Clinical trial results:
EVINEC: Safety and Tolerability of Everolimus as second-line treatment in poorly differentiated neuroendocrine carcinoma / neuroendocrine carcinoma G3 according to WHO 2010 and neuroendocrine tumor G3 - an investigtor initiated Phase II study.

Summary

EudraCT number	2012-004550-28
Trial protocol	DE
Global end of trial date	04 May 2020

Results information

Result version number	v1 (current)
This version publication date	01 November 2022
First version publication date	01 November 2022

Trial information

Trial identification

Sponsor protocol code	AIO-NET-0112

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02113800
WHO universal trial number (UTN)	-
Other trial identifiers	Novartis-Nr: : CRAD001KDE55T

Notes:

Sponsors

Sponsor organisation name	AIO-Studien-gGmbH
Sponsor organisation address	Kuno-Fischer-Str. 8, Berlin, Germany, 14057
Public contact	AIO-Studien-gGmbH, AIO-Studien-gGmbH, +49 30814534431, info@aio-studien-ggmbh.de
Scientific contact	AIO-Studien-gGmbH, AIO-Studien-gGmbH, +49 30814534431, info@aio-studien-ggmbh.de

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	07 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 May 2020
Global end of trial reached?	Yes
Global end of trial date	04 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate tolerability and safety of everolimus in second-line treatment of poorly differentiated neuroendocrine carcinoma / neuroendocrine carcinoma G3 according to WHO 2010 and neuroendocrine tumors G3. Safety and tolerability of Everolimus can be inferred if type, frequency and seriousness of observed AEs is comparable to those determined in previous Everolimus trials in NET (Radiant-1,2 and 3).

Protection of trial subjects:

This study was planned, analyzed and conducted according to the study protocol and in accordance with the International Conference on Harmonization (ICH) ‚Guideline for Good Clinical Practice E6(R1)‘, CPMP/ICH/135/95, based on the principles of the Declaration of Helsinki (1964) and its October 1996 amendment (Somerset West, South Africa). The study was duly conducted in compliance with the German Arzneimittelgesetz (AMG; German Drug Law), and the corresponding Directive 2001/20/EC. Subjects were fully informed regarding all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 39
Worldwide total number of subjects	39
EEA total number of subjects	39

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)	28
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

42 patients were screened for study participation, 39 of whon were found eligible.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Everolimus 10 mg/d

Arm description: -

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

Dosage and administration details:

A dose of 10 mg was to be administered orally once daily at the same time every day, consistently either with or without food, swallowed whole with a glass of water.

Number of subjects in period 1	Everolimus 10 mg/d
Started	39
Completed	39

Baseline characteristics

Reporting groups	
Reporting group title	Treatment

Reporting group description: -

Reporting group values	Treatment	Total	
Number of subjects	39	39	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	57.0		
full range (min-max)	33 to 77	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	23	23	

End points

End points reporting groups

Reporting group title	Everolimus 10 mg/d
Reporting group description: -	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

Of 39 treated patients, 9 were excluded from the per protocol analysis set. Reasons were the retroactive histological tumor diagnosis as non-NEN by central pathology (3 patients), and major protocol violations (6 patients).

Primary: Overall survival

End point title	Overall survival[1]

End point description:

Primary objective of this study was limted to safety and tolerability. Hence, no primary efficacy endpoint was definded. One of the secondary endpoints, overall survival (OS), is given instead.

The median OS was 12.0 months for all NEN G3 patients together (95%-CI 7.0-23-9). A lower OS occurred in NEC G3 patients with 5.6 months (95%-CI 1.3-20.1) and for MANEC patients with 7.0 months (95%-CI 1.0-11.1) compared to NET G3 patients with 23.9 months (95%-CI 12.0-NC).

OS rate at 12 months in the PP Population was 49.0% (95%-CI 30.2%-65.4%). OS at 12 months was lowest in MANEC patients with 14.3% (95%-CI 0.7%-46.5%) and in NEC G3 patients with 30.0% (95%-CI 7.1%-57.8%) compared to NET G3 patients with 83.9% (95%-CI 49.4%-95.7%).

End point type	Primary

End point timeframe:

Overall survival (OS) was defined as the time from the date of first treatment to the date of death. Patients for whom not date of death was recorded were censored at the date of last contact.

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: Since the study had no primary efficacy endpoint, OS is given for this data field instead. No in-depth statistical analysis was perfomed.

End point values	Per protocol			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: Months				
median (confidence interval 95%)	12.0 (7.0 to 23.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

The median progressive free survival (PFS) was 2.2 months for all NEN G3 patients together (95%-CI 1.8-4.8).
PFS was shorter in NEC G3 with a median of 1.8 months (95% CI 0.9-2.0) and in MANEC with 2.2 months (95% CI 0.7-4.1) as compared to NET G3 patients with 5.2 months (95% CI 1.6-7.3).

PFS rate at 6 months was lowest in MANEC patients with 14.3% (95%-CI 0.7%-46.5%) and NEC G3 patients with
20.0% (95%-CI 3.1%-47.5%) compared to NET G3 patients with 41.7% (95%-CI 15.2%-66.5%).

End point type	Secondary

End point timeframe:

Progression-Free Survival (PFS) was defined as the time from first treatment to PD or death. Patients who had no PD and did not die were censored at the time of the last tumor assessment.

End point values	Everolimus 10 mg/d			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Months				
median (confidence interval 95%)	2.2 (1.8 to 4.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response, ORR and DCR

End point title	Best overall response, ORR and DCR

End point description:

Partial remission was observed for one patient, resulting in an Objective Response Rate (ORR) of 3.3%, [95%CI 0.6%-16.7%].

Disease control was documented for 14 NEN G3 patients, resulting in a disease control rate (DCR) of 46.7% [95%CI 30.2%-63.9%].

End point type	Secondary

End point timeframe:

Best response among all available response assessments

End point values	Everolimus 10 mg/d			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: CR, PR, SD and PD				
Complete Remission (CR)	0			
Partial Remission (PR)	1			
Stable Disease (SD)	13			
Progressive Disease (PD)	13			
No assessment	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Reporting of all adverse events started at the first treatment visit and ended on the EoT visit.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Everolimus 10 mg/d

Reporting group description: -

Serious adverse events	Everolimus 10 mg/d		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 39 (12.82%)		
number of deaths (all causes)	29		
number of deaths resulting from adverse events			
Investigations			
Weight decreased			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiation pneumonitis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cerebrovascular accident			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Melaena			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Everolimus 10 mg/d		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 39 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Tumor pain			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	6		
Vascular disorders			
Lymphoedema			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	5		
Fatigue			
subjects affected / exposed	14 / 39 (35.90%)		
occurrences (all)	16		
General physical health deterioration			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	5		
Influenza like illness			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	6		
Pain			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	7		
Pyrexia			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	6		
Swelling face			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		

Dyspnoea subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 5		
Epistaxis subjects affected / exposed occurrences (all)	8 / 39 (20.51%) 9		
Pneumonitis subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 3		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Depression subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Insomnia subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
C-reactive protein increased subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 4		
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Platelet count decreased subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 7		
Weight decreased subjects affected / exposed occurrences (all)	6 / 39 (15.38%) 8		
Cardiac disorders			

Angina pectoris			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Atrial tachycardia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Atrioventricular block			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Dysgeusia			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Paraesthesia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Taste disorder			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	5		
Anaemia of malignant disease			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Increased tendency to bruise			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Lymphadenopathy			

subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Lymphopenia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Eye disorders			
Eye swelling			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Visual impairment			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Abdominal mass			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	9 / 39 (23.08%)		
occurrences (all)	11		
Abdominal pain lower			

subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	5		
Aphthous ulcer			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	10		
Diarrhoea			
subjects affected / exposed	11 / 39 (28.21%)		
occurrences (all)	14		
Dry mouth			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	5		
Dyspepsia			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	14 / 39 (35.90%)		
occurrences (all)	14		
Stomatitis			
subjects affected / exposed	16 / 39 (41.03%)		
occurrences (all)	20		
Toothache			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	9		
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	5		

Dry skin			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Erythema			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Erythema multiforme			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Night sweats			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	8		
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	9		
Flank pain			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		

Pain in extremity subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 3		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Uninary tract infection subjects affected / exposed occurrences (all)	 3 / 39 (7.69%) 3 4 / 39 (10.26%) 4		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypercalcaemia subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all) Hypertriglyceridaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all) Iron deficiency subjects affected / exposed occurrences (all)	 9 / 39 (23.08%) 10 2 / 39 (5.13%) 2 3 / 39 (7.69%) 4 2 / 39 (5.13%) 2 2 / 39 (5.13%) 2 3 / 39 (7.69%) 3 3 / 39 (7.69%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 August 2015	Addition of IMP package sizes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported