Clinical trial results:
"An exploratory study regarding the use of the biomarker DAT for image diagnosis of clear cell renal cell carcinoma"

Summary

EudraCT number	2016-005182-31
Trial protocol	SE
Global end of trial date	04 July 2018

Results information

Result version number	v1 (current)
This version publication date	14 November 2018
First version publication date	14 November 2018
Summary attachment (see zip file)	Synopsis (SYNOPSIS.docx)

Trial information

Trial identification

Sponsor protocol code	RCCSCAN

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03185182
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lund University
Sponsor organisation address	Scheelevägen 8, Lund, Sweden,
Public contact	Håkan Axelson, Lund University, +46 0462226434, hakan.axelson@med.lu.se
Scientific contact	Håkan Axelson, Lund University, +46 0462226434, hakan.axelson@med.lu.se

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	18 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 July 2018
Global end of trial reached?	Yes
Global end of trial date	04 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to investigate whether DaTSCAN with subsequent SPECT can detect elevated DAT levels in at least a lesion identified with CT in patients with clear cell renal cell carcinoma, as assesed by pathologist?

DaTSCAN signal will be seen as positive, displaying intensity ≥3ggr higher than the background and correlating anatomically with at least one lesion found with CT.

DaTSCAN is used routinely to detect the loss of dopaminergic neurons in the striatum of patients with clinically uncertain Parkinsonian Syndromes. The active substance in DaTSCAN, Ioflupane specifically binds to DAT. By analyzing the focal uptake of Ioflupane (123I) with SPECT / CT the progression of the disease may be clarified. In light of our findings that clear cell renal cancer express significantly elevated levels of DAT, we postulate that DaTSCAN can be used for detection of clear cell renal cell carcinoma.

Protection of trial subjects:

Very few adverse effects are reported for DatSCAN use. In this study we used the same dose and route of administration as is praxis for DaTSCAN when used for diagnostic investigation of Parkinsons disease . Al beit uncommon, pain at the injection site has been previously reported when the solution was injected into a small vain. To minimise the potential for pain at the injection site during administration in this study, a slow intravenous injection (not less than 15 to 20 seconds) via an arm vein was therefore applied. The injections were performed by routined staff at Skåne University Hospital, Department of Clinical Physiology / Nuclear Medicine in Malmö, where usual clinical preparedness for allergic reactions after injection was available.

Background therapy:

Patients underwent appropriate thyroid blocking treatment prior to injection of DaTSCAN, to minimise thyroid uptake of radioactive iodine. In this study, this was achieved by oral administration of 2x 65 mg potassium iodide tablettes on the night before the DaTSCAN investigation and another 2x 65 mg potassium iodine tabletts 1 hour prior to injection of DaTSCAN.

Evidence for comparator:

NA

Actual start date of recruitment	14 July 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	Sweden: 5
Worldwide total number of subjects	5
EEA total number of subjects	5

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)	4
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited continously in this study. Five patients were recruited, all at the Urological Clinic at Skåne University Hospital, Jan Waldenströms gata 7, 205 02 Malmö, Sweden. The first patient was recruited 2017-07-14 and the last patient was recruited at 2018-05-23.

Pre-assignment

Screening details:

Patients were recruited continously in this study. Screening critera: suspected dissiminated renal cancer, age 18-70. Five patients were screened for the study and all five patients were considered suitable for enrollment.

Period 1

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

Arms

Arm title	Study population

Arm description:

This is a exploratory open single arm trial, including a small number of patients with suspected disseminated renal cell carcinoma.

The objective of the trial is to investigate whether DaTSCAN with subsequent SPECT can be used for detection of clear cell renal cell carcinoma (ccRCC) tumors.

Recruited patients with suspected disseminated kidney cancer will, after informed consent to participate in the study, be examined using CT and DaTSCAN followed by SPECT. DaTSCAN is injected intravenously and followed by SPECT examination 5h later. The images from the DaTSCAN investigation will be analyzed and anatomically compared to CT-scan from the same the patient. Any adverse effects during the study will be reported.

Arm type	Experimental
Investigational medicinal product name	DaTSCAN
Investigational medicinal product code	PR1
Other name	Ioflupane (I123)
Pharmaceutical forms	Injection, Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

A one time dose is given via intravenous injection of 185 MBq.
The patient takes potassium iodine tablets prior to the DatSCAN injection to protect the thyroid gland. At the time of the DaTSCAN examination, the patient is injected intravenously at slow rate with 185MBq DaTSCAN solution.

With the help of activity gauge, the responsible nurse draws the right amount of DaTSCAN, 185MBq, into the syringe to be given to the subject. The exact time is recorded and specified in the label machine. The label is printed and put on the syringe with the following information: patient name, drug, batch, dose and draw time. Thereafter, the drug is administered directly to the patient. Afterwards, the remaining activity in the syringe is measured and the exact dose is recorded in the patient's journal.

The patient then waits for 5h before diagnostic examination with SPECT.

Number of subjects in period 1	Study population
Started	5
Early Stopping rule	5
Completed	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
All included subjects in the study, which comply with the inclusion and exclusion criteria	

Reporting group values	Overall trial	Total	
Number of subjects	5	5	
Age categorical			
All subjects were between the ages of 23 and 68 years when included.			
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)	4	4	
From 65-84 years	1	1	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	2	2	

Subject analysis sets	
Subject analysis set title	subjects with verified ccRCC
Subject analysis set type	Full analysis
Subject analysis set description:	
Included subjects with pathologically verified clear cell renal cell carcinoma ccRCC	
Subject analysis set title	Subjects with non-ccRCC
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects included in the study that were not of the clear cell subtype, according to pathological assessment	

Reporting group values	subjects with verified ccRCC	Subjects with non-ccRCC	
Number of subjects	4	1	
Age categorical			
All subjects were between the ages of 23 and 68 years when included.			
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)	3	1	
From 65-84 years	1	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	2	1	
Male	2		

End points

End points reporting groups

Reporting group title	Study population

Reporting group description:

This is a exploratory open single arm trial, including a small number of patients with suspected disseminated renal cell carcinoma.

The objective of the trial is to investigate whether DaTSCAN with subsequent SPECT can be used for detection of clear cell renal cell carcinoma (ccRCC) tumors.

Recruited patients with suspected disseminated kidney cancer will, after informed consent to participate in the study, be examined using CT and DaTSCAN followed by SPECT. DaTSCAN is injected intravenously and followed by SPECT examination 5h later. The images from the DaTSCAN investigation will be analyzed and anatomically compared to CT-scan from the same the patient. Any adverse effects during the study will be reported.

Subject analysis set title	subjects with verified ccRCC
Subject analysis set type	Full analysis

Subject analysis set description:

Included subjects with pathologically verified clear cell renal cell carcinoma ccRCC

Subject analysis set title	Subjects with non-ccRCC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects included in the study that were not of the clear cell subtype, according to pathological assessment

Primary: Proportion of subjects with pathologically verified ccRCC wich displayed positive DaTSCAN signal in at least one of the lesions identified with CT

End point title	Proportion of subjects with pathologically verified ccRCC wich displayed positive DaTSCAN signal in at least one of the lesions identified with CT[1]

End point description:

Proportion of subjects with pathologically verified clear cell renal cell carcinoma (ccRCC) wich displayed positive DaTSCAN signal in at least one of the lesions identified with CT

End point type	Primary

End point timeframe:

From start to end of trial. 2017-07-14 to 2018-07-04

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 results of the trial were planned to be presented with descriptive statistics. However, the "early stopping rule" was applied and the study was stopped after analysis of five patients, where four patients had ccRCC and all five displayed negative DaTSCAN-signal. Thus, no statistical calculations could be performed on this material.

End point values	Study population	subjects with verified ccRCC	Subjects with non-ccRCC	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	5	4	1	
Units: Number of enrolled subjects				
number (not applicable)				
DaTSCAN signal >3 times background	0	0	0	
DatSCAN signal <3 times background	5	4	1	

Attachments (see zip file)	Primary endpoint DaTSCAN analysis/Datscan analys.jpg Demography/Dempgraphy.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: proportion of Datscan positivity in non-clear cell RCC

End point title	proportion of Datscan positivity in non-clear cell RCC

End point description:

To investigate whether DaTSCAN displays no positive signal in CT lesions in research subjects with tumors classified as non-clear cell renal cell carcinoma by pathologist. Negative signal was considered <3 times background signal in lesion identified by CT.

End point type	Secondary

End point timeframe:

All patients was consequtively evaluated after completed examination. Timeframe is thus from first included patient 2017-07-14 to the last included patient 2018-07-04

End point values	Study population	Subjects with non-ccRCC		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	1[2]	1		
Units: percentage				
DaTSCAN negativity in non-ccRCC lesions	1	1		
DaTSCAN positivity in non-ccRCC lesions	0	0		

Notes:

[2] - One out of five enrolled patients had non-ccRCC subtype according to pathological assessment

Statistical analyses

No statistical analyses for this end point

Secondary: Infiltration of cancer cells in surgically removed DaTSCAN positive lymph nodes

End point title	Infiltration of cancer cells in surgically removed DaTSCAN positive lymph nodes

End point description:

Does surgically removed DaTSCAN positive lymph nodes exhibit infiltration of clear cell renal cell carcinoma cells, regardless of the CT status? Measured as proportion of patients with DaTSCAN positive lymph nodes that contained tumor cells.
DaTSCAN signal was considered positive when >3 times higher signal intensity to background.

N.B. No lymph nodes displayed positive DaTSCAN-signal in any of the included patients, neither were any lymphnodes removed and analyzed for infiltrationg tumor cells in any of the patients.

End point type	Secondary

End point timeframe:

Full trial from surgery of first inrolled subject to surgery of last enrolled subject.

End point values	Study population	subjects with verified ccRCC	Subjects with non-ccRCC	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	5	4	1	
Units: proportion of patients				
DaTSCAN positive lymph nodes	0	0	0	

Attachments (see zip file)	Characterization of lesions identified byCT/lesions.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Does DAT mRNA levels reflect DaTSCAN signal in surgically removed tumor material?

End point title	Does DAT mRNA levels reflect DaTSCAN signal in surgically removed tumor material?

End point description:

DAT-mRNA expression in primary tumor correlate with DaTSCAN signal where the surgically removed tumor material with high DaTSCAN intensity also exhibit high mRNA levels of DAT?

Surgically removed material from patients whom had given consent according to ethical approvals: LU680-08 and LU289-07, would be analyzed for mRNA levels of DAT expressed as mRNA expression relative to b-actin.

End point type	Secondary

End point timeframe:

From first operated patient 2017-08-03 to end of study 2018-09-12

End point values	Study population			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: relative mRNA expression				
geometric mean (standard deviation)	()			

Notes:

[3] - No surgically removed material was accessible for analysis and no positive DATSCAN signal was seen

Attachments (see zip file)	compiled endpoint results/Datscan analys.jpg

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

AE were reported consecutively for each patient while included in the trial at the following timepoints: datscan injection, spect analysis, followup phone call.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Study population

Reporting group description:

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Serious adverse events	Study population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (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	Study population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The were no events reported during this study. Incidents may be observed by a doctor / nurse or reported by the subjects themselves. The subjects were asked an open question "Have you had any health problems since taking potassium iodide?" at each relevant study visit (below).

- When injecting DaTSCAN (Ioflupan I123)
- Immediately after the SPECT investigation
- 2 days after the DaTSCAN examination (through telephone interview from research nurse)

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Only 5 out of 10 intended patients were recruited in the study due to "early stopping rule": "End study if 4 patients with verified ccRCC all display negative DaTSCAN signal in all lesions.

Notes: