Sponsor

Novartis

Generic Drug Name

Pasireotide LAR and everolimus

Trial Indication

Advanced metastatic neuroendocrine tumors

Protocol Number

CSOM230F2102

Protocol Title

An open-label Phase I study evaluating the safety and tolerability of Pasireotide LAR in combination with Everolimus in advanced metastatic NETs – The COOPERATE-1 study

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

29-Nov-2010 to 11-Mar-2014

Reason for Termination

Given the difficulties with recruiting patients in some of the cohorts, recruitment stopped prematurely and the trial was terminated early, when the last enrolled patient completed the Core Phase of the study. Following termination of this study, eligible patients had the option to enroll into a local extension study.

Study Design/Methodology

This was an open-label Phase I study evaluating the safety and tolerability of pasireotide LAR in combination with everolimus in advanced metastatic NETs. The study had 4 different strata depending on functional or nonfunctional disease and pretreatment with somatostatin analogs (SSA) or not. The study consisted of 2 treatment groups: 1) Patients with functional disease were assigned to pasireotide LAR monotherapy followed by combination therapy with pasireotide LAR and everolimus; 2) patients with nonfunctional disease were randomized to receive either a) pasireotide LAR monotherapy followed by combination therapy with

pasireotide LAR and everolimus or b) everolimus monotherapy followed by combination therapy with pasireotide LAR and everolimus. This allocation resulted in 6 different cohorts.

The following treatment labels were used to identify the patient cohorts:

- Cohort 1: Functional NET, SSA pretreated, pasireotide LAR monotherapy
- Cohort 2: Functional NET, SSA treatment naive, pasireotide LAR monotherapy
- Cohort 3: non-functional NET, SSA pretreated, pasireotide LAR monotherapy
- Cohort 4: non-functional NET, SSA pretreated, everolimus monotherapy
- Cohort 5: non-functional NET, SSA treatment naive, pasireotide LAR monotherapy
- Cohort 6: non-functional NET, SSA treatment naive, everolimus monotherapy

Centers

4 centers in Germany

Publication

None

Objectives

- The primary objective was to evaluate the safety and tolerability profile of pasireotide LAR in combination with everolimus in patients with advanced metastatic neuroendocrine tumors (NETs) after 3 months of combination treatment.
- The secondary objectives included evaluation of safety and tolerability of pasireotide LAR and/or everolimus throughout the study, to assess pharmacokinetic (PK) exposures of pasireotide LAR and everolimus during monotherapy and in combination therapy, assess potential drug-drug interactions between pasireotide LAR and everolimus during combination therapy, assess symptom control (bowel movements and flushing episodes) with pasireotide LAR in combination with everolimus in patients with functional tumors, assess the biochemical response (chromogranin A, CgA) to pasireotide LAR in combination with everolimus.

Test Products, Doses, and Modes of Administration

Everolimus: tablets of 5 mg strength, blister-packed under aluminum foil in units of 10 tablets and dosed po daily.

Pasireotide LAR: powder in vials containing 20 mg and 40 mg with ampoules containing 2 mL of vehicle. Reconstituted pasireotide LAR (40 or 60 mg) was administered im every 28 days (q28d).

Pasireotide sc was supplied in ampoules containing 600 µg/1 mL and intended as rescue medication.

Statistical Methods

Patients were assigned into 6 distinct cohorts based on tumor characteristic, pre-enrollment treatment status and safety Run-in Phase treatment. Therefore most of the efficacy and safety analyses were performed by these 6 cohorts as well as by the "All patients" cohort. For the "All patients" cohort, all patients were pooled together. In addition, selected safety analyses were also done by pooling selected cohorts into a single group of patients. Categorical data was presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum was presented, unless otherwise stated. Contrary to the protocol description, the 25th and 75th percentiles were not presented for the summary of quantitative data. This is consistent with the descriptive summaries done for other studies in this project. No interim analysis was planned for this study.

The following populations were defined for analysis:

The full analysis set consists of all patients who completed the safety Run-in Phase of the study.

The safety analysis set (SAS) consists of all patients who received at least 1 dose of pasireotide LAR in combination with at least 1 dose of everolimus within 28 days of a dose of pasireotide LAR and had at least 1 post Month 1 baseline safety assessment.

The enrolled set consists of patients who received at least 1 dose of pasireotide LAR or everolimus in the safety Run-in Phase.

The PK set consists of all patients who completed the safety Run-in Phase of the study and who received a dose of pasireotide LAR in combination with everolimus and had evaluable PK data in both monotherapy and combination Phases. The PK set was used for the PK analysis to assess potential drug-drug interactions. Summary of PK concentration was done using the enrolled set.

Study Population: Key Inclusion/Exclusion Criteria

- Eligibility criteria included male or female adult patients (≥ 18 years of age) with advanced (unresectable, metastatic) well differentiated (low-grade or intermediate-grade) NETs of gastroenteropancreatic or pulmonary origin with measurable disease in the liver at baseline. Patients with nonfunctional tumors had to have progressed within 12 months prior to study enrollment.
- Main exclusion criteria included patients with previous treatment with radiolabeled SSAs within 12 months prior to reporting baseline symptoms as well as previous treatment with mammalian target of rapamycin inhibitors or pasireotide. Patients who had any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study and women who were pregnant or lactating, were excluded from the study. Other protocol-defined inclusion/exclusion criteria apply.

Participant Flow Table

Patient disposition by cohort – Enrolled set

	Cohort 1 N=18	Cohort 2 N=1	Cohort 3 N=1	Cohort 4 N=2	Cohort 5 N=7	Cohort 6 N=7	All patients N=36
Safety Run-in Phase[1]							
Patients treated							
EOT	18 (100)	1 (100)	1 (100)	2 (100)	7 (100)	7 (100)	36 (100)
Primary reason for EOT							
Completed the safety Run-in Phase#	13 (72.2)	1 (100)	1 (100)	2 (100)	6 (85.7)	7 (100)	30 (83.3)
Adverse event(s)	2 (11.1)*	0	0	0	1 (14.3)	0	3 (8.3)
Patient withdrew consent	1 (5.6)*	0	0	0	0	0	1 (2.8)
Death	1 (5.6)	0	0	0	0	0	1 (2.8)
Protocol deviation	1 (5.6)	0	0	0	0	0	1 (2.8)
Started Core safety Phase[1]	13 (72.2)	1 (100)	1 (100)	2 (100)	6 (85.7)	7 (100)	30 (83.3)
Core safety Phase[2]							
Patients treated							
EOT	13 (100)	1 (100)	1 (100)	2 (100)	6 (100)	7 (100)	30 (100)
Primary reason for EOT							
Completed the Core safety Phase	11 (84.6)	0	1 (100)	1 (50.0)	6 (100)	7 (100)	26 (86.7)
Adverse event(s)	2 (15.4)	0	0	1 (50.0)	0	0	3 (10.0)
Patient withdrew consent	0	1 (100)	0	0	0	0	1 (3.3)
Entered Extension Phase[2]	10 (76.9)	0	1 (100)	0	6 (100)	7 (100)	24 (80.0)
Extension Phase[3]							
Patients treated							
EOT	10 (100)	0	1 (100)	0	6 (100)	7 (100)	24 (100)
Primary reason for EOT							
Completed the Extension Phase	4 (40.0)	0	0	0	2 (33.3)	4 (57.1)	10 (41.7)
Adverse event(s)	1 (10.0)	0	0	0	1 (16.7)	1 (14.3)	3 (12.5)
Disease progression	0	0	0	0	1 (16.7)	1 (14.3)	2 (8.3)
Protocol deviation	0	0	0	0	1 (16.7)	0	1 (4.2)
Study terminated by Sponsor	5 (50.0)	0	1 (100)	0	1 (16.7)	1 (14.3)	8 (33.3)

	Cohort 1 N=18	Cohort 2 N=1	Cohort 3 N=1	Cohort 4 N=2	Cohort 5 N=7	Cohort 6 N=7	All patients N=36

EOT: end of treatment.

started Core safety Phase.

* One patient discontinued due to AE and one patient withdrew consent only at the end of the safety Run-in Phase. As both received 3 injections of pasireotide monotherapy they are nevertheless counted in the FAS.

[1] All percentages in this section use N as the denominator.

[2] All percentages in this section use the number of patients who started the Core safety Phase as the denominator.

[3] All percentages in this section use the number of patients who entered the Extension Phase as the denominator.

Baseline Characteristics

Demographic summary by cohort – Enrolled set

Demographic Variable	Cohort 1 N=18 n (%)	Cohort 2 N=1 n (%)	Cohort 3 N=1 n (%)	Cohort 4 N=2 n (%)	Cohort 5 N=7 n (%)	Cohort 6 N=7 n (%)	All patients N=36 n (%)
Age (years)							
n	18	1	1	2	7	7	36
Mean(SD)	58.6 (10.83)	38.0 (0)	79.0 (0)	62.5 (13.44)	54.9 (5.01)	60.3 (11.91)	58.4 (10.91)
Median	57.0	38.0	79.0	62.5	55.0	59.0	55.5
Range	40-80	38-38	79-79	53-72	48-64	47-74	38-80
Age category (years)							
<65	12 (66.7)	1 (100)	0	1 (50.0)	7 (100)	4 (57.1)	25 (69.4)
≥ 65	6 (33.3)	0	1 (100)	1 (50.0)	0	3 (42.9)	11 (30.6)
Gender							
Female	9 (50.0)	0	1 (100)	1 (50.0)	3 (42.9)	4 (57.1)	18 (50.0)
Male	9 (50.0)	1 (100)	0	1 (50.0)	4 (57.1)	3 (42.9)	18 (50.0)
Race							
Caucasian	18 (100)	1 (100)	1 (100)	1 (50.0)	7 (100)	7 (100)	35 (97.2)
Other	0	0	0	1 (50.0)	0	0	1 (2.8)
ECOG performance status							
0	11 (61.1)	0	1 (100)	2 (100)	2 (28.6)	3 (42.9)	19 (52.8)
1	7 (38.9)	1 (100)	0	0	4 (57.1)	4 (57.1)	16 (44.4)
2	0	0	0	0	1 (14.3)	0	1 (2.8)

ECOG: Eastern Cooperative Oncology Group.

Disease characteristics by cohort – Enrolled set

Disease history	Cohort 1 N=18 n (%)	Cohort 2 N=1 n (%)	Cohort 3 N=1 n (%)	Cohort 4 N=2 n (%)	Cohort 5 N=7 n (%)	Cohort 6 N=7 n (%)	All patients N=36 n (%)
Primary site of cancer							
Lung	0	1 (100)	0	0	1 (14.3)	2 (28.6)	4 (11.1)
Pancreas	1 (5.6)	0	0	1 (50.0)	1 (14.3)	2 (28.6)	5 (13.9)
Stomach	0	0	0	0	0	1 (14.3)	1 (2.8)
Small intestine	13 (72.2)	0	1 (100)	1 (50.0)	1 (14.3)	0	16 (44.4)
Colon	1 (5.6)	0	0	0	0	0	1 (2.8)
Rectum	0	0	0	0	3 (42.9)	2 (28.6)	5 (13.9)
Other	3 (16.7)	0	0	0	1 (14.3)	0	4 (11.1)
Details of tumor histology/cytology							
Carcinoid	2 (11.1)	0	0	0	0	1 (14.3)	3 (8.3)
Neuroendocrine carcinoma	16 (88.9)	1 (100)	1 (100)	2 (100)	6 (85.7)	5 (71.4)	31 (86.1)
Atypical carcinoid	0	0	0	0	1 (14.3)	1 (14.3)	2 (5.6)
Histologic grade							
Well differentiated	15 (83.3)	1 (100)	0	2 (100)	4 (57.1)	3 (42.9)	25 (69.4)
Moderately differentiated	3 (16.7)	0	1 (100)	0	3 (42.9)	4 (57.1)	11 (30.6)
Stage at initial diagnosis							
I	0	0	0	0	0	1 (14.3)	1 (2.8)
II	1 (5.6)	0	0	0	1 (14.3)	2 (28.6)	4 (11.1)
III	2 (11.1)	0	0	0	1 (14.3)	0	3 (8.3)
IV	15 (83.3)	1 (100)	1 (100)	2 (100)	5 (71.4)	4 (57.1)	28 (77.8)
Time since initial diagnosis of primary site (months)							
n	18	1	1	2	7	7	36
Mean (SD)	38.8 (35.11)	2.6 (0)	20.0 (0)	81.0 (32.06)	23.7 (22.70)	69.3 (101.05)	42.6 (53.22)
Median	27.5	2.6	20.0	81.0	12.7	42.8	27.7
Range	5-115	3-3	20-20	58-104	3-65	4-292	3-292
Types of lesions at baseline							
Target only	1 (5.6)	0	0	0	1 (14.3)	0	2 (5.6)
Both target and non-target	17 (94.4)	1 (100)	1 (100)	2 (100)	6 (85.7)	7 (100)	34 (94.4)

Summary of Efficacy

Primary Outcome Results

Refer to Safety Result section for primary outcome result.

Secondary Outcome Results

Change from month 1 baseline in the mean daily number of bowel movements by cohort – Full analysis set

Visit		Cohort 1 N=15 n(%)
Month 1 baseline	n	10
	Mean (SD)	3.3 (2.75)
	Median	2.4
	Range	0.9-8.2
Month 1	n	10
	Mean (SD)	0.6 (0.82)
	Median	0.5
	Range	-0.2-2.4
Month 2	n	10
	Mean (SD)	0.5 (1.04)
	Median	0.3
	Range	-1.0-2.4
Month 3	n	9
	Mean (SD)	0.2 (1.05)
	Median	0.2
	Range	-1.8-2.2
Month 4	n	8
	Mean (SD)	0.4 (0.74)
	Median	0.2
	Range	-0.4-1.9
Month 5	n	6
	Mean (SD)	0.1 (0.47)
	Median	0.2
	Range	-0.9-0.5
Month 6	n	5
	Mean (SD)	-0.2 (0.37)
	Median	-0.4
	Range	-0.6-0.4
Month 7	n	5
	Mean (SD)	-0.3 (0.43)

Visit		Cohort 1 N=15 n(%)
	Median	-0.1
	Range	-1.0-0.1
Month 8	n	5
	Mean (SD)	0.0 (0.51)
	Median	-0.1
	Range	-0.7-0.5
Month 9	n	5
	Mean (SD)	-0.0 (0.79)
	Median	-0.1
	Range	-0.8-1.3
Month 10	n	2
	Mean (SD)	0.8 (1.46)
	Median	0.8
	Range	-0.2-1.9
Month 11	n	3
	Mean (SD)	0.0 (0.13)
	Median	0.0
	Range	-0.1-0.1
Month 12	n	3
	Mean (SD)	0.6 (1.31)
	Median	0.3
	Range	-0.6-2.0

Only patients with baseline and post-baseline values are included.

Change from month 1 baseline in the mean weekly number of flushing episodes by cohort – Full analysis set

Visit		Cohort 1 N=15 n(%)
Month 1 baseline	n	10
	Mean (SD)	9.0 (9.46)
	Median	5.8
	Range	0.0-31.6
Month 1	n	10
	Mean (SD)	-2.3 (4.29)
	Median	-1.5
	Range	-11.5-4.3
Month 2	n	10
	Mean (SD)	-3.5 (4.40)

Visit		Cohort 1 N=15 n(%)
	Median	-2.1
	Range	-13.0-1.5
Month 3	n	9
	Mean (SD)	-3.5 (4.41)
	Median	-2.0
	Range	-12.5-1.4
Month 4	n	8
	Mean (SD)	-5.6 (4.02)
	Median	-4.9
	Range	-10.8-0.0
Month 5	n	6
	Mean (SD)	-8.0 (5.60)
	Median	-8.8
	Range	-13.8-(-1.5)
Month 6	n	5
	Mean (SD)	-8.7 (5.00)
	Median	-8.4
	Range	-14.8-(-1.5)
Month 7	n	5
	Mean (SD)	-9.1 (5.37)
	Median	-8.4
	Range	-14.8-(-1.5)
Month 8	n	5
	Mean (SD)	-7.1 (5.19)
	Median	-7.3
	Range	-12.8-(-1.5)
Month 9	n	5
	Mean (SD)	-8.1 (5.53)
	Median	-7.3
	Range	-13.8-(-1.5)
Month 10	n	2
	Mean (SD)	-7.6 (8.66)
	Median	-7.6
	Range	-13.8-(-1.5)
Month 11	n	3
	Mean (SD)	-7.9 (6.14)
	Median	-8.4
	Range	-13.8-(-1.5)

Visit		Cohort 1 N=15 n(%)
Month 12	n	3
	Mean (SD)	-8.2 (6.21)
	Median	-9.4
	Range	-13.8-(-1.5)

Only patients with baseline and post-baseline values are included.

Responses of biochemical markers related to month 1 baseline during Core safety Phase by cohort – Full analysis set

		Cohort 1 N=15 n (%)	Cohort 2 N=1 n (%)	Cohort 3 N=1 n (%)	Cohort 4 N=2 n (%)	Cohort 5 N=6 n (%)	Cohort 6 N=7 n (%)	All patients N=32 n (%)
CgA	At risk	9 (100)	0	1 (100)	1 (100)	4 (100)	6 (100)	21 (100)
	≥ 50% reduction compared to BL	1 (11.1)	0	0	0	0	3 (50.0)	4 (19.0)
	Normalization	0	0	0	1 (100)	0	4 (66.7)	5 (23.8)
	Response	1 (11.1)	0	0	1 (100)	0	4 (66.7)	6 (28.6)
5-HIAA	At risk	7 (100)	0	-	-	-	-	7 (100)
	≥ 50% reduction compared to BL	4 (57.1)	0	-	-	-	-	4 (57.1)
	Normalization	0	0	-	-	-	-	0
	Response	4 (57.1)	0	-	-	-	-	4 (57.1)

5-HIAA: 5-hydroxyindoleacetic acid; BL: baseline; CgA: chromogranin A

Categories are not exclusive.

At risk comprises all patients with a non-missing level at baseline which is outside normal ranges and has at least one non-missing level post-baseline.

Percentages are calculated based on the number of patients at risk.

Response is defined as normalization or a ≥ 50% reduction of biochemical marker level compared to baseline.

Tumor response

At the end of the Core Phase, 22 patients (out of 32) presented a stable disease as best overall response, whereas 2 patients had progressive disease. For 8 patients the best overall response was unknown. For 6 of these 8 patients no RECIST data was available post Month 1 baseline. The disease control rate (DCR) for 22 out of 32 patients was 68.8% (95% CI: 49.99, 83.88).

In the 12 months of combination therapy 1 additional patient had stable disease as best overall response, 2 had progressive disease and for 7 patients the best overall response was unknown. For 6 of these 7 patients no RECIST data was available post Month 1 baseline. The DCR for 23 out of 32 patients was 71.9% (95% CI: 53.25, 86.25).

Summary of Safety

Safety Results

AEs regardless of relationship to study drug during the Core safety Phase by primary system organ class and cohort– Safety analysis set

Primary System Organ Class	Cohort 1 N=13		Cohort 2 N=1		Cohort 3 N=1		Cohort 4 N=2		Cohort 5 N=6		Cohort 6 N=7		All patients N=30	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Any primary system organ class	13 (100)	7 (53.8)	1 (100)	1 (100)	1 (100)	0	2 (100)	2 (100)	6 (100)	2 (33.3)	6 (85.7)	5 (71.4)	29 (96.7)	17 (56.7)
Metabolism and nutrition disorders	8 (61.5)	3 (23.1)	0	0	1 (100)	0	1 (50.0)	1 (50.0)	3 (50.0)	1 (16.7)	6 (85.7)	3 (42.9)	19 (63.3)	8 (26.7)
Gastrointestinal disorders	8 (61.5)	1 (7.7)	0	0	1 (100)	0	1 (50.0)	0	4 (66.7)	0	4 (57.1)	0	18 (60.0)	1 (3.3)
Infections and infestations	6 (46.2)	3 (23.1)	0	0	0	0	2 (100)	1 (50.0)	3 (50.0)	0	4 (57.1)	0	15 (50.0)	4 (13.3)
Blood and lymphatic system disorders	8 (61.5)	1 (7.7)	0	0	0	0	1 (50.0)	0	2 (33.3)	1 (16.7)	2 (28.6)	0	13 (43.3)	2 (6.7)
General disorders and administration site conditions	5 (38.5)	1 (7.7)	0	0	1 (100)	0	0	0	3 (50.0)	1 (16.7)	1 (14.3)	0	10 (33.3)	2 (6.7)
Investigations	3 (23.1)	0	0	0	0	0	0	0	0	0	3 (42.9)	1 (14.3)	6 (20.0)	1 (3.3)
Musculoskeletal and connective tissue disorders	4 (30.8)	1 (7.7)	0	0	0	0	0	0	1 (16.7)	0	1 (14.3)	1 (14.3)	6 (20.0)	2 (6.7)
Nervous system disorders	3 (23.1)	0	0	0	0	0	1 (50.0)	0	1 (16.7)	1 (16.7)	1 (14.3)	0	6 (20.0)	1 (3.3)
Skin and subcutaneous tissue disorders	4 (30.8)	0	0	0	0	0	0	0	1 (16.7)	0	1 (14.3)	0	6 (20.0)	0
Vascular disorders	2 (15.4)	0	0	0	1 (100)	0	2 (100)	1 (50.0)	0	0	1 (14.3)	1 (14.3)	6 (20.0)	2 (6.7)
Renal and urinary disorders	2 (15.4)	1 (7.7)	0	0	0	0	1 (50.0)	0	2 (33.3)	1 (16.7)	0	0	5 (16.7)	2 (6.7)
Respiratory, thoracic and mediastinal disorders	3 (23.1)	0	0	0	0	0	0	0	0	0	1 (14.3)	0	3 (10.0)	1 (3.3)
Cardiac disorders	2 (15.4)	1 (7.7)	0	0	0	0	0	0	2 (33.3)	0	0	0	2 (6.7)	0
Endocrine disorders	0	0	0	0	0	0	0	0	0	0	1 (14.3)	0	2 (6.7)	0
Reproductive system and breast disorders	1 (7.7)	0	0	0	0	0	0	0	0	0	0	0	1 (3.3)	0
Hepatobiliary disorders	0	0	0	0	0	0	1 (50.0)	0	1 (16.7)	0	0	0	1 (3.3)	0
Injury, poisoning and procedural complications	0	0	0	0	0	0	0	0	0	0	0	0	1 (3.3)	1 (3.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	1 (100)	1 (100)	0	0	0	0	0	0	0	0	1 (3.3)	0

Primary System Organ Class	Cohort 1 N=13		Cohort 2 N=1		Cohort 3 N=1		Cohort 4 N=2		Cohort 5 N=6		Cohort 6 N=7		All patients N=30	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Psychiatric disorders	0	0	0	0	1 (100)	0	0	0	0	0	1 (14.3)	0	3 (10.0)	1 (3.3)

Primary system organ classes are sorted in descending frequency of all grades column, as reported in the all patients column.
A patient with multiple occurrences of an AE is counted only once in the AE category.
Adverse events occurring after the safety follow-up visit or during the safety Run-in or Extension Phase are not summarized.

Frequent adverse events (reported by 3 patients or more overall) regardless of relationship to study drug during the 12 months combination therapy by preferred term and cohort – Safety analysis set

Preferred Term	All patients N=30	
	All grades n (%)	Grade 3/4 n (%)
Any adverse events	30 (100)	22 (73.3)
Diabetes mellitus	12 (40.0)	10 (33.3)
Anaemia	11 (36.7)	3 (10.0)
Diarrhoea	11 (36.7)	1 (3.3)
Oedema peripheral	7 (23.3)	1 (3.3)
Gamma-glutamyltransferase increased	6 (20.0)	5 (16.7)
Leukopenia	6 (20.0)	0
Nasopharyngitis	6 (20.0)	0
Abdominal pain	5 (16.7)	0
Dry skin	5 (16.7)	0
Fatigue	5 (16.7)	0
Thrombocytopenia	5 (16.7)	0
Weight decreased	5 (16.7)	1 (3.3)
Folliculitis	4 (13.3)	0
Hyperglycaemia	4 (13.3)	1 (3.3)
Hypertension	4 (13.3)	2 (6.7)
Muscle spasms	4 (13.3)	0
Stomatitis	4 (13.3)	0
Vomiting	4 (13.3)	0
Dyspnoea	3 (10.0)	0
Flank pain	3 (10.0)	0
Hypokalaemia	3 (10.0)	0
Transaminases increased	3 (10.0)	2 (6.7)

Preferred terms are sorted in descending frequency of all grades column, as reported in the all patients column.

A patient with multiple occurrences of an AE is counted only once in the AE category.

Adverse events occurring after the safety follow-up visit or during the safety Run-in Phase are not summarized.

Summary of deaths and adverse events during the 12 months combination therapy by cohort – Safety analysis set

	Cohort 1 N=13	Cohort 2 N=1	Cohort 3 N=1	Cohort 4 N=2	Cohort 5 N=6	Cohort 6 N=7	All patients N=30
On treatment deaths[1]	1 (7.7)	0	0	1 (50.0)	0	0	2 (6.7)
SAEs	7 (53.8)	1 (100)	0	2 (100)	2 (33.3)	2 (28.6)	14 (46.7)
SAEs suspected to be study drug related	3 (23.1)	0	0	1 (50.0)	1 (16.7)	1 (14.3)	6 (20.0)
AEs leading to discontinuation	3 (23.1)	0	0	1 (50.0)	1 (16.7)	1 (14.3)	6 (20.0)
CNAEs - everolimus	11 (84.6)	0	1 (100)	2 (100)	6 (100)	7 (100)	27 (90.0)
CNAEs - pasireotide LAR	12 (92.3)	0	1 (100)	2 (100)	5 (83.3)	6 (85.7)	26 (86.7)

AEs: adverse events; CNAEs: clinically notable adverse events; LAR: long acting release; SAEs: serious adverse events.

Categories are not mutually exclusive.

[1]Deaths occurring after the safety follow-up visit or during the safety Run-in Phase are not summarized.

AEs occurring after the safety follow-up visit or during the safety Run-in Phase are not summarized.

Clinically notable AEs are the events for which there is a specific clinical interest in connection with study drug or events which are similar in nature.

Other Relevant Findings

No other relevant findings were reported.

Conclusion:

Based on the low incidence of AEs leading to discontinuation we conclude that everolimus in combination with pasireotide LAR treatment was safe and tolerable.

No safety concerns related to hematology, biochemistry and vital signs emerged.

There was no evidence of drug induced liver injury.

Based on the safety profile of the individual drugs, the safety profile of the combination therapy was as expected.

Most commonly reported AEs included diabetes and hyperglycemia with 3 patients reporting hyperglycemia and hypoglycemia as a SAEs. None of diabetes and hyperglycemia AEs resulted in death. Generally patients responded to anti-diabetic medications, without need for dose adjustment.

Combination therapy provided some evidence of efficacy based on improvement in flushing episode symptom control.

Tumor response consisted of disease stabilization, consistent with our prior studies.

Combination therapy had a strong antiproliferative effect based on Ki67 staining of tumor biopsy.

Due to the small number of patients enrolled in each cohort and the large IQR/SE in the data set, the tumor tissue biomarker results have to be interpreted with caution.

Overall, the results show no new safety findings reported for the combination treatment compared to the safety of everolimus and pasireotide when administered as monotherapy.

Date of Clinical Trial Report

17-Feb-2015

Date of Initial Inclusion on Novartis Clinical Trial Results website

24-Feb-2015

Date of Latest Update

Reason for Update