Clinical trial results:
A multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with 177Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours

Summary

EudraCT number	2011-005049-11
Trial protocol	GB ES IT BE PT FR AT
Global end of trial date	18 January 2021

Results information

Result version number	v1
This version publication date	22 October 2021
First version publication date	22 October 2021

Trial information

Trial identification

Sponsor protocol code	AAA-III-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01578239
WHO universal trial number (UTN)	-
Other trial identifiers	CAAA601A12301: Novartis

Notes:

Sponsors

Sponsor organisation name	Advanced Accelerator Applications SA
Sponsor organisation address	20, rue Diesel, Saint-Genis Pouilly, Switzerland, 01630
Public contact	Novartis Clinical Disclosure Office, Advanced Accelerator Applications SA, 41 613241111, Novartis.email@novartis.com
Scientific contact	Novartis Clinical Disclosure Office, Advanced Accelerator Applications SA, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 January 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare progression-free survival (PFS) after treatment with 177Lu-DOTA0-Tyr3-octreotate (Lutathera) plus best supportive care (30 mg Octreotide LAR) to treatment with high-dose (60 mg) Octreotide LAR in participants with inoperable, progressive [as determined by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1], somatostatin receptor positive, well-differentiated neuroendocrine tumors of the small bowel (midgut carcinoid tumors)

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United States: 137
Worldwide total number of subjects	231
EEA total number of subjects	70

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	119
From 65 to 84 years	110
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted in 41 sites across 8 countries.

Period 1

Period 1 title	Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	177Lu-DOTA0-Tyr3-Octreotate

Arm description:

- 30 mg Octreotide LAR treatment for symptom control continued until the end of study, unless the participant progressed or died. - Treatment consisted of a cumulative administered radioactivity of 29.6 Giga Becquerel (GBq) (800 mCi) 177Lu-DOTA0-Tyr3-Octreotate: Four administrations of 7.4 GBq (200 mCi). - Concomitant amino acids were given with each administration for kidney protection. - 177Lu-DOTA0-Tyr3-Octreotate was administered at 8 +/- 1-week intervals, which could be extended up to 16 weeks to accommodate resolving acute toxicity. - In case participants experienced clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, Octreotide s.c. rescue injections were allowed.

Arm type	Experimental
Investigational medicinal product name	177Lu-DOTA0-Tyr3-Octreotate
Investigational medicinal product code	
Other name	Lutathera
Pharmaceutical forms	Kit for radiopharmaceutical preparation
Routes of administration	Intravenous use

Dosage and administration details:

Four administrations of 7.4 GBq (200 mCi) 177Lu-DOTA0-Tyr3-Octreotate administered at 8 +/- 1-week intervals, which could be extended up to 16 weeks to accommodate resolving acute toxicity.

Investigational medicinal product name	Octreotide LAR
Investigational medicinal product code	
Other name	SANDOSTATIN LAR, Octreotide
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

30 mg Octreotide LAR treatment was given to the participants until the end of study for symptom control purpose, unless the participant progressed or died.

Arm title	Octreotide LAR

Arm description:

- 60 mg Octreotide LAR treatment every 4 weeks (i.m. injections) until the end of the study, unless the participant progressed or died. - In case participants experienced clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, s.c. Octreotide rescue injections were allowed.

Arm type	Active comparator

Investigational medicinal product name	Octreotide LAR
Investigational medicinal product code	
Other name	SANDOSTATIN LAR, Octreotide
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

60 mg Octreotide LAR treatment was given to the participants every 4 weeks (i.m. injections) until the end of the study, unless the participant progressed or died.

Number of subjects in period 1	177Lu-DOTA0-Tyr3-Octreotate	Octreotide LAR
Started	117	114
Full Analysis set (FAS)	117	114
Safety Analysis Set (SAF)	111	112
FAS-Entered long-term follow-up	101	99
Completed	50	13
Not completed	67	101
Physician decision	17	17
Consent withdrawn by subject	10	9
Adverse event, non-fatal	13	10
Progressive Disease	19	64
Not specified	6	1
Non-compliance	2	-

Period 2

Period 2 title	Long-term Follow-Up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	177Lu-DOTA0-Tyr3-Octreotate

Arm description:

- 30 mg Octreotide LAR treatment for symptom control continued until the end of study, unless the participant progressed or died. - Treatment consisted of a cumulative administered radioactivity of 29.6 Giga Becquerel (GBq) (800 mCi) 177Lu-DOTA0-Tyr3-Octreotate: Four administrations of 7.4 GBq (200 mCi). - Concomitant amino acids were given with each administration for kidney protection. - 177Lu-DOTA0-Tyr3-Octreotate was administered at 8 +/- 1-week intervals, which could be extended up to 16 weeks to accommodate resolving acute toxicity. - In case participants experienced clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, Octreotide s.c. rescue injections were allowed.

Arm type	Experimental

Investigational medicinal product name	177Lu-DOTA0-Tyr3-Octreotate
Investigational medicinal product code	
Other name	Lutathera
Pharmaceutical forms	Kit for radiopharmaceutical preparation
Routes of administration	Intravenous use

Dosage and administration details:

Four administrations of 7.4 GBq (200 mCi) 177Lu-DOTA0-Tyr3-Octreotate administered at 8 +/- 1-week intervals, which could be extended up to 16 weeks to accommodate resolving acute toxicity.

Investigational medicinal product name	Octreotide LAR
Investigational medicinal product code	
Other name	SANDOSTATIN LAR, Octreotide
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

30 mg Octreotide LAR treatment was given to the participants until the end of study for symptom control purpose, unless the participant progressed or died.

Arm title	Octreotide LAR

Arm description:

- 60 mg Octreotide LAR treatment every 4 weeks (i.m. injections) until the end of the study, unless the participant progressed or died. - In case participants experienced clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, s.c. Octreotide rescue injections were allowed.

Arm type	Active comparator
Investigational medicinal product name	Octreotide LAR
Investigational medicinal product code	
Other name	SANDOSTATIN LAR, Octreotide
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

60 mg Octreotide LAR treatment was given to the participants every 4 weeks (i.m. injections) until the end of the study, unless the participant progressed or died.

Number of subjects in period 2	177Lu-DOTA0-Tyr3-Octreotate	Octreotide LAR
Started	101	99
Completed	24	19
Not completed	77	80
Adverse event, serious fatal	69	64
Consent withdrawal	4	10
Not specified	2	2
Lost to follow-up	2	4

Baseline characteristics

Reporting groups	
Reporting group title	177Lu-DOTA0-Tyr3-Octreotate
Reporting group description:	
- 30 mg Octreotide LAR treatment for symptom control continued until the end of study, unless the participant progressed or died. - Treatment consisted of a cumulative administered radioactivity of 29.6 Giga Becquerel (GBq) (800 mCi) 177Lu-DOTA0-Tyr3-Octreotate: Four administrations of 7.4 GBq (200 mCi). - Concomitant amino acids were given with each administration for kidney protection. - 177Lu-DOTA0-Tyr3-Octreotate was administered at 8 +/- 1-week intervals, which could be extended up to 16 weeks to accommodate resolving acute toxicity. - In case participants experienced clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, Octreotide s.c. rescue injections were allowed.	
Reporting group title	Octreotide LAR
Reporting group description:	
- 60 mg Octreotide LAR treatment every 4 weeks (i.m. injections) until the end of the study, unless the participant progressed or died. - In case participants experienced clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, s.c. Octreotide rescue injections were allowed.	

Reporting group values	177Lu-DOTA0-Tyr3-Octreotate	Octreotide LAR	Total
Number of subjects	117	114	231
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	62	57	119
From 65-84 years	55	55	110
85 years and over	0	2	2
Age Continuous Units: years			
arithmetic mean	63.4	64.0	
standard deviation	± 9.34	± 9.80	-
Sex: Female, Male Units:			
Female	54	60	114
Male	63	54	117
Race/Ethnicity, Customized Units: Subjects			
Asian	1	0	1
Black or African American	5	5	10
Hispanic	6	3	9
White	93	96	189
Other	0	1	1
Not Applicable	12	9	21

End points

End points reporting groups

Reporting group title	177Lu-DOTA0-Tyr3-Octreotate

Reporting group description:

- 30 mg Octreotide LAR treatment for symptom control continued until the end of study, unless the participant progressed or died. - Treatment consisted of a cumulative administered radioactivity of 29.6 Giga Becquerel (GBq) (800 mCi) 177Lu-DOTA0-Tyr3-Octreotate: Four administrations of 7.4 GBq (200 mCi). - Concomitant amino acids were given with each administration for kidney protection. - 177Lu-DOTA0-Tyr3-Octreotate was administered at 8 +/- 1-week intervals, which could be extended up to 16 weeks to accommodate resolving acute toxicity. - In case participants experienced clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, Octreotide s.c. rescue injections were allowed.

Reporting group title	Octreotide LAR

Reporting group description:

- 60 mg Octreotide LAR treatment every 4 weeks (i.m. injections) until the end of the study, unless the participant progressed or died. - In case participants experienced clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, s.c. Octreotide rescue injections were allowed.

Reporting group title	177Lu-DOTA0-Tyr3-Octreotate

Reporting group description:

- 30 mg Octreotide LAR treatment for symptom control continued until the end of study, unless the participant progressed or died. - Treatment consisted of a cumulative administered radioactivity of 29.6 Giga Becquerel (GBq) (800 mCi) 177Lu-DOTA0-Tyr3-Octreotate: Four administrations of 7.4 GBq (200 mCi). - Concomitant amino acids were given with each administration for kidney protection. - 177Lu-DOTA0-Tyr3-Octreotate was administered at 8 +/- 1-week intervals, which could be extended up to 16 weeks to accommodate resolving acute toxicity. - In case participants experienced clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, Octreotide s.c. rescue injections were allowed.

Reporting group title	Octreotide LAR

Reporting group description:

- 60 mg Octreotide LAR treatment every 4 weeks (i.m. injections) until the end of the study, unless the participant progressed or died. - In case participants experienced clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, s.c. Octreotide rescue injections were allowed.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

Progression Free Survival (PFS) was defined as the time from randomization to documented centrally assessed disease progression, as evaluated by the Independent Review Committee (IRC), or death due to any cause. If a participant had no centrally assessed progression and had not died at the time of the primary endpoint analysis, the participant was regarded as censored in the context of a time to event analysis at the date of last evaluable tumor assessment. Disease progression was determined by objective tumor response status using Response Evaluation Criteria in Solid Tumors Criteria (RECIST v1.1).

End point type	Primary

End point timeframe:

From date of randomization until date of radiographic progression or date of death from any cause, whichever comes first until Primary Analysis cutoff date reached on 24July2015, assessed up to approximately 34 months

End point values	177Lu-DOTA0-Tyr3-Octreotate	Octreotide LAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	70		
Units: months				
median (confidence interval 95%)	999 (999 to 999)	8.5 (5.8 to 9.1)		

Statistical analyses

Statistical analysis title	Progression Free Survival (PFS)
Comparison groups	Octreotide LAR v 177Lu-DOTA0-Tyr3-Octreotate
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.177
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.108
upper limit	0.289

Notes:

[1] - Derived from a two-sided test between the two groups

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Objective Response Rate (ORR) was calculated as the proportion of patients with tumour size reduction (sum of partial responses (PR) and complete responses (CR)) according to RECIST 1.1.

End point type	Secondary

End point timeframe:

From date of randomization until date of progression or date of death from any cause, whichever comes first until Primary Analysis cutoff date reached on 24July2015, assessed up to approximately 34 months

End point values	177Lu-DOTA0-Tyr3-Octreotate	Octreotide LAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: Percentage of Participants				
median (confidence interval 95%)	14.7 (7.8 to 21.6)	4.0 (0.2 to 7.8)		

Statistical analyses

Statistical analysis title	Objective Response Rate (ORR)
Comparison groups	177Lu-DOTA0-Tyr3-Octreotate v Octreotide LAR
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0141
Method	Fisher exact

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival (OS) was defined as the time from the date of randomization to the date of death due to any cause or the date of last contact (censored observation) prior to the date of the data cut-off, and during the entire study period (i.e. the treatment period plus follow-up).

End point type	Secondary

End point timeframe:

From date of randomization until date of death from any cause up to final safety cut-off date reached on 18Jan2021, assessed up to approximately 100 months

End point values	177Lu-DOTA0-Tyr3-Octreotate	Octreotide LAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	69		
Units: Months				
median (confidence interval 95%)	76.3 (72.8 to 82.8)	76.5 (60.0 to 81.4)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Comparison groups	177Lu-DOTA0-Tyr3-Octreotate v Octreotide LAR

Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3039
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.17

Secondary: Rate of Overall Survival (OS)

End point title	Rate of Overall Survival (OS)

End point description:

Survival estimates were collected every 12 Months up to 60 Months to compare OS between the two treatment groups.

End point type	Secondary

End point timeframe:

12 months, 24 months, 36 months, 48 months, 60 months

End point values	177Lu-DOTA0-Tyr3-Octreotate	Octreotide LAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	69		
Units: Percentage of Survival Estimates				
number (confidence interval 95%)				
12 months	91.0 (84.0 to 95.1)	79.7 (70.8 to 86.1)		
24 months	76.0 (66.7 to 83.0)	62.7 (52.6 to 71.2)		
36 months	61.4 (51.4 to 69.9)	50.1 (40.0 to 59.4)		
48 months	49.5 (39.5 to 58.6)	41.8 (31.8 to 51.4)		
60 months	37.1 (27.8 to 46.4)	35.4 (25.7 to 45.2)		

Statistical analyses

Statistical analysis title	Rate of Overall Survival (OS)
Comparison groups	177Lu-DOTA0-Tyr3-Octreotate v Octreotide LAR

Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3039
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.17

Secondary: Time to Tumour Progression (TTP)

End point title	Time to Tumour Progression (TTP)

End point description:

Time to Tumour Progression (TTP) was defined as the time from randomization to progression centrally assessed. It included patients who dropped out due to toxicity, but omitted patients who died without measured progression (censored to last follow-up date or death date).

End point type	Secondary

End point timeframe:

From date of randomization until date of progression or date of death from any cause, whichever comes first until Primary Analysis cutoff date reached on 24July2015, assessed up to approximately 34 months

End point values	177Lu-DOTA0-Tyr3-Octreotate	Octreotide LAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	61		
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	8.7 (6.0 to 11.1)		

Statistical analyses

Statistical analysis title	Time to Tumour Progression (TTP)
Comparison groups	177Lu-DOTA0-Tyr3-Octreotate v Octreotide LAR
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.137

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.077
upper limit	0.242

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

The Duration of Response (DoR) was defined as the time from initially meeting the criteria for response (CR or PR) until the time of progression by RECIST 1.1.

End point type	Secondary

End point timeframe:

From date of randomization until date of progression or date of death from any cause, whichever comes first until Primary Analysis cutoff date reached on 24July2015, assessed up to approximately 34 months

End point values	177Lu-DOTA0-Tyr3-Octreotate	Octreotide LAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: Months				
median (confidence interval 95%)	999 (2.8 to 999)	1.9 (1.9 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

The distribution of adverse events was done via the analysis of frequencies for Adverse Event (AEs), Serious Adverse Event (SAEs) and Deaths, through the monitoring of relevant clinical and laboratory safety parameters.

End point type	Secondary

End point timeframe:

From informed consent signature through study completion reached at final safety cutoff date on 18July2021, assessed up to approximately 101 Months

End point values	177Lu-DOTA0-Tyr3-Octreotate	Octreotide LAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	112		
Units: Participants				
Adverse Events (AEs)	105	90		
Serious Adverse Events (SAEs)	40	31		
Deaths during treatment period	4	5		
Deaths during follow-up period	66	63		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the EORTC QLQ-C30 Questionnaire

End point title	Change from Baseline in the EORTC QLQ-C30 Questionnaire

End point description:

The Quality of Life Questionnaire C30 (QLQ-C30) was developed by the European Organization for Research and Treatment of Cancer (EORTC) to assess quality of life in cancer patients. It includes five function domains (physical, emotional, social, role, cognitive), eight symptoms (fatigue, pain, nausea/vomiting, constipation, diarrhea, insomnia, dyspnea, and appetite loss), as well as global health/quality-of-life and financial impact. Subjects respond on a four-point scale from "not at all" to "very much" for most items. Raw scores are linearly transformed so each score ranged a 0-100, where higher scores indicate worse symptoms (e.g., more severe/worsened) and lower scores indicate less symptoms (e.g., less severe/improvement).

End point type	Secondary

End point timeframe:

Inclusion (Baseline) (BL), Week 72, Week 120

End point values	177Lu-DOTA0-Tyr3-Octreotate	Octreotide LAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	112		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Physical function: chg from BL @ wk 72 (n=33,11)	3.232 (± 12.4857)	-4.242 (± 10.0101)		
Physical function: chg from BL @ wk 120 (n=2,0)	-3.333 (± 4.7140)	-4.242 (± 10.0101)		
Role function: chg from BL @ wk 72 (n=33,11)	5.051 (± 33.1989)	-3.030 (± 16.3608)		
Role function: chg from BL @ wk 120 (n=2,0)	8.333 (± 11.7851)	76.305 (± 30.3682)		
Emotional function: chg from BL @ wk 72 (n=33,11)	7.744 (± 22.6602)	6.061 (± 17.9083)		
Emotional function: chg from BL @ wk 120 (n=2,0)	12.500 (± 5.8926)	999 (± 999)		
Cognitive function: chg from BL @ wk 72 (n=33,11)	5.556 (± 15.9571)	1.515 (± 13.8535)		

Cognitive function: chg from BL @ wk 120 (n=2,0)	16.667 (± 23.5702)	6.061 (± 17.9083)		
Social function: chg from BL @ wk 72 (n=33,11)	8.586 (± 28.9039)	-7.576 (± 18.8025)		
Social function: chg from BL @ wk 120 (n=2,0)	8.333 (± 35.3553)	81.746 (± 22.6461)		
Global Health: chg from BL @ wk 72 (n=33,11)	5.556 (± 21.4155)	1.515 (± 10.4205)		
Global Health: chg from BL @ wk 120 (n=2,0)	-16.667 (± 0.0000)	999 (± 999)		
Fatigue: chg from BL @ wk 72 (n=33,11)	-7.239 (± 24.7084)	-2.020 (± 13.8939)		
Fatigue: chg from BL @ wk 120 (n=2,0)	11.111 (± 0.0000)	-7.576 (± 18.8025)		
Nausea & Vomiting: chg from BL @ wk 72 (n=33,11)	-4.545 (± 15.1799)	-4.545 (± 7.7850)		
Nausea & Vomiting: chg from BL @ wk 120 (n=2,0)	0.000 (± 0.0000)	66.369 (± 23.0841)		
Pain: chg from BL @ wk 72 (n=33,11)	-8.586 (± 22.4850)	-3.030 (± 10.0504)		
Pain: chg from BL @ wk 120 (n=2,0)	0.000 (± 23.5702)	999 (± 999)		
Dyspnoea: chg from BL @ wk 72 (n=33,11)	-3.030 (± 22.6134)	3.030 (± 27.7070)		
Dyspnoea: chg from BL @ wk 120 (n=2,0)	0.000 (± 0.0000)	-2.020 (± 13.8939)		
Insomnia: chg from BL @ wk 72 (n=33,11)	0.000 (± 26.3523)	6.061 (± 29.1288)		
Insomnia: chg from BL @ wk 120 (n=2,0)	33.333 (± 47.1405)	9.839 (± 19.3099)		
Appetite loss: chg from BL @ wk 72 (n=33,11)	-8.081 (± 20.4639)	9.091 (± 21.5557)		
Appetite loss: chg from BL @ wk 120 (n=2,0)	0.000 (± 0.0000)	999 (± 999)		
Constipation: chg from BL @ wk 72 (n=33,11)	0.000 (± 18.6339)	0.000 (± 14.9071)		
Constipation: chg from BL @ wk 120 (n=2,0)	0.000 (± 0.0000)	-3.030 (± 10.0504)		
Diarrhoea: chg from BL @ wk 72 (n=33,11)	-12.121 (± 36.1499)	-3.030 (± 27.7070)		
Diarrhoea: chg from BL @ wk 120 (n=2,0)	-16.667 (± 23.5702)	18.072 (± 26.6977)		
Financial diffic.: chg from BL @ wk 72 (n=33,11)	-7.071 (± 33.0798)	6.061 (± 20.1008)		
Financial diffic.: chg from BL @ wk 120 (n=2,0)	-16.667 (± 70.7107)	999 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the EORTC Quality of Life Questionnaire - Neuroendocrine Carcinoid Module (EORTC QLQ-GINET21)

End point title	Change from Baseline in the EORTC Quality of Life Questionnaire - Neuroendocrine Carcinoid Module (EORTC QLQ-GINET21)

End point description:

The Quality of Life GI Neuroendocrine Tumor survey (QLQ GINET21) contains a total of 21 items: four

single-item assessments relating to muscle and/or bone pain (MBP), body image (BI), information (INF) and sexual functioning (SX), together with 17 items organized into five proposed scales: endocrine symptoms (ED; three items), GI symptoms (GI; five items), treatment-related symptoms (TR; three items), social functioning (SF) and disease-related worries (DRW; three items). The response format of the questionnaire is a four-point Likert scale. Responses are linearly transformed to a 0-100 scale using EORTC guidelines, with higher scores reflecting more severe symptoms.

End point type	Secondary

End point timeframe:

Inclusion (Baseline) (BL), Week 72, Week 120

End point values	177Lu-DOTA0-Tyr3-Octreotate	Octreotide LAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	111		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Endocrine scale: chg from BL @ wk 72 (n=33,11)	-8.754 (± 20.1762)	-11.111 (± 21.0819)		
Endocrine scale: chg from BL @ wk 120 (n=2,0)	0.000 (± 0.0000)	-11.111 (± 21.0819)		
G.I. scale: chg from BL @ wk 72 (n=33,11)	-2.727 (± 15.3083)	2.424 (± 10.0101)		
G.I. scale: chg from BL @ wk 120 (n=2,0)	-13.333 (± 0.0000)	22.718 (± 19.9443)		
Treatment scale: chg from BL @ wk 72 (n=21,5)	-8.995 (± 14.9563)	0.000 (± 11.1111)		
Treatment scale: chg from BL @ wk 120 (n=1,0)	-16.667 (± 999)	999 (± 999)		
Social funct. scale: chg from BL @ wk 72 (n=33,11)	-7.576 (± 23.3985)	-7.576 (± 21.1217)		
Social funct. scale: chg from BL @ wk 120 (n=2,0)	11.111 (± 0.0000)	0.000 (± 11.1111)		
Diseases rel. wo.: chg from BL @ wk 72 (n=33,11)	-6.061 (± 27.9289)	1.010 (± 33.7765)		
Diseases rel. wo.: chg from BL @ wk 120 (n=2,0)	33.333 (± 31.4270)	36.145 (± 26.2073)		
Muscle/Bone pain: chg from BL @ wk 72 (n=33,10)	-5.051 (± 33.4594)	-16.667 (± 36.0041)		
Muscle/Bone pain: chg from BL @ wk 120 (n=2,0)	-16.667 (± 23.5702)	999 (± 999)		
Sexual function: chg from BL @ wk 72 (n=21,7)	6.349 (± 40.3031)	14.286 (± 17.8174)		
Sexual function: chg from BL @ wk 120 (n=2,0)	50.000 (± 70.7107)	1.010 (± 33.7765)		
Information/Com.: chg from BL @ wk 72 (n=33,11)	-4.040 (± 26.0309)	-12.121 (± 30.8139)		
Information/Com.: chg from BL @ wk 120 (n=2,0)	0.000 (± 0.0000)	34.146 (± 32.7000)		
Body image: chg from BL @ wk 72 (n=33,11)	-4.040 (± 18.1766)	-3.030 (± 17.9787)		
Body image: chg from BL @ wk 120 (n=2,0)	16.667 (± 23.5702)	999 (± 999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From informed consent signature through study completion reached at final safety cutoff date on 18July2021, assessed up to approximately 101 Months.	
Adverse event reporting additional description:	
Any sign or symptom that occurs after written informed consent provided.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Lu-DOTA-Tyr-Octreotate
Reporting group description:	
Lu-DOTA-Tyr-Octreotate	
Reporting group title	Total
Reporting group description:	
Total	
Reporting group title	Octreotide LAR
Reporting group description:	
Octreotide LAR	

Serious adverse events	Lu-DOTA-Tyr-Octreotate	Total	Octreotide LAR
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 111 (36.04%)	71 / 223 (31.84%)	31 / 112 (27.68%)
number of deaths (all causes)	70	138	68
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 111 (0.90%)	2 / 223 (0.90%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer stage I			

subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carcinoid crisis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	2 / 111 (1.80%)	7 / 223 (3.14%)	5 / 112 (4.46%)
occurrences causally related to treatment / all	0 / 2	0 / 8	0 / 6
deaths causally related to treatment / all	0 / 2	0 / 7	0 / 5
Neoplasm progression			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Non-small cell lung cancer			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Oesophageal adenocarcinoma			
subjects affected / exposed	2 / 111 (1.80%)	2 / 223 (0.90%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Prostate cancer			

subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Refractory cytopenia with multilineage dysplasia			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour invasion			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Inferior vena cava syndrome			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Syncope			

subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Coronary artery bypass			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Complication of device insertion			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Device occlusion			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	2 / 111 (1.80%)	4 / 223 (1.79%)	2 / 112 (1.79%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 1
Generalised oedema			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Injection site hypersensitivity			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cough			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	2 / 111 (1.80%)	2 / 223 (0.90%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			

subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb traumatic amputation			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural complication			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriospasm coronary			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardiac failure congestive			

subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Silent myocardial infarction			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic cerebral infarction			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient global amnesia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			
subjects affected / exposed	2 / 111 (1.80%)	2 / 223 (0.90%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			

subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Neutropenia			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Refractory cytopenia with unilineage dysplasia			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 111 (2.70%)	4 / 223 (1.79%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 111 (0.00%)	2 / 223 (0.90%)	2 / 112 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 111 (0.90%)	2 / 223 (0.90%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal obstruction			

subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant bowel obstruction			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			

subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 111 (0.90%)	3 / 223 (1.35%)	2 / 112 (1.79%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 111 (1.80%)	4 / 223 (1.79%)	2 / 112 (1.79%)
occurrences causally related to treatment / all	1 / 2	1 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular injury			

subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 111 (3.60%)	5 / 223 (2.24%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	3 / 4	3 / 5	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Acute prerenal failure			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 111 (0.90%)	2 / 223 (0.90%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	2 / 2	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 223 (0.45%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 111 (0.90%)	1 / 223 (0.45%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Lu-DOTA-Tyr-Octreotate	Total	Octreotide LAR
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 111 (94.59%)	195 / 223 (87.44%)	90 / 112 (80.36%)
Vascular disorders			
Flushing			
subjects affected / exposed	16 / 111 (14.41%)	26 / 223 (11.66%)	10 / 112 (8.93%)
occurrences (all)	19	31	12
Hypertension			
subjects affected / exposed	13 / 111 (11.71%)	21 / 223 (9.42%)	8 / 112 (7.14%)
occurrences (all)	20	28	8
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 111 (8.11%)	17 / 223 (7.62%)	8 / 112 (7.14%)
occurrences (all)	12	20	8
Fatigue			
subjects affected / exposed	43 / 111 (38.74%)	73 / 223 (32.74%)	30 / 112 (26.79%)
occurrences (all)	62	93	31
Influenza like illness			
subjects affected / exposed	6 / 111 (5.41%)	10 / 223 (4.48%)	4 / 112 (3.57%)
occurrences (all)	13	17	4
Oedema peripheral			
subjects affected / exposed	18 / 111 (16.22%)	28 / 223 (12.56%)	10 / 112 (8.93%)
occurrences (all)	24	34	10
Pyrexia			
subjects affected / exposed	8 / 111 (7.21%)	11 / 223 (4.93%)	3 / 112 (2.68%)
occurrences (all)	10	13	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 111 (10.81%)	20 / 223 (8.97%)	8 / 112 (7.14%)
occurrences (all)	14	22	8
Dyspnoea			
subjects affected / exposed	12 / 111 (10.81%)	21 / 223 (9.42%)	9 / 112 (8.04%)
occurrences (all)	15	25	10
Psychiatric disorders			
Anxiety			

subjects affected / exposed	13 / 111 (11.71%)	19 / 223 (8.52%)	6 / 112 (5.36%)
occurrences (all)	14	21	7
Insomnia			
subjects affected / exposed	3 / 111 (2.70%)	11 / 223 (4.93%)	8 / 112 (7.14%)
occurrences (all)	3	16	13
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 111 (6.31%)	14 / 223 (6.28%)	7 / 112 (6.25%)
occurrences (all)	10	20	10
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 111 (6.31%)	15 / 223 (6.73%)	8 / 112 (7.14%)
occurrences (all)	8	18	10
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 111 (4.50%)	13 / 223 (5.83%)	8 / 112 (7.14%)
occurrences (all)	7	19	12
Blood bilirubin increased			
subjects affected / exposed	7 / 111 (6.31%)	10 / 223 (4.48%)	3 / 112 (2.68%)
occurrences (all)	9	13	4
Blood creatinine increased			
subjects affected / exposed	7 / 111 (6.31%)	13 / 223 (5.83%)	6 / 112 (5.36%)
occurrences (all)	10	16	6
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 111 (6.31%)	16 / 223 (7.17%)	9 / 112 (8.04%)
occurrences (all)	10	20	10
Lymphocyte count decreased			
subjects affected / exposed	12 / 111 (10.81%)	14 / 223 (6.28%)	2 / 112 (1.79%)
occurrences (all)	22	24	2
Platelet count decreased			
subjects affected / exposed	13 / 111 (11.71%)	15 / 223 (6.73%)	2 / 112 (1.79%)
occurrences (all)	18	20	2
Weight decreased			
subjects affected / exposed	9 / 111 (8.11%)	17 / 223 (7.62%)	8 / 112 (7.14%)
occurrences (all)	11	21	10
White blood cell count decreased			

subjects affected / exposed	7 / 111 (6.31%)	8 / 223 (3.59%)	1 / 112 (0.89%)
occurrences (all)	12	14	2
Cardiac disorders			
Palpitations			
subjects affected / exposed	6 / 111 (5.41%)	12 / 223 (5.38%)	6 / 112 (5.36%)
occurrences (all)	7	13	6
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 111 (17.12%)	29 / 223 (13.00%)	10 / 112 (8.93%)
occurrences (all)	23	36	13
Dysgeusia			
subjects affected / exposed	9 / 111 (8.11%)	11 / 223 (4.93%)	2 / 112 (1.79%)
occurrences (all)	9	12	3
Headache			
subjects affected / exposed	21 / 111 (18.92%)	27 / 223 (12.11%)	6 / 112 (5.36%)
occurrences (all)	28	55	27
Syncope			
subjects affected / exposed	6 / 111 (5.41%)	8 / 223 (3.59%)	2 / 112 (1.79%)
occurrences (all)	6	8	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 111 (16.22%)	26 / 223 (11.66%)	8 / 112 (7.14%)
occurrences (all)	22	32	10
Lymphopenia			
subjects affected / exposed	18 / 111 (16.22%)	18 / 223 (8.07%)	0 / 112 (0.00%)
occurrences (all)	24	24	0
Thrombocytopenia			
subjects affected / exposed	16 / 111 (14.41%)	16 / 223 (7.17%)	0 / 112 (0.00%)
occurrences (all)	29	29	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	18 / 111 (16.22%)	32 / 223 (14.35%)	14 / 112 (12.50%)
occurrences (all)	23	39	16
Abdominal pain			
subjects affected / exposed	28 / 111 (25.23%)	49 / 223 (21.97%)	21 / 112 (18.75%)
occurrences (all)	41	64	23
Abdominal pain upper			

subjects affected / exposed	6 / 111 (5.41%)	8 / 223 (3.59%)	2 / 112 (1.79%)
occurrences (all)	9	13	4
Constipation			
subjects affected / exposed	11 / 111 (9.91%)	17 / 223 (7.62%)	6 / 112 (5.36%)
occurrences (all)	12	18	6
Diarrhoea			
subjects affected / exposed	32 / 111 (28.83%)	52 / 223 (23.32%)	20 / 112 (17.86%)
occurrences (all)	44	69	25
Dyspepsia			
subjects affected / exposed	7 / 111 (6.31%)	14 / 223 (6.28%)	7 / 112 (6.25%)
occurrences (all)	11	23	12
Flatulence			
subjects affected / exposed	7 / 111 (6.31%)	13 / 223 (5.83%)	6 / 112 (5.36%)
occurrences (all)	7	13	6
Nausea			
subjects affected / exposed	74 / 111 (66.67%)	87 / 223 (39.01%)	13 / 112 (11.61%)
occurrences (all)	162	176	14
Vomiting			
subjects affected / exposed	59 / 111 (53.15%)	68 / 223 (30.49%)	9 / 112 (8.04%)
occurrences (all)	126	138	12
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	13 / 111 (11.71%)	15 / 223 (6.73%)	2 / 112 (1.79%)
occurrences (all)	14	16	2
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	7 / 111 (6.31%)	10 / 223 (4.48%)	3 / 112 (2.68%)
occurrences (all)	9	13	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 111 (10.81%)	23 / 223 (10.31%)	11 / 112 (9.82%)
occurrences (all)	16	32	16
Back pain			
subjects affected / exposed	15 / 111 (13.51%)	26 / 223 (11.66%)	11 / 112 (9.82%)
occurrences (all)	21	33	12
Muscle spasms			

subjects affected / exposed	7 / 111 (6.31%)	9 / 223 (4.04%)	2 / 112 (1.79%)
occurrences (all)	11	14	3
Musculoskeletal pain			
subjects affected / exposed	5 / 111 (4.50%)	11 / 223 (4.93%)	6 / 112 (5.36%)
occurrences (all)	5	13	8
Pain in extremity			
subjects affected / exposed	12 / 111 (10.81%)	18 / 223 (8.07%)	6 / 112 (5.36%)
occurrences (all)	16	23	7
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	7 / 111 (6.31%)	14 / 223 (6.28%)	7 / 112 (6.25%)
occurrences (all)	7	15	8
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	24 / 111 (21.62%)	36 / 223 (16.14%)	12 / 112 (10.71%)
occurrences (all)	37	49	12
Hyperglycaemia			
subjects affected / exposed	11 / 111 (9.91%)	21 / 223 (9.42%)	10 / 112 (8.93%)
occurrences (all)	17	30	13
Hypokalaemia			
subjects affected / exposed	9 / 111 (8.11%)	19 / 223 (8.52%)	10 / 112 (8.93%)
occurrences (all)	10	21	11
Hyponatraemia			
subjects affected / exposed	7 / 111 (6.31%)	11 / 223 (4.93%)	4 / 112 (3.57%)
occurrences (all)	8	14	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2012	The protocol was amended to include the following main changes: ● The definitions of PFS, TTP, and OS were modified so that they were based on the time from the date of randomization, instead of the time from the date of first treatment ● The exclusion criteria were supplemented with the criterion 'lactation' ● Clarification about safety assessments and the performance of additional safety assessments regarding blood chemistry and urine tests was added to the study schedule for both treatment groups ● Instructions were added to ensure that laboratory parameters met required treatment criteria before administration of study drug, and participant observation after treatment with the study drug was extended ● Further details on the DSMB role and activities were added ● Further details on the substudy conduct and data analysis were implemented ● Appendices 15 (Recommended Precautions for Participants Treated with 177Lu-DOTA0-Tyr3-octreotate (Lutathera)) and 17 (Randomization Procedure of Participants after Enrolment) were modified and Appendix 19 (Determination of Lutathera Administered Radioactivity) were added to the protocol.
24 July 2013	The protocol was amended to include the following main changes: ● Per FDA request, the biased coin randomization scheme was replaced by a stratified permuted block randomization scheme with a balanced ratio (1:1) between the 2 treatment groups and the stratification for specific center enrolment was deleted (at the time of the randomization scheme change, 28 participants were already randomized) ● The method to control the family-wise type I error rate for OS and ORR was included as well as a detailed description of the statistical analysis for OS ● The end of study definition was modified and the description of the primary analysis adapted accordingly ● Participant replacement for the primary analysis was excluded and the primary log-rank test further specified ● Clarifications were added regarding the conduct of the urinalysis, the CT/MRI timings, the allowed tumor location, the study population characteristics, timing and procedures of the OctreoScan®, and the allowed time-windows for the Octreotide LAR injections ● Discontinuation criteria for individual participants were specified in more detail ● Further options for additional allowed amino acid solutions, details on the drug administration procedures in the Octreotide LAR group, details about the administration procedures of rescue medication, and details about the handling of study medication were added ● Further details on SAE and AESI reporting were included.
23 September 2013	The protocol was amended to include the following main changes to the conduct and procedures of the NETTER-1 substudy: ● Additional details on the dosimetry substudy procedures were added with regard to the performance of further optional dosimetry ● The number of sites participating in the substudy was increased.

25 March 2014	The protocol amended to include these main changes: ● Sample size adjusted, follow-up period increased from 3 to 5 years to detect statistically significant and clinically relevant difference in OS between the 2 study groups ● Study design adapted so that primary analysis conducted after 74 PFS events (74 centrally confirmed disease progression or death events) ● Secondary endpoints of DoR and PFS2 added as exploratory objectives ●End of Study (EOS) defined as reaching 158 deaths or 5 years had elapsed since the date of randomization of the last randomized participant, whichever occurred first ● Specifications added for the use of unstratified log-rank test in the primary analysis of PFS ● Details added on Dose Modifying Toxicity criteria and procedures ● Timing for safety assessments adapted to comply with new EOS ● Flowcharts and visits of the treatment/assessment period were adapted to comply with the new study design ● Substudy exclusion criteria regarding subsequent treatments modified ● Definitions regarding screening failures, study termination, and study withdrawal were added to the discontinuation criteria for individual participants ● A description about the handling of discrepancies in the evaluation of the progressive status between Investigator and central assessor added ● Clarification on procedures for dropouts, replacements and deliberate treatment interruption added ● Details on Octreotide LAR administration added ● Details on supportive information from histology added, clarifications on the CT/MRI scan timing and procedures, specifications on concomitant medication collection ● Recommendations added regarding amino acids solution infusion for treatment of nausea/vomiting and the use of anti-emetics ● Substudy updated with additional information on ECG assessments, collection of physical examination, vital signs, timing of the exams in relation to the 177Lu-DOTA0-Tyr3-octreotate treatment, dosimetry, PK, and cardiac assessments
05 June 2014	The protocol was amended to include the following main changes to the conduct and procedures of the substudy: ● Recruitment, randomization, and data analysis details for the substudy were specified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: