Clinical trial results:
Al18F-NOTA-octreotide PET imaging of the somatostatin receptor in neuroendocrine tumors

Summary

EudraCT number	2020-000549-15
Trial protocol	BE
Global end of trial date	13 June 2022

Results information

Result version number	v1 (current)
This version publication date	24 June 2023
First version publication date	24 June 2023

Trial information

Trial identification

Sponsor protocol code	S63678

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04552847
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospitals Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Christophe Deroose, University Hospitals Leuven, 0032 16343715, christophe.deroose@uzleuven.be
Scientific contact	Christophe Deroose, University Hospitals Leuven, 0032 16343715, christophe.deroose@uzleuven.be

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	13 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 February 2022
Global end of trial reached?	Yes
Global end of trial date	13 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Demonstrate the non-inferior diagnostic performance of Al18F-NOTA-octreotide PET imaging in comparison with the current golden standard, 68Ga-DOTA-SSA PET, in NET patients

Protection of trial subjects:

Female participants of childbearing potential must agree to use highly effective medically accepted contraceptive methods to prevent pregnancy.

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	07 October 2020
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	Belgium: 85
Worldwide total number of subjects	85
EEA total number of subjects	85

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	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were contacted at the time when they were scheduled for or undergoing a 68Ga-DOTAsomatostatin analogue (68Ga-DOTA-SSA) PET/CT or other procedures at the nuclear medicine unit. They were also recruited by members of the study team during their contact with the patient.

Pre-assignment

Screening details:

Patients with cytologically/histologically confirmed neuroendocrine tumors of all grades of gastroenteropancreatic, pulmonary, neural crest or unknown primary origin with at least 1 known tumoral lesion below the level of the submandibular and parotid glands and a routine clinical clinical 68Ga-DOTA-SSA PET within 3 months prior or after the study.

Pre-assignment period milestones

Number of subjects started	85
Number of subjects completed	85

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:

NA

Arms

Are arms mutually exclusive?	Yes
Arm title	PET/CT (Part A)

Arm description:

Seventy-five NET patients who underwent a whole-body PET with low-dose CT scan 2 hours after Al18F-NOTA-octreotide injection.

Arm type	Experimental
Investigational medicinal product name	[18F]AlF-NOTA-octreotide
Investigational medicinal product code	
Other name	Al18F-NOTA-octreotide, [18F]AlF-OC, Al18F-OC
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

4 MBq/kg
1 day, single dose
no treatment: diagnostic scanning

Arm title	PET/MR (Part B)

Arm description:

Ten NET patients who underwent a whole-body PET/MR scan 2 hours after Al18F-NOTA-octreotide injection.

Arm type	Experimental

Investigational medicinal product name	[18F]AlF-NOTA-octreotide
Investigational medicinal product code	
Other name	Al18F-NOTA-octreotide, [18F]AlF-OC, Al18F-OC
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

4 MBq/kg
1 day, single dose
no treatment: diagnostic scanning

Number of subjects in period 1	PET/CT (Part A)	PET/MR (Part B)
Started	75	10
Completed	75	10

Baseline characteristics

Reporting groups	
Reporting group title	PET/CT (Part A)
Reporting group description:	
Seventy-five NET patients who underwent a whole-body PET with low-dose CT scan 2 hours after Al18F-NOTA-octreotide injection.	
Reporting group title	PET/MR (Part B)
Reporting group description:	
Ten NET patients who underwent a whole-body PET/MR scan 2 hours after Al18F-NOTA-octreotide injection.	

Reporting group values	PET/CT (Part A)	PET/MR (Part B)	Total
Number of subjects	75	10	85
Age categorical Units: Subjects			
Adults (18-64 years)	37	8	45
From 65-84 years	38	2	40
Gender categorical Units: Subjects			
Female	29	4	33
Male	46	6	52
Primary tumor Units: Subjects			
Intestine	45	4	49
Pancreas	18	2	20
Lung	7	2	9
Unknown primary	4	2	6
Paraganglioma	1	0	1
Tumor grade Units: Subjects			
G1	35	2	37
G1/G2	2	2	4
G2	34	6	40
G3	2	0	2
NA	2	0	2

End points

End points reporting groups

Reporting group title	PET/CT (Part A)
Reporting group description: Seventy-five NET patients who underwent a whole-body PET with low-dose CT scan 2 hours after Al18F-NOTA-octreotide injection.	
Reporting group title	PET/MR (Part B)
Reporting group description: Ten NET patients who underwent a whole-body PET/MR scan 2 hours after Al18F-NOTA-octreotide injection.	
Subject analysis set title	68Ga-DOTATATE/NOC (part A)
Subject analysis set type	Full analysis
Subject analysis set description: Routine clinical 68Ga-DOTA-TATE or -NOC PET/CT scan of the patients in part A	
Subject analysis set title	Al18F-NOTA-octreotide (part A)
Subject analysis set type	Full analysis
Subject analysis set description: Al18F-NOTA-octreotide PET/CT scan of the patients in part A	
Subject analysis set title	68Ga-DOTATATE (part A)
Subject analysis set type	Full analysis
Subject analysis set description: Patients with a routine clinical 68Ga-DOTATATE PET/CT scan in part A	
Subject analysis set title	68Ga-DOTANOC (part A)
Subject analysis set type	Full analysis
Subject analysis set description: Patients with a routine clinical 68Ga-DOTANOC PET/CT scan in part A	
Subject analysis set title	G1 (part A)
Subject analysis set type	Full analysis
Subject analysis set description: Patients with a tumor grade G1 in part A	
Subject analysis set title	G2 (part A)
Subject analysis set type	Full analysis
Subject analysis set description: Patients with a tumor grade G2 in part A	
Subject analysis set title	Primary: intestine (part A)
Subject analysis set type	Full analysis
Subject analysis set description: Patients with a tumor of intestinal origin in part A	
Subject analysis set title	Primary: pancreas (part A)
Subject analysis set type	Full analysis
Subject analysis set description: Patients with a tumor of pancreatic origin in part A	

Primary: Differential Detection Ratio (DDR)

End point title	Differential Detection Ratio (DDR)[1][2]
End point description: The primary objective, i.e. non-inferiority of 18F-AlF-OC compared with 68Ga-DOTATATE/NOC, would be met if the lower margin of the 95% confidence interval (95% CI) for the mean DDR was higher than -15%.	
End point type	Primary

End point timeframe:

End of study

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: The statistics for this endpoint are encompassed in the reported 95% confidence interval.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistics for this endpoint are encompassed in the reported 95% confidence interval.

End point values	PET/CT (Part A)			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: percent				
arithmetic mean (confidence interval 95%)	15.8 (9.6 to 22.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Detection rate analysis on the organ level (DR data - part A)

End point title	Detection rate analysis on the organ level (DR data - part A)

End point description:

End point type	Secondary

End point timeframe:

End of study

End point values	68Ga-DOTATATE/NOC (part A)	Al18F-NOTA-octreotide (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	75	75		
Units: mean DR (%)				
number (not applicable)				
Liver	60.3	93.3		
Bone	79.8	77.0		
Lymph nodes	74.1	96.0		
Lung	73.6	98.1		
Peritoneum	55.5	89.3		
Pancreas	84.6	100.0		
Pleura	50.0	66.7		
Small intestine	78.8	90.9		
Rectum	100.0	100.0		
Soft tissue	62.5	100.0		
Muscle	77.6	85.3		

Heart	100.0	100.0		
Salivary glands	0.0	100.0		
Breast	100.0	100.0		
Paraganglia	100.0	100.0		
Thyroid	0.0	100.0		
Stomach	100.0	100.0		
All (incl. head region)	75.7	91.4		
All (excl. head region)	75.3	91.1		

Statistical analyses

Statistical analysis title	Comparison DR Liver lesions
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.00001
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - 54 patients had liver lesions

Statistical analysis title	Comparison DR Bone lesions
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	= 0.78
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - 50 patients had bone lesions

Statistical analysis title	Comparison DR Lymph node lesions
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	< 0.00001
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - 63 patients had lymph node lesions

Statistical analysis title	Comparison DR Lung lesions
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
P-value	= 0.027
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - 18 patients had lung lesions

Statistical analysis title	Comparison DR Peritoneum lesions
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	= 0.008
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - 28 patients had peritoneal lesions

Statistical analysis title	Comparison DR Pancreas lesions
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
P-value	= 0.1
Method	Wilcoxon (Mann-Whitney)

Notes:

[8] - 13 patients had pancreas lesions

Statistical analysis title	Comparison DR All lesions (incl. head region)
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.00001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison DR All lesions (excl. head region)
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.00001
Method	Wilcoxon (Mann-Whitney)

Secondary: Detection rate analysis on the organ level (DDR data - part A)

End point title	Detection rate analysis on the organ level (DDR data - part

End point description:

End point type	Secondary

End point timeframe:

End of study

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistics for this endpoint are encompassed in the reported 95% confidence interval.

End point values	PET/CT (Part A)			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: percent				
arithmetic mean (confidence interval 95%)				
Liver	33.1 (21.7 to 44.4)			
Bone	-2.8 (-17.8 to 12.2)			
Lymph nodes	21.9 (14.0 to 29.8)			
Lung	24.6 (3.3 to 45.8)			
Peritoneum	33.8 (11.7 to 55.9)			
Pancreas	15.4 (-3.7 to 34.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: DDR analysis according to routine 68Ga-DOTA-SSA tracer (part A)

End point title	DDR analysis according to routine 68Ga-DOTA-SSA tracer (part A)

End point description:

End point type	Secondary

End point timeframe:
End of study

End point values	68Ga-DOTATATE (part A)	68Ga-DOTANOC (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	19		
Units: percent				
arithmetic mean (confidence interval 95%)	11.8 (4.3 to 19.3)	27.5 (17.8 to 37.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: DR analysis 68Ga-DOTATATE subgroup (part A)

End point title	DR analysis 68Ga-DOTATATE subgroup (part A)

End point description:

End point type	Secondary

End point timeframe:
End of study

End point values	Al18F-NOTA-octreotide (part A)	68Ga-DOTATATE (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	56		
Units: mean DR (%)				
number (not applicable)				
Liver	92.3	57.7		
Bone	71.4	90.5		
Lymph nodes	94.7	75.0		
Lung	97.6	73.1		
Peritoneum	87.6	53.1		
Pancreas	100.0	85.0		
Pleura	33.3	100.0		
Small intestine	100.0	78.8		
Rectum	100.0	100.0		
Soft tissue	100.0	50.0		
MUscle	80.4	70.1		
Heart	100.0	100.0		
Salivary glands	100.0	0.0		
Breast	100.0	100.0		

Paraganglia	100.0	100.0		
Thyroid	100.0	0.0		
Stomach	100.0	100.0		
All	89.8	77.9		

Statistical analyses

Statistical analysis title	Comparison DR Liver lesions
Comparison groups	Al18F-NOTA-octreotide (part A) v 68Ga-DOTATATE (part A)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Notes:

[10] - 38 patients had liver lesions

Statistical analysis title	Comparison DR Bone lesions
Comparison groups	Al18F-NOTA-octreotide (part A) v 68Ga-DOTATATE (part A)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	= 0.02
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - 39 patients had bone lesions

Statistical analysis title	Comparison DR Lymph node lesions
Comparison groups	Al18F-NOTA-octreotide (part A) v 68Ga-DOTATATE (part A)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Notes:

[12] - 47 patients had lymph node lesions

Statistical analysis title	Comparison DR Lung lesions
Comparison groups	Al18F-NOTA-octreotide (part A) v 68Ga-DOTATATE (part A)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
P-value	= 0.046
Method	Wilcoxon (Mann-Whitney)

Notes:

[13] - 14 patients had lung lesions

Statistical analysis title	Comparison DR Peritoneum lesions
Comparison groups	Al18F-NOTA-octreotide (part A) v 68Ga-DOTATATE (part A)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
P-value	= 0.019
Method	Wilcoxon (Mann-Whitney)

Notes:

[14] - 24 patients had peritoneal lesions

Statistical analysis title	Comparison DR Pancreas lesions
Comparison groups	Al18F-NOTA-octreotide (part A) v 68Ga-DOTATATE (part A)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
P-value	= 0.18
Method	Wilcoxon (Mann-Whitney)

Notes:

[15] - 10 patients had pancreas lesions

Statistical analysis title	Comparison DR All lesions
Comparison groups	Al18F-NOTA-octreotide (part A) v 68Ga-DOTATATE (part A)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.002
Method	Wilcoxon (Mann-Whitney)

Secondary: DR analysis 68Ga-DOTANOC subgroup (part A)

End point title	DR analysis 68Ga-DOTANOC subgroup (part A)

End point description:

End point type	Secondary

End point timeframe:

End of study

End point values	Al18F-NOTA-octreotide (part A)	68Ga-DOTANOC (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	19		
Units: mean DR (%)				
number (not applicable)				
Liver	95.9	66.4		
Bone	97.0	41.7		

Lymph nodes	99.8	71.4		
Lung	100.0	75.0		
Peritoneum	99.5	70.0		
Pancreas	100.0	83.3		
Pleura	100.0	0.0		
Small intestine	80.0	80.0		
Soft tissue	100.0	100.0		
Muscle	100.0	100.0		
Heart	100.0	100.0		
All	96.4	69.1		

Statistical analyses

Statistical analysis title	Comparison DR Liver lesions
Comparison groups	Al18F-NOTA-octreotide (part A) v 68Ga-DOTANOC (part A)
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority[16]
P-value	= 0.002
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - 16 patients had liver lesions

Statistical analysis title	Comparison DR Bone lesions
Comparison groups	Al18F-NOTA-octreotide (part A) v 68Ga-DOTANOC (part A)
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
P-value	= 0.008
Method	Wilcoxon (Mann-Whitney)

Notes:

[17] - 11 patients had bone lesions

Statistical analysis title	Comparison DR Lymph node lesions
Comparison groups	Al18F-NOTA-octreotide (part A) v 68Ga-DOTANOC (part A)
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority[18]
P-value	= 0.005
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - 16 patients had lymph node lesions

Statistical analysis title	Comparison DR Lung lesions
Comparison groups	Al18F-NOTA-octreotide (part A) v 68Ga-DOTANOC (part A)

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority[19]
P-value	= 0.32
Method	Wilcoxon (Mann-Whitney)

Notes:

[19] - 4 patients had lung lesions

Statistical analysis title	Comparison DR Peritoneum lesions
Comparison groups	Al18F-NOTA-octreotide (part A) v 68Ga-DOTANOC (part A)
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority[20]
P-value	= 0.11
Method	Wilcoxon (Mann-Whitney)

Notes:

[20] - 4 patients had peritoneal lesions

Statistical analysis title	Comparison DR Pancreas lesions
Comparison groups	Al18F-NOTA-octreotide (part A) v 68Ga-DOTANOC (part A)
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
P-value	= 0.32
Method	Wilcoxon (Mann-Whitney)

Notes:

[21] - 3 patients had pancreas lesions

Statistical analysis title	Comparison DR All lesions
Comparison groups	Al18F-NOTA-octreotide (part A) v 68Ga-DOTANOC (part A)
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: DDR analysis according to tumor grade (part A)

End point title	DDR analysis according to tumor grade (part A)

End point description:

End point type	Secondary

End point timeframe:

End of study

End point values	G1 (part A)	G2 (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	34		
Units: percent				
arithmetic mean (confidence interval 95%)	14.9 (6.0 to 23.8)	16.6 (6.3 to 27.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: DR analysis according to tumor grade (part A)

End point title	DR analysis according to tumor grade (part A)

End point description:

End point type	Secondary

End point timeframe:

End of study

End point values	68Ga-DOTATATE/NOC (part A)	Al18F-NOTA-octreotide (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	75	75		
Units: mean DR (%)				
number (not applicable)				
G1	75.0	89.9		
G2	75.5	92.1		
G3	62.0	97.4		

Statistical analyses

Statistical analysis title	DR comparison G1 subgroup
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority[22]
P-value	= 0.003
Method	Wilcoxon (Mann-Whitney)

Notes:

[22] - n = 35

Statistical analysis title	DR comparison G2 subgroup

Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority[23]
P-value	= 0.002
Method	Wilcoxon (Mann-Whitney)

Notes:

[23] - n = 34

Secondary: Lesion uptake analysis in SUVmax (part A)

End point title	Lesion uptake analysis in SUVmax (part A)

End point description:

End point type	Secondary

End point timeframe:

End of study

End point values	68Ga-DOTATATE/NOC (part A)	Al18F-NOTA-octreotide (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	75	75		
Units: SUVmax				
arithmetic mean (standard deviation)				
Liver	22.4 (± 11.4)	21.5 (± 12.4)		
Bone	11.4 (± 8.3)	8.6 (± 6.3)		
Lymph nodes	20.9 (± 14.3)	19.9 (± 16.9)		
Lung	24.8 (± 29.5)	16.9 (± 17.0)		
Peritoneum	16.3 (± 11.9)	14.9 (± 9.9)		
Pancreas	51.1 (± 38.6)	51.9 (± 45.6)		
Pleura	14.6 (± 0)	5.7 (± 0)		
Small intestine	20.7 (± 13.1)	24.2 (± 17.2)		
Rectum	16.8 (± 17.1)	21.4 (± 16.1)		
Soft tissue	6.9 (± 2.5)	7.3 (± 3.0)		
Muscle	4.4 (± 3.0)	4.2 (± 1.6)		
Heart	12.7 (± 10.5)	13.3 (± 11.4)		
Breast	6.8 (± 5.8)	9.5 (± 8.9)		
Paraganglia	58.9 (± 0)	35.6 (± 0)		
Max. 20 per patient	27.7 (± 16.9)	24.7 (± 16.3)		
Max. 5 per organ	28.9 (± 17.9)	25.3 (± 16.2)		
All	22.4 (± 15.6)	20.0 (± 14.5)		

Statistical analyses

Statistical analysis title	Comparison SUVmax Liver
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.76
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SUVmax Bone
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SUVmax Lymph nodes
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.19
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SUVmax Lung
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.088
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SUVmax Peritoneum
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.87
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SUVmax Pancreas
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.94
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SUVmax Max. 20 per patient
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.036
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SUVmax Max. 5 per organ
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.032
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SUVmax All
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.067
Method	Wilcoxon (Mann-Whitney)

Secondary: Lesion uptake analysis in TBR (part A)

End point title	Lesion uptake analysis in TBR (part A)
End point description:	

End point type	Secondary
End point timeframe:	
End of study	

End point values	68Ga-DOTATATE/NOC (part A)	Al18F-NOTA-octreotide (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	75	75		
Units: TBR				
arithmetic mean (standard deviation)				
Liver	4.8 (± 3.8)	6.7 (± 5.2)		
Bone	10.1 (± 7.3)	13.8 (± 9.9)		
Lymph nodes	36.5 (± 24.2)	49.9 (± 40.8)		
Lung	44.0 (± 61.2)	42.7 (± 50.4)		
Peritoneum	29.2 (± 24.4)	33.7 (± 25.6)		
Pancreas	90.3 (± 65.4)	141.1 (± 113.8)		
Pleura	29.8 (± 0)	14.6 (± 0)		
Small intestine	34.4 (± 15.8)	52.3 (± 29.3)		
Rectum	49.8 (± 61.5)	137.1 (± 162.3)		
Soft tissue	13.0 (± 4.0)	24.1 (± 11.8)		
Muscle	8.1 (± 5.6)	14.6 (± 9.6)		
Heart	23.0 (± 20.1)	32.1 (± 26.5)		
Breast	11.1 (± 6.4)	18.6 (± 12.8)		
Paraganglia	83.0 (± 0)	77.3 (± 0)		
Max. 20 per patient	29.2 (± 33.1)	37.6 (± 40.0)		
Max. 5 per organ	33.0 (± 33.1)	42.3 (± 40.0)		
All	25.1 (± 32.7)	31.7 (± 36.5)		

Statistical analyses

Statistical analysis title	Comparison TBR Liver
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part

	A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison TBR Bone
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison TBR Lymph nodes
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison TBR Lung
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.95
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison TBR Peritoneum
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.091
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison TBR Pancreas
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.006
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison TBR Max. 20 per patient
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison TBR Max. 5 per organ
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.002
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison TBR All
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Lesion uptake in SUVmax according to routine 68Ga-DOTA-SSA tracer (part A)

End point title	Lesion uptake in SUVmax according to routine 68Ga-DOTA-SSA tracer (part A)

End point description:

End point type	Secondary

End point timeframe:

End of study

End point values	68Ga-DOTATATE/NOC (part A)	Al18F-NOTA-octreotide (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	75	75		
Units: SUVmax				
arithmetic mean (standard deviation)				
68Ga-DOTATATE	23.3 (± 16.9)	19.0 (± 14.8)		
68Ga-DOTANOC	19.6 (± 11.2)	23.1 (± 13.7)		

Statistical analyses

Statistical analysis title	Comparison SUVmax 68Ga-DOTATATE
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.002
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SUVmax 68Ga-DOTANOC
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Lesion uptake in TBR according to routine 68Ga-DOTA-SSA tracer (part A)

End point title	Lesion uptake in TBR according to routine 68Ga-DOTA-SSA tracer (part A)

End point description:

End point type	Secondary

End point timeframe:

End of study

End point values	68Ga-DOTATATE/NOC (part A)	Al18F-NOTA-octreotide (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	75	75		
Units: TBR				
arithmetic mean (standard deviation)				
68Ga-DOTATATE	26.6 (± 36.4)	31.8 (± 38.9)		
68Ga-DOTANOC	20.7 (± 17.7)	31.2 (± 29.2)		

Statistical analyses

Statistical analysis title	Comparison TBR 68Ga-DOTATATE
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.12
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison TBR 68Ga-DOTANOC
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Lesion uptake in SUVmax according to tumor grade (part A)

End point title	Lesion uptake in SUVmax according to tumor grade (part A)
End point description:	

End point type	Secondary
End point timeframe:	
End of study	

End point values	68Ga-DOTATATE/NOC (part A)	Al18F-NOTA-octreotide (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	75	75		
Units: SUVmax				
arithmetic mean (standard deviation)				
G1	22.9 (± 16.8)	17.9 (± 11.5)		
G2	22.1 (± 14.5)	22.4 (± 17.7)		
G3	15.2 (± 4.2)	19.0 (± 0.6)		

Statistical analyses

Statistical analysis title	Comparison SUVmax G1
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.008
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SUVmax G2
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9
Method	Wilcoxon (Mann-Whitney)

Secondary: Lesion uptake in TBR according to tumor grade (part A)

End point title	Lesion uptake in TBR according to tumor grade (part A)
End point description:	

End point type	Secondary
End point timeframe:	
End of study	

End point values	68Ga-DOTATATE/NOC (part A)	Al18F-NOTA-octreotide (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	75	75		
Units: TBR				
arithmetic mean (standard deviation)				
G1	26.7 (± 41.4)	27.9 (± 36.1)		
G2	23.3 (± 22.5)	35.8 (± 39.2)		
G3	10.3 (± 9.5)	15.3 (± 8.7)		

Statistical analyses

Statistical analysis title	Comparison TBR G1
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison TBR G2
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.003
Method	Wilcoxon (Mann-Whitney)

Secondary: TNM staging based on both [Ga68]-DOTATATE/-NOC and [18F]AlF-NOTA-octreotide images

End point title	TNM staging based on both [Ga68]-DOTATATE/-NOC and [18F]AlF-NOTA-octreotide images

End point description:

TNM staging based on both [Ga68]-DOTATATE/-NOC and [18F]AlF-NOTA-octreotide images of all study patients from arm A

End point type	Secondary

End point timeframe:

Overall study duration

End point values	68Ga-DOTATATE/NOC (part A)	Al18F-NOTA-octreotide (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	75	75		
Units: number of patients				
T0N0M1a	4	3		
T0N0M1b	1	2		
T0N0M1c	4	3		
T0N1M0	1	1		
T0N1M1a	5	5		
T0N1M1b	3	3		
T0N1M1c	18	19		
T0N2M1b	2	2		
T0N2M1c	5	5		
T1cN0M0	1	1		
T1N0M0	1	1		
T1N1M1a	1	0		
T1N1M1c	2	3		
T2N0M0	1	1		
T2N0M1a	2	2		
T2N1M0	2	2		
T2N1M1a	3	2		
T2N1M1b	2	2		
T2N1M1c	9	9		
T2N2M1c	0	2		
T3N1M0	1	1		
T3N1M1a	1	1		
T3N1M1c	3	3		
T3N2M1b	1	1		
T4N2M1b	1	1		

T2N2M1b	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in TNM staging based on both Ga68-DOTATATE/-NOC and [18F]AlF-NOTA-octreotide images

End point title	Differences in TNM staging based on both Ga68-DOTATATE/-NOC and [18F]AlF-NOTA-octreotide images[24]

End point description:

To assess differences in TNM staging based on both 68Ga-DOTATATE/-NOC and AlF-NOTA-octreotide PET images.
Upstaging = higher TNM stage based on AlF-NOTA-oc images
Downstaging = lower TNM stage based on AlF-NOTA-oc images

End point type	Secondary

End point timeframe:

Overall study timeline

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis needed, number of patients with a difference in TNM staging

End point values	PET/CT (Part A)			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: Number of cases				
Total differences in TNM	10			
Upstaging	7			
Downstaging	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in clinical management when using [18F]AlF-NOTA-octreotide

End point title	Differences in clinical management when using [18F]AlF-NOTA-octreotide[25]

End point description:

To assess differences in clinical management based on both PET tracers. For each patient, the images from the SSTR PET ([68Ga]Ga-DOTA-SSA or [18F]AlF-OC; in random order and with the experts blinded to the exact tracer used), were presented at a multidisciplinary tumor board-like setting and a final consensus decision for patient management will be recorded. Subsequently, they will be presented with the PET images from the other tracer and asked if they want to change their decision based on the new images.
Minor change = intramodality change

Major change = intermodality change

End point type	Secondary

End point timeframe:

Overall study timeline

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis needed, number of patients with a therapy change based on AlF-NOTA-octreotide

End point values	PET/CT (Part A)			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: Number of cases with management change				
Total changes in management	10			
Therapy upgrade	10			
Therapy downgrade	0			
Minor change	7			
Major change	3			

Statistical analyses

No statistical analyses for this end point

Post-hoc: DDR analysis according to primary (part A)

End point title	DDR analysis according to primary (part A)

End point description:

End point type	Post-hoc

End point timeframe:

End of study

End point values	Primary: intestine (part A)	Primary: pancreas (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	18		
Units: percent				
arithmetic mean (confidence interval 95%)	17.8 (9.2 to 26.4)	8.4 (-1.2 to 18.0)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: DR analysis according to primary (part A)	
End point title	DR analysis according to primary (part A)
End point description:	
End point type	Post-hoc
End point timeframe:	
End of study	

End point values	68Ga-DOTATATE/NOC (part A)	Al18F-NOTA-octreotide (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63	63		
Units: mean DR (%)				
number (not applicable)				
Intestine	72.6	90.4		
Pancreas	84.2	92.7		

Statistical analyses

Statistical analysis title	DR comparison Intestinal primary subgroup
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	126
Analysis specification	Post-hoc
Analysis type	non-inferiority[26]
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Notes:
[26] - n = 45

Statistical analysis title	DR comparison Pancreatic primary subgroup
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	126
Analysis specification	Post-hoc
Analysis type	non-inferiority[27]
P-value	= 0.087
Method	Wilcoxon (Mann-Whitney)

Notes:
[27] - n = 18

Post-hoc: Lesion uptake in SUVmax according to primary (part A)	
End point title	Lesion uptake in SUVmax according to primary (part A)

End point description:

End point type	Post-hoc

End point timeframe:
End of study

End point values	68Ga-DOTATATE/NOC (part A)	Al18F-NOTA-octreotide (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63	63		
Units: SUVmax				
arithmetic mean (standard deviation)				
Intestine	17.8 (± 6.0)	16.3 (± 9.4)		
Pancreas	28.0 (± 16.7)	26.9 (± 19.9)		

Statistical analyses

Statistical analysis title	Comparison SUVmax Intestinal primary
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	126
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.18
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SUVmax Pancreatic primary
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	126
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.4
Method	Wilcoxon (Mann-Whitney)

Post-hoc: Lesion uptake in TBR according to primary (part A)

End point title	Lesion uptake in TBR according to primary (part A)

End point description:

End point type	Post-hoc

End point timeframe:
End of study

End point values	68Ga-DOTATATE/NOC (part A)	Al18F-NOTA-octreotide (part A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63	63		
Units: TBR				
arithmetic mean (standard deviation)				
Intestine	17.8 (± 13.0)	22.6 (± 20.2)		
Pancreas	26.3 (± 26.6)	40.7 (± 43.9)		

Statistical analyses

Statistical analysis title	Comparison TBR Intestinal primary
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	126
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.008
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison TBR Pancreatic primary
Comparison groups	68Ga-DOTATATE/NOC (part A) v Al18F-NOTA-octreotide (part A)
Number of subjects included in analysis	126
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.043
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: until discharge from the hospital after the study scan	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups	
Reporting group title	All participants

Reporting group description: -

Serious adverse events	All participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 85 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	All participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 85 (25.88%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 85 (25.88%)		
occurrences (all)	22		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported