Clinical trial results:
Multicenter 3-arm trial to evaluate the efficacy and safety of Pasireotide LAR or Everolimus alone or in combination in patients with well differentiated neuroendocrine carcinoma of the lung and thymus - LUNA Trial

Summary

EudraCT number	2011-002872-17
Trial protocol	GB IT SE ES FR NL DK DE GR
Global end of trial date	10 February 2020

Results information

Result version number	v1 (current)
This version publication date	22 February 2021
First version publication date	22 February 2021

Trial information

Trial identification

Sponsor protocol code	CSOM230DIC03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01563354
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG , 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG , 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	10 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the efficacy of pasireotide long-acting release (LAR) and alone or in combination in progressive patients with a well differentiated neuroendocrine tumorr (NET) of the lung or thymus. The primary endpoint was defined as the proportion of patients who were progression-free at 9 months, according to RECIST version 1.1.

The EudraCT system does not accept NA. The EMA work around is that 999 is entered to represent "not available", "not estimable" or "not evaluable" data.

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	16 August 2013
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	Denmark: 5
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Italy: 39
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 20
Worldwide total number of subjects	124
EEA total number of subjects	104

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
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)	63
From 65 to 84 years	61
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Two patients completed the core phase of the study but they did not enter the extension phase one due to worsening in clinical conditions and one for Physician decision.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pasireotide LAR

Arm description:

Pasireotide long acting release (LAR) 60 mg will be administered as an intra muscular (i.m.) depot injection once every 28 days starting on Day 1

Arm type	Experimental
Investigational medicinal product name	Pasireotide long-acting release (LAR)
Investigational medicinal product code	SOM230
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Long-acting release 60 mg was administered as an intra muscular depot injection once every 28 days starting at Day 1

Arm title	Everolimus

Arm description:

Everolimus 10 mg taken orally (p.o) once daily starting on Day 1

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg tablets administered orally once a day

Arm title	Pasireotide LAR and Everolimus Combination

Arm description:

Pasireotide LAR 60 mg i.m. injected once every 28 days + Everolimus 10 mg p.o. daily starting on Day 1

Arm type	Experimental
Investigational medicinal product name	Pasireotide LAR and Everolimus Combination
Investigational medicinal product code	SOM230 + RAD001
Other name	
Pharmaceutical forms	Injection, Tablet
Routes of administration	Intramuscular use, Oral use

Dosage and administration details:

Pasireotide LAR 60 mg i.m. injected once every 28 days + Everolimus 10 mg p.o. daily

Number of subjects in period 1	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination
Started	41	42	41
Entered Extension Phase	12	14	15
Completed	12	14	15
Not completed	29	28	26
Adverse event, serious fatal	1	5	2
Consent withdrawn by subject	1	-	3
Disease progression	18	7	8
Adverse event, non-fatal	5	15	13
Protocol deviation	2	-	-
PI decision - did not enter extension	-	1	-
Lost to follow-up	1	-	-
Clinically got worse-did not enter extension	1	-	-

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Pasireotide LAR

Arm description:

Pasireotide long acting release (LAR) 60 mg will be administered as an intra muscular (i.m.) depot injection once every 28 days starting on Day 1

Arm type	Experimental
Investigational medicinal product name	Pasireotide long-acting release (LAR)
Investigational medicinal product code	SOM230
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Long-acting release
60 mg was administered as an intra muscular depot injection once every 28 days starting at Day 1

Arm title	Everolimus

Arm description:

Everolimus 10 mg taken orally (p.o) once daily starting on Day 1

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg tablets administered orally once a day

Arm title	Pasireotide LAR and Everolimus Combination

Arm description:

Pasireotide LAR 60 mg i.m. injected once every 28 days + Everolimus 10 mg p.o. daily starting on Day 1

Arm type	Experimental
Investigational medicinal product name	Pasireotide LAR and Everolimus Combination
Investigational medicinal product code	SOM230 + RAD001
Other name	
Pharmaceutical forms	Injection, Tablet
Routes of administration	Intramuscular use, Oral use

Dosage and administration details:

Pasireotide LAR 60 mg i.m. injected once every 28 days + Everolimus 10 mg p.o. daily

Number of subjects in period 2	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination
Started	12	14	15
Completed	0	0	0
Not completed	12	14	15
Consent withdrawn by subject	-	1	-
Disease progression	9	8	10
Administration problems	3	2	3
Adverse event, non-fatal	-	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Pasireotide LAR
Reporting group description:	
Pasireotide long acting release (LAR) 60 mg will be administered as an intra muscular (i.m.) depot injection once every 28 days starting on Day 1	
Reporting group title	Everolimus
Reporting group description:	
Everolimus 10 mg taken orally (p.o) once daily starting on Day 1	
Reporting group title	Pasireotide LAR and Everolimus Combination
Reporting group description:	
Pasireotide LAR 60 mg i.m. injected once every 28 days + Everolimus 10 mg p.o. daily starting on Day 1	

Reporting group values	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination
Number of subjects	41	42	41
Age Categorical Units: participants			
18 to <65	21	18	24
≥65 to 84	20	24	17
Sex: Female, Male Units:			
Female	15	19	13
Male	26	23	28
Race/Ethnicity, Customized Units: Subjects			
Caucasian	40	42	40
Black	1	0	0
Asian	0	0	1

Reporting group values	Total		
Number of subjects	124		
Age Categorical Units: participants			
18 to <65	63		
≥65 to 84	61		
Sex: Female, Male Units:			
Female	47		
Male	77		
Race/Ethnicity, Customized Units: Subjects			
Caucasian	122		
Black	1		
Asian	1		

End points

End points reporting groups

Reporting group title	Pasireotide LAR
Reporting group description:	
Pasireotide long acting release (LAR) 60 mg will be administered as an intra muscular (i.m.) depot injection once every 28 days starting on Day 1	
Reporting group title	Everolimus
Reporting group description:	
Everolimus 10 mg taken orally (p.o) once daily starting on Day 1	
Reporting group title	Pasireotide LAR and Everolimus Combination
Reporting group description:	
Pasireotide LAR 60 mg i.m. injected once every 28 days + Everolimus 10 mg p.o. daily starting on Day 1	
Reporting group title	Pasireotide LAR
Reporting group description:	
Pasireotide long acting release (LAR) 60 mg will be administered as an intra muscular (i.m.) depot injection once every 28 days starting on Day 1	
Reporting group title	Everolimus
Reporting group description:	
Everolimus 10 mg taken orally (p.o) once daily starting on Day 1	
Reporting group title	Pasireotide LAR and Everolimus Combination
Reporting group description:	
Pasireotide LAR 60 mg i.m. injected once every 28 days + Everolimus 10 mg p.o. daily starting on Day 1	

Primary: Percentage of participants progression-free at 9 months based on Response Evaluation Criteria In Solid Tumors v1.1 (RECIST v1.1)

End point title	Percentage of participants progression-free at 9 months based on Response Evaluation Criteria In Solid Tumors v1.1 (RECIST v1.1)[1]
End point description:	
Patients with Complete Response (CR), Partial Response (PR), or Stable Disease (SD) at Month 9 were to be considered as "progression-free" based on RECIST v1.1. Patients with missing tumor assessment, or with overall lesion response "unknown" at Month 9 were considered as "non progression-free", unless any of the following assessments at Week 48 or Week 52 indicate CR, PR, or SD, in which case the patient was to be considered as progression-free at Month 9. Patients discontinuing the study for any reason prior to the 9 month assessment were to be considered as "non progression-free".	
End point type	Primary
End point timeframe:	
Baseline up to 9 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No analysis was done

End point values	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	42	41	
Units: percentage of participants				
number (confidence interval 95%)				
Complete response	0 (0.0 to 8.6)	0 (0.0 to 8.4)	0 (0.0 to 8.6)	

Partial response	2.4 (0.1 to 12.9)	2.4 (0.1 to 12.6)	2.4 (0.1 to 12.9)	
Stable disease	34.1 (20.1 to 50.6)	31.0 (17.6 to 47.1)	48.8 (32.9 to 64.9)	
Progression-free (PF) at Month 9	39.0 (24.2 to 55.5)	33.3 (19.6 to 49.5)	58.5 (42.1 to 73.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of progression-free survival (PFS) based on RECIST v1.1

End point title	Summary of progression-free survival (PFS) based on RECIST v1.1

End point description:

Time from first study drug administration to objective tumor progression or death from any cause according to RECIST v1.1

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to 69 months

End point values	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	42	41	
Units: months				
median (confidence interval 95%)	8.51 (5.68 to 14.03)	12.48 (5.55 to 20.21)	16.53 (11.10 to 23.26)	

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier estimates of progression-free survival (PFS)

End point title	Kaplan-Meier estimates of progression-free survival (PFS)

End point description:

Percent (%) event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Percent event-free probability estimates are obtained from the Kaplan-Meier survival estimates. Events are time from first study drug administration to objective tumor progression or death from any cause according to RECIST v1.1.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to 69 months

End point values	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	42	41	
Units: event free probability estimates				
number (confidence interval 95%)				
3 months	83.6 (67.1 to 92.3)	91.2 (75.1 to 97.1)	88.6 (72.4 to 95.5)	
6 months	68.2 (49.8 to 81.1)	63.5 (44.7 to 77.4)	85.5 (68.6 to 93.7)	
9 months	49.6 (31.9 to 65.1)	56.9 (38.1 to 71.9)	79.2 (61.1 to 89.5)	
12 months	39.9 (23.3 to 56.0)	50.2 (31.9 to 66.0)	55.5 (36.4 to 71.0)	
15 months	32.6 (17.2 to 49.1)	46.8 (28.9 to 62.9)	51.2 (32.1 to 67.5)	
18 months	21.8 (9.1 to 37.8)	38.6 (21.4 to 55.6)	42.7 (24.2 to 60.1)	
21 months	14.5 (4.7 to 29.6)	29.4 (13.6 to 47.2)	38.0 (20.0 to 55.9)	
24 months	14.5 (4.7 to 29.6)	19.6 (6.7 to 37.4)	28.5 (12.5 to 46.9)	
27 months	14.5 (4.7 to 29.6)	19.6 (6.7 to 37.4)	28.5 (12.5 to 46.9)	
30 months	10.9 (2.8 to 25.2)	9.8 (1.8 to 26.2)	19.0 (6.3 to 36.9)	
33 months	10.9 (2.8 to 25.2)	9.8 (1.8 to 26.2)	19.0 (6.3 to 36.9)	
36 months	10.9 (2.8 to 25.2)	9.8 (1.8 to 26.2)	14.2 (3.7 to 31.5)	
39 months	10.9 (2.8 to 25.2)	9.8 (1.8 to 26.2)	14.2 (3.7 to 31.5)	
42 months	10.9 (2.8 to 25.2)	9.8 (1.8 to 26.2)	14.2 (3.7 to 31.5)	
45 months	10.9 (2.8 to 25.2)	9.8 (1.8 to 26.2)	14.2 (3.7 to 31.5)	
48 months	10.9 (2.8 to 25.2)	9.8 (1.8 to 26.2)	14.2 (3.7 to 31.5)	
51 months	10.9 (2.8 to 25.2)	999.9 (999.9 to 999.9)	14.2 (3.7 to 31.5)	
54 months	10.9 (2.8 to 25.2)	999.9 (999.9 to 999.9)	14.2 (3.7 to 31.5)	
57 months	10.9 (2.8 to 25.2)	999.9 (999.9 to 999.9)	7.1 (0.6 to 25.2)	
60 months	10.9 (2.8 to 25.2)	999.9 (999.9 to 999.9)	7.1 (0.6 to 25.2)	
63 months	10.9 (2.8 to 25.2)	999.9 (999.9 to 999.9)	7.1 (0.6 to 25.2)	
66 months	999.9 (999.9 to 999.9)	999.9 (999.9 to 999.9)	7.1 (0.6 to 25.2)	
69 months	999.9 (999.9 to 999.9)	999.9 (999.9 to 999.9)	7.1 (0.6 to 25.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who met criteria for time to response

End point title	Number of participants who met criteria for time to response

End point description:

Time from start of treatment to the first observed objective tumor response (partial response or complete response) observed according to RECIST v1.1. Due to the low number of events, the quartiles were non estimable

End point type	Secondary

End point timeframe:

Every 3 months up to Year 1

End point values	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	42	41	
Units: participants	1	1	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who met criteria for Duration of Response

End point title	Number of participants who met criteria for Duration of Response

End point description:

Time from onset of the first objective tumor response (partial response or complete response) to objective tumor progression or death from any cause. Due to the low number of events, the duration of response could not be estimated.

End point type	Secondary

End point timeframe:

Every 3 months up to Year 1

End point values	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	42	41	
Units: participants	1	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: 12-month Disease Control Rate (DCR) and Objective Response Rate (ORR)

End point title	12-month Disease Control Rate (DCR) and Objective Response Rate (ORR)

End point description:

Objective response rate (ORR) was defined as the percentage of patients showing a best overall response (BOR) of CR or PR during the core study according to RECIST v1.1 criteria. The best overall response is interpreted as the best response recorded from the start of the treatment until disease progression/recurrence, death from any cause or until the patient withdraws consent, whichever is earliest. DCR was was defined as the percentage of participants with a best overall response of complete response, partial response or stable disease during 12 months of treatment according to RECIST v1.1.

End point type	Secondary

End point timeframe:

Baseline up to Month 12

End point values	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	42	41	
Units: percentage of participants				
number (confidence interval 95%)				
Objective response (CR+PR)	2.4 (0.1 to 12.9)	2.4 (0.1 to 12.6)	4.9 (0.6 to 16.5)	
Disease control rate (CR+PR+SD)	80.5 (65.1 to 91.2)	73.8 (58.0 to 86.1)	78.0 (62.4 to 89.4)	
Complete response (CR)	0 (0.0 to 8.6)	0 (0.0 to 8.4)	0 (0.0 to 8.6)	
Partial response (PR)	2.4 (0.1 to 12.9)	2.4 (0.1 to 12.6)	4.9 (0.6 to 16.5)	
Stable disease	78.0 (62.4 to 89.4)	71.4 (55.4 to 84.3)	73.2 (57.1 to 85.8)	
Progressive disease	14.6 (-999.9 to 999.9)	4.8 (-999.9 to 999.9)	7.3 (-999.9 to 999.9)	
Unknown	2.4 (-999.9 to 999.9)	4.8 (-999.9 to 999.9)	0 (-999.9 to 999.9)	
Not assessed	2.4 (-999.9 to 999.9)	16.7 (-999.9 to 999.9)	14.6 (-999.9 to 999.9)	
Discontinued before month 12	68.3 (-999.9 to 999.9)	64.3 (-999.9 to 999.9)	63.4 (-999.9 to 999.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Biochemical response rate (BRR) for Chromogranin A (CgA) levels

End point title	Biochemical response rate (BRR) for Chromogranin A (CgA) levels

End point description:

Percentage of patients showing normalization or a decrease of ≥ 30% of serum CgA concentrations compared to baseline.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	27	35	
Units: percentage of participants				
number (confidence interval 95%)				
Week 12 n=34,27,35	20.6 (8.7 to 37.9)	7.4 (0.9 to 24.3)	17.1 (6.6 to 33.6)	
Week 24 n=34,27,35	8.8 (1.9 to 23.7)	7.4 (0.9 to 24.3)	20.0 (8.4 to 36.9)	
Week 36 n=34,27,35	8.8 (1.9 to 23.7)	3.7 (0.1 to 19.0)	11.4 (3.2 to 26.7)	
Week 48 n=34,27,35	8.8 (1.9 to 23.7)	0 (0.0 to 12.8)	11.4 (3.2 to 26.7)	
Week 52 n=34,27,35	5.9 (0.7 to 19.7)	0 (0.0 to 12.8)	5.7 (0.7 to 19.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of biochemical response (DBR), by treatment (Full Analysis Set)

End point title	Duration of biochemical response (DBR), by treatment (Full Analysis Set)

End point description:

Time from the first documentation of biochemical response to the first documentation of biochemical progression or to death due to any cause, whichever occurred first. Biochemical progression is defined as an increase of serum CgA levels ≥ 25% compared to baseline.

End point type	Secondary

End point timeframe:

Baseline up to Month 18

End point values	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	4	9	
Units: months				
median (confidence interval 95%)	14.75 (0.03 to 99.9)	2.00 (0.03 to 99.9)	8.38 (0.03 to 99.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier event-free probability estimate based on CgA levels

End point title	Kaplan-Meier event-free probability estimate based on CgA levels

End point description:

Kaplan Meier estimates are for Duration of biochemical response (DBR) outcome measure. Events are biochemical progressions i.e. an increase of CgA levels >= 25% compared to baseline or deaths due to any cause. Percent (%) Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to Month 18

End point values	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	4	9	
Units: event free probability estimates				
number (confidence interval 95%)				
3 months	75.0 (31.5 to 93.1)	37.5 (1.1 to 80.8)	77.8 (36.5 to 93.9)	
6 months	56.3 (14.7 to 84.2)	999.9 (999.9 to 999.9)	77.8 (36.5 to 93.9)	
9 months	56.3 (14.7 to 84.2)	999.9 (999.9 to 999.9)	44.4 (13.6 to 71.9)	
12 months	56.3 (14.7 to 84.2)	999.9 (999.9 to 999.9)	44.4 (13.6 to 71.9)	
15 months	37.5 (5.6 to 71.7)	999.9 (999.9 to 999.9)	44.4 (13.6 to 71.9)	
18 months	37.5 (5.6 to 71.7)	999.9 (999.9 to 999.9)	44.4 (13.6 to 71.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of biochemical progression-free survival based on CgA levels by treatment

End point title	Summary of biochemical progression-free survival based on CgA levels by treatment

End point description:

Time from the first documentation of biochemical response to the first documentation of biochemical progression or to death due to any cause, whichever
occurred first. Biochemical progression is defined as an increase of serum CgA levels ≥ 25% compared to baseline.

End point type	Secondary

End point timeframe:

Baseline up Month 24

End point values	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	42	41	
Units: months				
median (confidence interval 95%)	2.89 (2.79 to 5.49)	2.86 (2.79 to 3.52)	5.62 (3.9 to 8.31)	

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier event-free probability estimate for biochemical progression-free survival based on CgA levels

End point title	Kaplan-Meier event-free probability estimate for biochemical progression-free survival based on CgA levels

End point description:

Percent (%) Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Percent event-free probability estimates are obtained from the Kaplan-Meier survival estimates. Events are biochemical progressions, i.e., an increase of CgA levels >= 25% compared to baseline or deaths due to any cause.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to Month 24

End point values	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	42	41	
Units: event free probability estimates				
number (confidence interval 95%)				
3 months	43.1 (26.4 to 58.6)	35.4 (20.0 to 51.1)	77.1 (59.4 to 87.8)	

6 months	29.5 (15.0 to 45.6)	17.7 (7.2 to 32.0)	44.5 (27.6 to 60.0)	
9 months	18.5 (7.1 to 34.0)	11.0 (3.2 to 24.5)	29.7 (15.5 to 45.2)	
12 months	18.5 (7.1 to 34.0)	7.4 (1.4 to 20.0)	26.4 (13.0 to 41.9)	
15 months	18.5 (7.1 to 34.0)	999.9 (999.9 to 999.9)	18.1 (6.7 to 33.8)	
18 months	13.8 (4.1 to 29.4)	999.9 (999.9 to 999.9)	18.1 (6.7 to 33.8)	
21 months	13.8 (4.1 to 29.4)	999.9 (999.9 to 999.9)	18.1 (6.7 to 33.8)	
24 months	999.9 (999.9 to 999.9)	999.9 (999.9 to 999.9)	18.1 (6.7 to 33.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Biochemical response rate (BRR) for 5HIAA levels

End point title	Biochemical response rate (BRR) for 5HIAA levels

End point description:

The percentages are the biochemical response rates i.e. percentage of patients showing normalization i.e. return to within normal ranges, or a decrease of >= 50% from baseline of 5HIAA concentrations.

End point type	Secondary

End point timeframe:

Baseline up Week 52

End point values	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	18	20	
Units: percentage of participants				
number (confidence interval 95%)				
Week 12	20.0 (5.7 to 43.7)	11.1 (1.4 to 34.7)	10.0 (1.2 to 31.7)	
Week 24	5.0 (0.1 to 24.9)	11.1 (1.4 to 34.7)	20.0 (5.7 to 43.7)	
Week 36	5.0 (0.1 to 24.9)	11.1 (1.4 to 34.7)	5.0 (0.1 to 24.9)	
Week 48	5.0 (0.1 to 24.9)	0 (0.0 to 18.5)	5.0 (0.1 to 24.9)	
Week 52	5.0 (0.1 to 24.9)	0 (0.0 to 18.5)	10.0 (1.2 to 31.7)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 8 weeks post treatment up to maximum duration of 316 weeks

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Pasireotide LAR

Reporting group description:

Pasireotide LAR

Reporting group title	Everolimus

Reporting group description:

Everolimus

Reporting group title	Pasireotide LAR and Everolimus Combination

Reporting group description:

Pasireotide LAR and Everolimus Combination

Serious adverse events	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 41 (41.46%)	20 / 42 (47.62%)	16 / 41 (39.02%)
number of deaths (all causes)	2	7	3
number of deaths resulting from adverse events	0	1	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Axillary pain			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	0 / 41 (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
Face oedema			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	3 / 41 (7.32%)	2 / 42 (4.76%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Non-cardiac chest pain			

subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	0 / 41 (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
Oedema peripheral			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 41 (2.44%)	3 / 42 (7.14%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 41 (7.32%)	3 / 42 (7.14%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 3	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hydrothorax			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			

subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	3 / 41 (7.32%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 41 (2.44%)	2 / 42 (4.76%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 1
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			

subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
C-reactive protein increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria traumatic			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Radiation oesophagitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tachycardia paroxysmal			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Brain compression			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Spinal cord compression			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Constipation			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 41 (2.44%)	3 / 42 (7.14%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	2 / 2	1 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1

Dysphagia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystocholangitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			

subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Jaundice			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin haemorrhage			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 1
Anuria			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dysuria			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Carcinoid crisis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carcinoid syndrome			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cushing's syndrome			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Aspergillus infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Oesophageal candidiasis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	5 / 41 (12.20%)	2 / 42 (4.76%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 5	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 41 (4.88%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Diabetes mellitus			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperammonaemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			

subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hyponatraemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolic acidosis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	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	Pasireotide LAR	Everolimus	Pasireotide LAR and Everolimus Combination
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 41 (97.56%)	42 / 42 (100.00%)	40 / 41 (97.56%)
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 41 (2.44%)	2 / 42 (4.76%)	4 / 41 (9.76%)
occurrences (all)	1	2	5
Hypertension			
subjects affected / exposed	2 / 41 (4.88%)	2 / 42 (4.76%)	3 / 41 (7.32%)
occurrences (all)	6	8	4
Hypotension			

subjects affected / exposed	3 / 41 (7.32%)	2 / 42 (4.76%)	1 / 41 (2.44%)
occurrences (all)	3	2	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 41 (26.83%)	12 / 42 (28.57%)	16 / 41 (39.02%)
occurrences (all)	20	28	48
Chills			
subjects affected / exposed	4 / 41 (9.76%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences (all)	4	0	0
Fatigue			
subjects affected / exposed	6 / 41 (14.63%)	9 / 42 (21.43%)	16 / 41 (39.02%)
occurrences (all)	10	13	26
Non-cardiac chest pain			
subjects affected / exposed	3 / 41 (7.32%)	4 / 42 (9.52%)	3 / 41 (7.32%)
occurrences (all)	3	6	4
Oedema peripheral			
subjects affected / exposed	8 / 41 (19.51%)	13 / 42 (30.95%)	12 / 41 (29.27%)
occurrences (all)	9	25	21
Pyrexia			
subjects affected / exposed	7 / 41 (17.07%)	7 / 42 (16.67%)	6 / 41 (14.63%)
occurrences (all)	9	12	13
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	0	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 41 (21.95%)	12 / 42 (28.57%)	14 / 41 (34.15%)
occurrences (all)	10	19	19
Dyspnoea			
subjects affected / exposed	8 / 41 (19.51%)	11 / 42 (26.19%)	6 / 41 (14.63%)
occurrences (all)	12	15	11
Epistaxis			
subjects affected / exposed	0 / 41 (0.00%)	5 / 42 (11.90%)	3 / 41 (7.32%)
occurrences (all)	0	6	3

Haemoptysis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	3 / 41 (7.32%)
occurrences (all)	0	1	3
Pneumonitis			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	4 / 41 (9.76%)
occurrences (all)	0	2	4
Productive cough			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	7 / 41 (17.07%)
occurrences (all)	0	2	10
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 41 (4.88%)	4 / 42 (9.52%)	3 / 41 (7.32%)
occurrences (all)	2	4	3
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 41 (7.32%)	3 / 42 (7.14%)	3 / 41 (7.32%)
occurrences (all)	6	3	4
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 41 (9.76%)	3 / 42 (7.14%)	1 / 41 (2.44%)
occurrences (all)	5	4	1
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 41 (17.07%)	2 / 42 (4.76%)	2 / 41 (4.88%)
occurrences (all)	15	3	3
Blood creatinine increased			
subjects affected / exposed	2 / 41 (4.88%)	1 / 42 (2.38%)	3 / 41 (7.32%)
occurrences (all)	4	3	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	10 / 41 (24.39%)	4 / 42 (9.52%)	4 / 41 (9.76%)
occurrences (all)	15	6	9
Glycosylated haemoglobin increased			
subjects affected / exposed	3 / 41 (7.32%)	1 / 42 (2.38%)	3 / 41 (7.32%)
occurrences (all)	4	1	4
Platelet count decreased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	3 / 41 (7.32%)
occurrences (all)	0	1	5
Weight decreased			

subjects affected / exposed	18 / 41 (43.90%)	18 / 42 (42.86%)	24 / 41 (58.54%)
occurrences (all)	30	30	47
Cardiac disorders			
Palpitations			
subjects affected / exposed	4 / 41 (9.76%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences (all)	5	1	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 41 (14.63%)	2 / 42 (4.76%)	2 / 41 (4.88%)
occurrences (all)	7	4	2
Dysgeusia			
subjects affected / exposed	4 / 41 (9.76%)	5 / 42 (11.90%)	4 / 41 (9.76%)
occurrences (all)	4	5	4
Headache			
subjects affected / exposed	7 / 41 (17.07%)	4 / 42 (9.52%)	6 / 41 (14.63%)
occurrences (all)	12	9	8
Presyncope			
subjects affected / exposed	3 / 41 (7.32%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences (all)	4	0	0
Taste disorder			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	0	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 41 (21.95%)	14 / 42 (33.33%)	10 / 41 (24.39%)
occurrences (all)	21	21	16
Leukopenia			
subjects affected / exposed	0 / 41 (0.00%)	3 / 42 (7.14%)	3 / 41 (7.32%)
occurrences (all)	0	4	3
Thrombocytopenia			
subjects affected / exposed	0 / 41 (0.00%)	9 / 42 (21.43%)	7 / 41 (17.07%)
occurrences (all)	0	16	14
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 41 (7.32%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	15 / 41 (36.59%)	6 / 42 (14.29%)	6 / 41 (14.63%)
occurrences (all)	28	6	8
Abdominal pain upper			
subjects affected / exposed	5 / 41 (12.20%)	5 / 42 (11.90%)	3 / 41 (7.32%)
occurrences (all)	9	6	6
Aphthous ulcer			
subjects affected / exposed	0 / 41 (0.00%)	3 / 42 (7.14%)	0 / 41 (0.00%)
occurrences (all)	0	11	0
Constipation			
subjects affected / exposed	9 / 41 (21.95%)	6 / 42 (14.29%)	0 / 41 (0.00%)
occurrences (all)	12	8	0
Diarrhoea			
subjects affected / exposed	17 / 41 (41.46%)	21 / 42 (50.00%)	33 / 41 (80.49%)
occurrences (all)	76	46	103
Dyspepsia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	3 / 41 (7.32%)
occurrences (all)	1	0	3
Dysphagia			
subjects affected / exposed	0 / 41 (0.00%)	4 / 42 (9.52%)	0 / 41 (0.00%)
occurrences (all)	0	9	0
Flatulence			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	4 / 41 (9.76%)
occurrences (all)	2	0	6
Haemorrhoids			
subjects affected / exposed	3 / 41 (7.32%)	1 / 42 (2.38%)	4 / 41 (9.76%)
occurrences (all)	3	2	4
Mouth ulceration			
subjects affected / exposed	0 / 41 (0.00%)	3 / 42 (7.14%)	6 / 41 (14.63%)
occurrences (all)	0	4	12
Nausea			
subjects affected / exposed	11 / 41 (26.83%)	10 / 42 (23.81%)	8 / 41 (19.51%)
occurrences (all)	21	16	10
Steatorrhoea			
subjects affected / exposed	4 / 41 (9.76%)	0 / 42 (0.00%)	2 / 41 (4.88%)
occurrences (all)	6	0	3

Stomatitis			
subjects affected / exposed	2 / 41 (4.88%)	26 / 42 (61.90%)	14 / 41 (34.15%)
occurrences (all)	2	50	29
Toothache			
subjects affected / exposed	2 / 41 (4.88%)	1 / 42 (2.38%)	4 / 41 (9.76%)
occurrences (all)	2	1	4
Vomiting			
subjects affected / exposed	5 / 41 (12.20%)	5 / 42 (11.90%)	4 / 41 (9.76%)
occurrences (all)	11	5	5
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 41 (0.00%)	3 / 42 (7.14%)	4 / 41 (9.76%)
occurrences (all)	0	4	4
Onychoclasis			
subjects affected / exposed	0 / 41 (0.00%)	3 / 42 (7.14%)	3 / 41 (7.32%)
occurrences (all)	0	3	4
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 41 (0.00%)	3 / 42 (7.14%)	2 / 41 (4.88%)
occurrences (all)	0	3	2
Pruritus			
subjects affected / exposed	2 / 41 (4.88%)	2 / 42 (4.76%)	7 / 41 (17.07%)
occurrences (all)	2	2	11
Rash			
subjects affected / exposed	3 / 41 (7.32%)	12 / 42 (28.57%)	6 / 41 (14.63%)
occurrences (all)	3	22	11
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 41 (7.32%)	2 / 42 (4.76%)	1 / 41 (2.44%)
occurrences (all)	3	2	1
Polyuria			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	3 / 41 (7.32%)
occurrences (all)	1	0	3
Renal failure			
subjects affected / exposed	2 / 41 (4.88%)	4 / 42 (9.52%)	0 / 41 (0.00%)
occurrences (all)	2	6	0
Urinary incontinence			

subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	0	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 41 (7.32%)	1 / 42 (2.38%)	3 / 41 (7.32%)
occurrences (all)	6	2	4
Back pain			
subjects affected / exposed	10 / 41 (24.39%)	6 / 42 (14.29%)	7 / 41 (17.07%)
occurrences (all)	13	7	7
Bone pain			
subjects affected / exposed	2 / 41 (4.88%)	2 / 42 (4.76%)	3 / 41 (7.32%)
occurrences (all)	3	2	3
Joint swelling			
subjects affected / exposed	2 / 41 (4.88%)	1 / 42 (2.38%)	3 / 41 (7.32%)
occurrences (all)	2	1	3
Muscle spasms			
subjects affected / exposed	5 / 41 (12.20%)	2 / 42 (4.76%)	1 / 41 (2.44%)
occurrences (all)	6	2	2
Musculoskeletal chest pain			
subjects affected / exposed	4 / 41 (9.76%)	2 / 42 (4.76%)	2 / 41 (4.88%)
occurrences (all)	4	2	3
Musculoskeletal pain			
subjects affected / exposed	4 / 41 (9.76%)	1 / 42 (2.38%)	2 / 41 (4.88%)
occurrences (all)	4	1	2
Neck pain			
subjects affected / exposed	3 / 41 (7.32%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences (all)	3	1	0
Pain in extremity			
subjects affected / exposed	3 / 41 (7.32%)	1 / 42 (2.38%)	4 / 41 (9.76%)
occurrences (all)	3	1	5
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 41 (4.88%)	3 / 42 (7.14%)	1 / 41 (2.44%)
occurrences (all)	11	3	1
Cystitis			

subjects affected / exposed	1 / 41 (2.44%)	4 / 42 (9.52%)	0 / 41 (0.00%)
occurrences (all)	1	5	0
Folliculitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	4 / 41 (9.76%)
occurrences (all)	0	1	6
Influenza			
subjects affected / exposed	5 / 41 (12.20%)	2 / 42 (4.76%)	2 / 41 (4.88%)
occurrences (all)	9	3	6
Lower respiratory tract infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	4 / 41 (9.76%)
occurrences (all)	0	1	4
Rhinitis			
subjects affected / exposed	3 / 41 (7.32%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences (all)	3	2	0
Urinary tract infection			
subjects affected / exposed	4 / 41 (9.76%)	2 / 42 (4.76%)	7 / 41 (17.07%)
occurrences (all)	4	12	8
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 41 (24.39%)	16 / 42 (38.10%)	13 / 41 (31.71%)
occurrences (all)	13	24	20
Diabetes mellitus			
subjects affected / exposed	9 / 41 (21.95%)	4 / 42 (9.52%)	8 / 41 (19.51%)
occurrences (all)	13	4	13
Hypercholesterolaemia			
subjects affected / exposed	1 / 41 (2.44%)	7 / 42 (16.67%)	5 / 41 (12.20%)
occurrences (all)	1	8	5
Hyperglycaemia			
subjects affected / exposed	18 / 41 (43.90%)	14 / 42 (33.33%)	36 / 41 (87.80%)
occurrences (all)	43	32	123
Hypertriglyceridaemia			
subjects affected / exposed	3 / 41 (7.32%)	9 / 42 (21.43%)	5 / 41 (12.20%)
occurrences (all)	5	14	7
Hypoglycaemia			
subjects affected / exposed	2 / 41 (4.88%)	2 / 42 (4.76%)	3 / 41 (7.32%)
occurrences (all)	5	2	4

Hypokalaemia			
subjects affected / exposed	2 / 41 (4.88%)	3 / 42 (7.14%)	5 / 41 (12.20%)
occurrences (all)	2	4	6
Hypomagnesaemia			
subjects affected / exposed	4 / 41 (9.76%)	2 / 42 (4.76%)	3 / 41 (7.32%)
occurrences (all)	6	2	5
Hyponatraemia			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	3 / 41 (7.32%)
occurrences (all)	2	0	4
Hypophosphataemia			
subjects affected / exposed	1 / 41 (2.44%)	3 / 42 (7.14%)	5 / 41 (12.20%)
occurrences (all)	1	6	12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2011	The original version (finalized on 06-Oct-2011) of the study protocol was amended before submission to Competent Authorities/Ethics Committee to increase the hepatic-related safety measures for patients treated with pasireotide LAR.
11 December 2012	The study protocol was amended mainly to clarify the importance of routine patient glucose self-monitoring, to detect and treat hyperglycemia as early as possible, and to give specific guidance on dose adjustment in the different treatment arms.
16 July 2013	Amendment was in part to satisfy requests from Competent Authority to: Implement an exclusion criterion for female patients pregnant and breast-feeding, impleement a more frequent monitoring of the Thyroid Function Tests, implement a more detailed guidance for physicians in the response to a QTc prolongation on ECG and also to update the Pasireotide LAR IB edition 13 dated 24-May-2013.
07 October 2014	Protocol was amended mainly to remove the replacement policy (to avoid the introduction of biases in the study), to change the timepoint at which the primary endpoint was evaluated (from month 12 to month 9) and to update information on everolimus and pasireotide LAR based on the new versions of the respective Investigator Brochures (ed. 13, 12-May-2014 for everolimus; ed. 14, 02-Jun-2014 for pasireotide LAR).
07 November 2016	The protocol amendment modified the duration of the extension phase from 'until disease progression' to 'until they no longer demonstrate benefit or fulfill any of the study discontinuation criteria'. The end of study definition was modified from 'the last visit 2 years after the start of treatment of the last randomized patient or when all patients have progressed whichever comes first' to 'when all patients have discontinued the study'.

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.

The EudraCT system does not accept NA. The EMA work around is that 999 is entered to represent "not available", "not estimable" or "not evaluable" data.

Notes: