Clinical trial results:
“Technical and diagnostic performances of PET/CT with 64Cu(II)Cl2 in localization of metastases from prostate carcinoma, in patients undergoing restaging for disease progression during ADT”

Summary

EudraCT number	2014-001158-41
Trial protocol	IT
Global end of trial date	01 April 2017
Results information	
Result version number	v1 (current)
This version publication date	11 April 2018
First version publication date	11 April 2018
Summary attachment (see zip file)	Synopsis CSR 2014-001158-41 (Synopsis CSR 2014-001158-41.pdf)

Trial information

Trial identification	
Sponsor protocol code	P.64CU.001.01
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	n.a: n.a

Notes:

Sponsors	
Sponsor organisation name	Sparkle srl
Sponsor organisation address	Contrada Cavallino snc , Montecosaro, (MC), Italy, 62010
Public contact	project manager, sparkle srl, 0039 0733229739, p.panichelli@sparklepet.it
Scientific contact	project manager, sparkle srl, 0039 0733229739, p.panichelli@sparklepet.it

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	01 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2017
Global end of trial reached?	Yes
Global end of trial date	01 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Initial assessment of the diagnostic sensibility, on a per-patient-basis, of whole body PET/CT, performed after the administration of 64Cu (II) Cl2, in the localization of metastatic lesions from PCa, of bones, lungs and lymph nodes (regional pelvic and/or lumbar and subfrenic nodes), preliminarly diagnosed on the basis of a Gold Standard surrogate, consisting of the integration of clinical and instrumental methods.

Protection of trial subjects:

The 64-copper chloride administered was equivalent of about 1-2 micrograms (1-2 millionths of gram, or, if preferred, 1-2 thousandths of milligram) of copper. Therefore, it was injected a maximum quantity equal to 1 / 50,000 of that of all the copper normally present in the organism, equal to 1/750 of that normally assumed daily with food (which is usually 1.5 milligrams / day). The administration of such an amount of copper chloride can not have, as far as it is widely known on the toxicity of copper, any side effects.
Based on dosimetry, the biological effect resulting from radiation can be precisely calculated. The radiation dose, biologically effective, associated with the 64-copper-chloride administration provided by the Protocol of Experimentation, is equal to about 20 milliSieverts (the milli-Sievert is a unit of measurement of the biological effect of radiation). However, a certain amount of radiation is also absorbed because of the beam of X ray emitted by the tomograph for the realization of CT images, and, in total, the "effective dose" absorbed by you during the examination will amount to about 32 milliSieverts.
This radiation dose is approximately equivalent to two and a half times that attributable to a "whole body" CT, of a diagnostic type, a medical examination performed frequently in the oncological patient.

Background therapy:

all enrolled patients were treated exclusivly with the IMP: 64Cu(II)Cl2/64-Copper Chloride. One single intravenous administration of 64Cu (II) Cl2 with activity equal to MBq = [20x body weight / 4 MBq] +/- 10%, was administrated.No comparators or non-test products were used.

Evidence for comparator:

No comparators were used.

Actual start date of recruitment	28 June 2016
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	Italy: 51

Worldwide total number of subjects	51
EEA total number of subjects	51

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)	16
From 65 to 84 years	33
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

patients are recruited among these groups: Metastatic disease at the onset, diagnosed under staging; radically treated patients due to primary disease, with biochemical relapse, and in which metastases are identified; patients with metastatic disease recognized andmonitored by serial assays of PSA. 51 patients recruited.

Pre-assignment

Screening details:

age>=50;historical primitive PC;ADT treatment;previous metastatic disease on bone/ lung / lymph node; disease progression/restaging during ADT; whole body CT 20days before;whole body CT within 8months before or MRI or 18F-FCH PET/CT 20days before;no other neoplastic diseases excepted non-melanoma skin cancers;Karnofski's index >80%

Period 1

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

Arms

Arm title	experimental

Arm description: -

Arm type	Experimental
Investigational medicinal product name	64CuCl2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Single intravenous administration of 64Cu (II) Cl2 with activity equal to: MBq = [20x body weight / 4 MBq] +/- 10%

Number of subjects in period 1	experimental
Started	51
from enrolment to IMP administration	51
from IMP administration to followup	50
Completed	50
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	overall baseline period

Reporting group description: -

Reporting group values	overall baseline period	Total	
Number of subjects	51	51	
Age categorical			
Patients with metastatic disease at the onset, diagnosed under staging; radically treated patients due to primary disease, which are subject to restaging for BCR, and in which metastases are identified; these patients may be, or not, in ADT at the time of diagnosis of metastatic disease. Patients with metastatic disease recognized and are monitored by serial assays of PSA.			
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)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
adults (50 and over)	51	51	
Age continuous			
Units: years			
median	68		
standard deviation	± 9	-	
Gender categorical			
all the patients were adult male with previous historical diagnosis of primitive prostate carcinoma			
Units: Subjects			
Female	0	0	
Male	51	51	

End points

End points reporting groups

Reporting group title	experimental

Reporting group description: -

Primary: sensitivity of 64Cu(II)Cl2 PET/CT in the localization of metastatic lesions

End point title	sensitivity of 64Cu(II)Cl2 PET/CT in the localization of metastatic lesions[1]

End point description:

Initial assessment of the diagnostic sensibility, on a per patient-basis, of whole body PET/CT after administration of 64Cu(II)Cl2, in the localization of metastatic lesions from PCa, of bones, lungs and lymph nodes (regional pelvic and/or lumbar and subfrenic nodes), preliminary diagnosed on the basis of a Gold Standard surrogate, consisting of the integration of clinical and instrumental methods

End point type	Primary

End point timeframe:

at study completion (Last patient out)

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: This is a single arm trial and so, as EMA service desk answered (SD-164999) to our question, we can post the results without entering the details of the statistical analysis, since the system cannot currently accommodate one arm study.

End point values	experimental			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage	95			

Attachments (see zip file)	primary endpoint results/primary endpoint results.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Initial assessment on lesion diagnostic sensitivity

End point title	Initial assessment on lesion diagnostic sensitivity

End point description:

the assessment of the lesion-based sensitivity was represented by the numerical ratio between the lesions-index correctly identified by the Observers, and those pre-determined by the Investigator, calculated separately for each anatomic category (bone, lung and lymph node, pelvic bone).

End point type	Secondary

End point timeframe:

at each PET/CT scan at 1hour, 4hours, 24hours from the IMP administration

End point values	experimental			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage	97			

Attachments (see zip file)	sensitivity on lesion based results/sensitivity on lesion based

Statistical analyses

No statistical analyses for this end point

Secondary: image quality analysis based on Target/Background

End point title	image quality analysis based on Target/Background

End point description:

The evaluation of the "target/background" ratio (T/B) is based on the measurement of: 1. the value of max SUV detected at the PET/CT in all the "index, bone, pulmonary and pelvic lymph nodes", with high diagnostic confidence, previously identified by the Investigator, in each examined subject. 2. the SUV max value of the average mm.glute of each side, and calculation of the mean and of the SUV max value of the mediastinum higher than the origin of the large vessels and in presence of pulmonary uptake sites: SUV max value of pulmonary tissue against lateral to the lesion, if free from alterations, or of free lung tissue, contralateral or homolateral to the lesion, at the same anatomical level in the height organ. 3. the T/B value as SUV max ratio (lesion)/SUV max (background), for each scan b. For lymph node metastases: SUV ratio max mts/SUV max mediastinum, c. For pulmonary metastases: SUV ratio max mts/SUVmax lung versus lateral 4.T/B index trend can be represented in graph

End point type	Secondary

End point timeframe:

at each PET/CT scan at 1hour, 4hours, 24hours from the IMP administration

End point values	experimental			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: continuos variable				
arithmetic mean (standard deviation)	5.4 (± 5.68)			

Attachments (see zip file)	Target to background results/Target to background results.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: intra observer diagnostic reproducibility

End point title	intra observer diagnostic reproducibility

End point description:

Evaluation of intra-observer diagnostic reproducibility has been obtained verifying the fraction of concordant diagnosis (and the relative limits of confidence), expressed by the same Observer, when the same scan has been proposed again to the Observer, for the second time, at variable distance from the first one. Intra-observer reproducibility was analyzed for both patient-based and base-lesion analysis.

End point type	Secondary

End point timeframe:

at trial completition

End point values	experimental			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage	100			

Attachments (see zip file)	intra-observer diagnostic reproducibility/intra-observer

Statistical analyses

No statistical analyses for this end point

Secondary: inter observer diagnostic reproducibility

End point title	inter observer diagnostic reproducibility

End point description:

inter-observer reproducibility was evaluated by the concordance of each of the diagnostic readings randomly submitted to each Observer, with reference to the equivalent readings made by the other two Observers. The analysis was performed both on a patient-based and on a lesion basis, and expressed by calculating the Cohen k index (and the related confidence limits) using the "bootstrap block" method.

End point type	Secondary

End point timeframe:

covered all the trial period included the PET/CT scans analysis by the observers

End point values	experimental			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage	95			

Attachments (see zip file)	inter-observer diagnostic reproducibility/inter-observer

Statistical analyses

No statistical analyses for this end point

Secondary: optimization of post injection times

End point title	optimization of post injection times

End point description:

The definition of the optimal post-injective time for the execution of the 64Cu (II) Cl2 PET / CT examination in terms of: • Maximization the sensitivity of the patient-based methodology, • Maximization of the sensitivity of the method on a lesion basis, • Target-to-background contrast maximization, • Maximization of intra-observer diagnostic reproducibility (on a patient-based and on a lesion-based), • Maximization of inter-observer diagnostic reproducibility (on a patient-based and on a lesion-based). This implies the definition of the aforementioned parameters independently for each of the post-injection scan times that were performed (1, 4 and 24 hours after IMP administration).

End point type	Secondary

End point timeframe:

1, 4 and 24 hours after IMP administration

End point values	experimental			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage	95			

Attachments (see zip file)	optimal scan time/optimal scan time.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: safety profile

End point title	safety profile

End point description:

evaluation of the frequency and of the clinical importance, as well as of the possible causality relationship with the administration of the IMP of the adverse events,

End point type	Secondary

End point timeframe:

from IMP administration to last patient last visit at day 10 since IMP administration

End point values	experimental			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage	0			

Attachments (see zip file)	safety profile results/safety profile results.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: kinetic of IMP

End point title	kinetic of IMP

End point description:

The Investigator, performed the PET / CT examination for each subject, to calculate the absorbed dose, has manually outlined volumes of interest (VOI) on the organs whose kinetics were to be evaluated (tumor, surrounding tissue, liver, kidney, region vertebral-lumbar and soft tissues) and dosimetry directly using PET / CT coregistered images (both at 1h and at 4h and 24h from the injection). For these organs the masses were calculated and, from the quantification of the activity through the study of the kinetic, the cumulative activity. Using the Olinda / EXM program the S factor for the various organs was calculated. Therefore, using the MIRD (Medical Internal Radiation Dose) formalism, for the organs of greatest dosimetric interest, depending on the activity administered, the absorbed dose will be calculated.

End point type	Secondary

End point timeframe:

at 1h and at 4h and 24h from the injection

End point values	experimental			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: mGy/MBq				
arithmetic mean (standard deviation)	5.4 (± 5.68)			

Attachments (see zip file)	kinetics evaluation/Kinetics evaluation.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

the adverse event reporting started since the administration of the IMP to the last safety follow-up after 10 days.

Adverse event reporting additional description:

AE were collected during the follow up visits at 4hours, 24 hours and 10 days from the IMP administration and at any time by self-reporting signaling by the patient.
no AE has been verified during the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	AE reporting group

Reporting group description:

All the subjects who received the IMP dose (total 50 patients) were included in the AE reporting Group (50 patients).

Serious adverse events	AE reporting group		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (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	AE reporting group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 50 (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: Due to the short period of the trial, 10 days from IMP administration to the last followup visit, no adverse events occured

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