreotate:

- 13 subjects were affected by serious adverse events.
- 37 subjects were affected by non-serious adverse events.

Notes:

1. The adverse event and serious adverse event assessment method was systematic.
2. The MedDRA version used was the version 26.0
3. Recurrence or progression of underlying malignancy is not reported as an AE or SAE if it is clearly consistent with the suspected recurrence or progression of the underlying cancer but will be reported on the CRF.

   Second primary malignancy unrelated to the study drug should not be reported as an AE or SAE but will be however reported on the CRF on the appropriate form (SPM form).

   Hospitalization due solely to the recurrence or progression of underlying malignancy should NOT be reported as an SAE.

   Clinical symptoms of recurrence or progression may be reported as AEs or SAEs if the symptoms cannot be determined as exclusively due to the recurrence or progression of the underlying malignancy, or does not fit the expected pattern of recurrence or progression for the disease under study.

   Deaths related to progression of the underlying disease during the course of the study will not be reported as a SAE, but should be reported on the appropriate CRF section (unless the patient has withdrawn consent).

   Similarly, clinical symptoms of underlying malignancy may be reported as AEs or SAEs if the symptoms cannot be determined as exclusively due to the underlying malignancy, or does not fit the expected pattern of the disease under study.

4.2 Serious adverse events

The table hereunder presents all serious adverse events sorted by MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PT).

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All SAE occurrences	SAE occurrences causally related to ^{177}Lu-octreotate	Number of fatalities	Number of fatalities-causally related to ^{177}Lu-octreotate
Blood and lymphatic system disorders					
Anaemia	1	1	1		
Cardiac disorders					
Cardiac failure	1	1			
Gastrointestinal disorders					
Abdominal pain upper	1	1	1		
Ascites	2	2	1		
Intestinal ischaemia	1	1			
Pancreatitis acute	1	1	1		
Small intestinal obstruction	1	1			
Subileus	2	2			
General disorders and administration site conditions					
Inflammation	1	1			
General disorders and administration site conditions					
Pyrexia	1	1	1		
Hepatobiliary disorders					
Cholecystitis acute	1	1			
Immune system disorders					
Anaphylactic reaction	1	1		1	
Infections and infestations					
Bacteroides infection	1	1			
Injury, poisoning and procedural complications					
Incisional hernia	1	1			
Spinal compression fracture	1	1			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Myelodysplastic syndrome	2	2	1*		
Renal and urinary disorders					
Hydronephrosis	1	1			

**Not reported as AE because the event occurred more than 12 weeks after the last administration of IMP.*

4.3 Non-serious adverse events

The frequency threshold for reporting non-serious adverse events is 0 %.

The below table presents all non-serious adverse events sorted by MedDRA System Organ Class (SOC), MedDRA Preferred Terms (PT).

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AEs occurrences causally related to to ^{177}Lu-octreotate
Blood and lymphatic system disorders			
Anaemia	23	47	45
Hilar lymphadenopathy	1	1	
Leukocytosis	2	2	
Cardiac disorders			
Mitral valve incompetence	1	1	
Tricuspid valve sclerosis	1	1	
Ventricular arrhythmia	1	1	
Congenital, familial and genetic disorders			
Phimosis	1	1	
Ear and labyrinth disorders			
Tinnitus	1	1	
Vertigo	4	5	4
Endocrine disorders			
Hypothyroidism	3	3	3
Eye disorders			
Cataract	1	1	
Eye disorder	1	1	
Glaucoma	1	1	
Visual field defect	1	1	
Visual impairment	1	1	
Vitreous detachment	1	1	
Gastrointestinal disorders			
Abdominal pain	6	9	5
Abdominal pain lower	1	1	
Abdominal pain upper	5	8	
Chronic gastritis	1	1	
Constipation	9	11	
Diarrhoea	10	12	7
Diverticulum	1	1	
Dry mouth	1	1	

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AEs occurrences causally related to to ^{177}Lu-octreotate
Dyspepsia	1	1	
Dysphagia	2	2	
Gastric ulcer	1	1	
Gastritis	1	1	
Gastrointestinal pain	2	2	1
Gastrooesophageal reflux disease	1	1	
Haemorrhoidal haemorrhage	2	2	
Hiatus hernia	1	1	
Intestinal obstruction	1	1	
Nausea	15	28	24
Reflux gastritis	1	1	1
Vomiting	11	18	15
General disorders and administration site conditions			
Catheter site pain	1	1	
Catheter site pruritus	1	1	
Fatigue	19	22	20
Induration	1	1	
Infusion site extravasation	1	1	
Malaise	1	1	
Oedema	2	2	
Oedema peripheral	2	2	
Pyrexia	4	4	1
Hepatobiliary disorders			
Ocular icterus	1	1	
Infections and infestations			
Bronchitis	4	4	
Folliculitis	1	1	
Gastroenteritis	3	3	
Infection	1	1	
Otitis	1	1	
Pneumonia mycoplasmal	1	1	
Post procedural infection	1	1	
Respiratory tract infection	1	1	
Skin infection	1	1	
Upper respiratory tract infection	4	6	

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AEs occurrences causally related to to ^{177}Lu-octreotate
Urinary tract infection	2	2	
Wound infection	1	1	
Injury, poisoning and procedural complications			
Contusion	1	1	
Spinal compression fracture	1	1	
Investigations			
Alanine aminotransferase increased	10	16	8
APTT increased	1	1	
Aspartate aminotransferase increased	9	17	6
Blood alkaline phosphatase increased	7	11	5
Blood bilirubin increased	2	2	
Blood cholesterol increased	1	1	
Blood lactate dehydrogenase increased	1	1	
Gamma-glutamyltransferase increased	12	22	19
International normalised ratio increased	1	2	
Lymphocyte count decreased	24	32	32
Lymphocyte count increased	1	1	1
Neutrophil count decreased	4	6	6
N-terminal prohormone brain natriuretic peptide increased	1	1	
Platelet count decreased	19	41	41
Weight decreased	2	2	
Weight increased	1	1	1
White blood cell count decreased	12	23	23
Metabolism and nutrition disorders			
Decreased appetite	2	3	
Hypercalcaemia	2	3	
Hypercholesterolaemia	1	1	
Hyperkalaemia	1	1	
Hyperuricaemia	1	2	
Hypocalcaemia	1	1	
Iron deficiency	1	1	
Vitamin D deficiency	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia	5	5	
Back pain	4	4	

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AEs occurrences causally related to to ^{177}Lu-octreotate
Bone pain	1	1	
Joint stiffness	1	1	
Myalgia	1	1	
Pain in extremity	3	3	
Periarthritis	1	1	
Spinal pain	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma	1	1	
Nervous system disorders			
Carpal tunnel syndrome	1	1	
Dysgeusia	4	6	6
Headache	7	7	3
Paresis	1	1	
Presyncope	2	2	
Psychiatric disorders			
Anxiety	2	2	
Depression	1	1	
Insomnia	1	4	
Renal and urinary disorders			
Chronic kidney disease	3	3	3
Micturition urgency	1	1	
Pollakiuria	1	1	
Urethral stenosis	1	1	
Reproductive system and breast disorders			
Benign prostatic hypertrophy	1	1	
Prostatitis	1	1	
Vaginal haemorrhage	1	1	
Respiratory, thoracic and mediastinal disorders			
Cough	2	2	
Hiccups	3	5	5
Hypoventilation	1	1	
Pleural effusion	3	4	
Wheezing	2	2	
Skin and subcutaneous tissue disorders			
Alopecia	17	23	23

MedDRA **Primary** **SOC** *MedDRA PT*	Number of subjects affected	All AE occurrences	AEs occurrences causally related to to ^{177}Lu-octreotate
Dermatitis allergic	1	1	
Eczema	1	1	
Erythema	1	1	
Hirsutism	1	1	1
Hyperhidrosis	1	1	
Pruritus	2	4	3
Urticaria	1	3	
Vascular disorders			
Flushing	4	9	8
Hot flush	2	2	1
Hypertension	1	1	
Hypotension	1	1	

5 ADDITIONAL INFORMATION

5.1 Global substantial modifications

The global substantial modifications are summarised in the below table.

Amendment date	Description
Initial EC approval 22/11/2012 CA / FANC Comments	• Protocol v1.0 • ICF v1.1.
AMDT 1 EC approval 20/12/2012 CA comments/GNAs FANC /	• Protocol v2.0 • ICF v2.0
AMDT 2 EC approval 28/03/2013 CA approval 27/05/2013 FANC approval 22/04/2013	• Protocol v3.0 • ICF v3.0
AMDT EC approval 07/11/2013 CA / FANC /	• Protocol v3.3 • ICF v3.1
AMDT 3 EC approval 05/06/2014 CA / FANC /	• Protocol v4.0 • ICF v4.0
AMDT 4 EC approval 07/05/2015	• Protocol v5.0 • ICF v5.1

Amendment date	Description
CA approval 08/06/2015 FANC approval 24/06/2015	
AMDT 5 EC approval 20/08/2015 CA approval 07/09/2015 FANC approval 17/09/2015	• Protocol v6.0 • ICF v6.0
AMDT 6 EC approval 22/10/2015 CA / FANC /	• Addendum A & B
AMDT 7 EC approval 14/07/2016 CA approval 28/09/2016 FANC approval 25/08/2016	• Protocol v7.2 • ICF v7.0 • Addendum C v1.0 – 01/07/2016
AMDT 8 EC approval 22/06/2017 CA approval 13/06/2017 FANC /	• RSI change
AMDT 9 EC approval 06/12/2018 CA / FANC /	• ICF v8.0 • GDPR information letter
AMDT 10 EC approval 17/06/2021 CA approval 11/06/2021 FANC /	• Protocol v8.0
AMDT 11 EC approval 21/10/2021 CA / FANC /	• Institut Jules Bordet move
AMDT 12 EC approval 09/03/2022 CA / FANC /	• New insurer

5.2 Global interruptions and re-starts

There were no global interruptions to the trial.

5.3 Limitations, addressing sources of potential bias and imprecisions and caveats

There were no limitations and caveats.