Clinical trial results:
PET/CT imaging of angiogenesis in patients with neuroendocrine tumors using 68Ga-NODAGA-E[c(RGDyK)]2

Summary

EudraCT number	2017-002512-14
Trial protocol	DK
Global end of trial date	31 December 2021

Results information

Result version number	v1 (current)
This version publication date	30 January 2023
First version publication date	30 January 2023

Trial information

Trial identification

Sponsor protocol code	AK2017-2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03271281
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigshospitalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, 2100
Public contact	Professor Andreas Kjær, Departement of Clinical Physiology and Nuclear Medicine, Rigshospitalet, akjaer@sund.ku.dk
Scientific contact	Professor Andreas Kjær, Departement of Clinical Physiology and Nuclear Medicine, Rigshospitalet, akjaer@sund.ku.dk

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	31 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2021
Global end of trial reached?	Yes
Global end of trial date	31 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In this study with integrin alphavbeta3 imaging we include patients diagnosed with neuroendocrine tumors in order to investigate tumor visualization and prognostic performance of integrin alphavbeta3 imaging by [68Ga]Ga-NODAGA-E[c(RGDyK)]2 PET/CT

Protection of trial subjects:

It is emphasized that participation in the study is voluntary and will have no influence on the otherwise planned treatment, whether the patient will participate or not. The study is conducted in accordance with the Helsinki Declaration and the Good Clinical Practice (GCP). All clinical information about the participants is protected under the act on processing of Personal Data and the Danish Health Legislation. Overall, it is considered that the project is ethically sound, as there are no significant risks associated with the integrin alphavbeta3 PET/CT imaging procedure.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 December 2017
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	Denmark: 113
Worldwide total number of subjects	113
EEA total number of subjects	113

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)	45
From 65 to 84 years	68

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Prospective inclusion patients with lung or gastro-entero-pancreatic neuroendocrine neoplasms.

Pre-assignment

Screening details:

We prospectively included 113 patients, whereof 14 patients did not undergo a [68Ga]Ga-NODAGA-E[c(RGDyK)]2 PET/CT due to worsening of disease (n=4), withdrawal of consent (n=2), died before PET/CT (n=3), logistically not possible to perform PET/CT (n=2), and not possible to perform PET/CT due to COVID-19 restrictions (n=3).

Pre-assignment period milestones

Number of subjects started	113
Number of subjects completed	113

Period 1

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

Blinding implementation details:

An experienced board-certified nuclear medicine physician together with an experienced board-certified radiologist analyzed side-by-side the [68Ga]Ga-NODAGA-E[c(RGDyK)]2 PET/CT scans. The readers had access to previous imaging studies, but were blinded to other patient data and follow-up data.

Arms

Arm title	Experimental arm

Arm description: -

Arm type	Experimental
Investigational medicinal product name	[68Ga]Ga-NODAGA-E[c(RGDyK)]2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

One injection of up to 226 MBq [68Ga]Ga-NODAGA-E[c(RGDyK)]2

Number of subjects in period 1	Experimental arm
Started	113
Completed	99
Not completed	14
Consent withdrawn by subject	2
worsening of disease	4
death before PET/CT	3

not possible to perform PET/CT due to COVID-19 res	3
logistically not possible to perform PET/CT	2

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)

Reporting group description:

All patients fullfilling the inclusion/exclusion criteria and included in the study

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	113	113	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	45	45	
From 65-84 years	68	68	
85 years and over	0	0	
Age continuous Units: years			
median	68		
full range (min-max)	44 to 83	-	
Gender categorical Units: Subjects			
Female	49	49	
Male	64	64	

Subject analysis sets

Subject analysis set title	Primary analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who underwent [68Ga]Ga-NODAGA-E[c(RGDyK)]2 PET/CT and had evaluable lesions (visible lesions on PET and or CT)

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who underwent [68Ga]Ga-NODAGA-E[c(RGDyK)]2 PET/CT

Subject analysis set title	Secondary analyses set - low integrin alphavbeta3
Subject analysis set type	Per protocol

Subject analysis set description:

Patients were dicotomized by tumor uptake of 68Ga-NODAGA-E[c(RGDyK)]2 in a group of low and high uptake

Subject analysis set title	Secondary analyses set - high integrin alphavbeta3
Subject analysis set type	Per protocol

Subject analysis set description:

Patients were dicotomized by tumor uptake of 68Ga-NODAGA-E[c(RGDyK)]2 in a group of low and high uptake

Reporting group values	Primary analysis set	Safety set	Secondary analyses set - low integrin alphavbeta3
Number of subjects	97	99	32
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median	67	67	63.5
full range (min-max)	44 to 83	44 to 83	44 to 76
Gender categorical			
Units: Subjects			
Female	43	44	14
Male	54	55	18

Reporting group values	Secondary analyses set - high integrin alphavbeta3		
Number of subjects	65		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median	68		
full range (min-max)	44 to 83		
Gender categorical			
Units: Subjects			
Female	29		
Male	36		

End points

End points reporting groups

Reporting group title	Experimental arm
Reporting group description: -	
Subject analysis set title	Primary analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients who underwent [68Ga]Ga-NODAGA-E[c(RGDyK)]2 PET/CT and had evaluable lesions (visible lesions on PET and or CT)	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who underwent [68Ga]Ga-NODAGA-E[c(RGDyK)]2 PET/CT	
Subject analysis set title	Secondary analyses set - low integrin alphavbeta3
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients were dicotomized by tumor uptake of 68Ga-NODAGA-E[c(RGDyK)]2 in a group of low and high uptake	
Subject analysis set title	Secondary analyses set - high integrin alphavbeta3
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients were dicotomized by tumor uptake of 68Ga-NODAGA-E[c(RGDyK)]2 in a group of low and high uptake	

Primary: 68Ga-NODAGA-E[c(RGDyK)]2 PET positive lesions

End point title	68Ga-NODAGA-E[c(RGDyK)]2 PET positive lesions[1]
End point description:	
A tumor lesion to liver ratio (TLR) was calculated as tumor lesion SUVmax/normal liver SUVmean. A cutoff of TLR ≥ 2 was used to define positive lesions.	
End point type	Primary
End point timeframe:	
Assessed following the performance 68Ga-NODAGA-E[c(RGDyK)]2 PET/CT	

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: Descriptive analysis of the number of patients with 68Ga-NODAGA-E[c(RGDyK)]2 PET positive lesions

End point values	Primary analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: number of patients				
Positive	74			
Negative	23			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

End point type	Secondary

End point timeframe:

During at least 1 year follow-up after 68Ga-NODAGA-E[c(RGDyK)]2 PET/CT

End point values	Primary analysis set	Secondary analyses set - low integrin alphavbeta3	Secondary analyses set - high integrin alphavbeta3	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	97	32	65	
Units: number of patients				
Progressive disease	61	16	45	
Non-progressive disease	36	16	20	

Statistical analyses

Statistical analysis title	Cox regression analysis
Comparison groups	Secondary analyses set - low integrin alphavbeta3 v Secondary analyses set - high integrin alphavbeta3
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	2.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	3.78

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

At least one year follow-up after 68Ga-NODAGA-E[c(RGDyK)]2

End point values	Primary analysis set	Secondary analyses set - low integrin alphavbeta3	Secondary analyses set - high integrin alphavbeta3	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	97	32	65	
Units: number of patients				
Dead	25	2	23	
Alive	72	30	42	

Statistical analyses

Statistical analysis title	Cox regression analysis
Comparison groups	Secondary analyses set - low integrin alphavbeta3 v Secondary analyses set - high integrin alphavbeta3
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	6.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.64
upper limit	29.51

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Within 24 hours of 68Ga-NODAGA-E[c(RGDyK)]2 PET/CT	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	5

Reporting groups	
Reporting group title	All patients scanned

Reporting group description: -

Serious adverse events	All patients scanned		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 99 (0.00%)		
number of deaths (all causes)	26		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All patients scanned		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 99 (3.03%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences (all)	1		
Infusion related reaction	Additional description: in relation to injection of CT contrast		
subjects affected / exposed	1 / 99 (1.01%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2018	New principal investigator

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported