Clinical trial results:
[18F]PSMA-11 PET/CT for prostate cancer – phase 3 clinical trial

Summary

EudraCT number	2018-003168-29
Trial protocol	BE
Global end of trial date	20 September 2020

Results information

Result version number	v1 (current)
This version publication date	05 December 2021
First version publication date	05 December 2021

Trial information

Trial identification

Sponsor protocol code	AGO/2018/003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03911310
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ghent University Hospital
Sponsor organisation address	Corneel Heymanslaan 10, Gent, Belgium, 9000
Public contact	Kathia De Man, Ghent University Hospital, 0032 093325461, kathia.deman@uzgent.be
Scientific contact	Kathia De Man, Ghent University Hospital, 0032 093325461, kathia.deman@uzgent.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	20 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the position of [18F]PSMA-11 PET/CT within the field of available radiotracers for diagnosis of prostate cancer. For this, the diagnostic performances of [18F]PSMA-11 will be compared to those of the current state-of-the-art radiotracer [68Ga]PSMA-11.

Protection of trial subjects:

- 18F]PSMA-11 and [68Ga]PSMA-11 are injected in a very low quantity to perform the PET scans. Consequently, product-related adverse reactions are not to be expected.
- as CT contrast is used in this trial, allergic reactions or a tempory slight reduction in kidney function might occur. In this regard, patients with a history of anaphylactic shock after CT contrast, as well as patients with a serum creatinine concentration > 2.0 mg/dL or estimated glomerular filtration rate < 30 ml/min, are not allowed to participate in this trial. In addition, the renal risk is further reduced by keeping the dose of contrast medium as low as possible during the study (dose calculation based on weight class) and keeping the patient sufficiently hydrated.
- The study drug taken in this study may pose an unprecedented risk to an embryo or foetus. Therefore, it is important that the patient avoid pregnancy with a partner and to use contraception (using a condom and possibly additional contraception by the partner) for up to 90 days after the study. The patients participating in this trial also commit to tell their partner that they are participating in this study and to inform the partner of the possible risk to the unborn child.
- Both the PET and the CT scan use ionising radiation, which leads to a certain radiation exposure for the patient. Although the patient received 2 PET/CT scans, radiation exposure is minimized by performing only one diagnostic CT scan, and by promoting excretion of the radiotracer.
- in case the patient experiences any discomfort, the patient will receive appropriate treatment

Background therapy:

- Iodixanol CT contrast --> to perform the diagnostic CT scan
- Furosemide (in case that patient is not contra-indicated) --> to promote diuresis after radiotracer administration
- physiological saline --> to promote diuresis after radiotracer administration

Evidence for comparator:

Comparator: [68Ga]PSMA-11

evidence:
Bois F, Noirot C, Dietemann S, et al. [68Ga]Ga-PSMA-11 in prostate cancer: a comprehensive review. Am J Nucl Med Mol Imaging. 2020;10(6):349-374. Published 2020 Dec 15.

Actual start date of recruitment	25 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 96

Worldwide total number of subjects	96
EEA total number of subjects	96

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)	19
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

- a maximum of 12 weeks was foreseen between the time of signing the informed consent and acquiring both ([18F]PSMA-11 and [68Ga]PSMA-11) PET/CT scans.

Pre-assignment

Screening details:

Inclusion criteria:
Patients diagnosed with prostate cancer, either in the setting of diagnosis of biochemical recurrence after previous treatment, or at primary diagnosis and staging

Exclusion criteria:
Age < 18 years
- Physically or mentally unfit to perform the sequential procedures
- Refusal of patient to be informed about accidental f

Period 1

Period 1 title	PET CT scans (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind[1]
Roles blinded	Subject, Data analyst

Blinding implementation details:

Concerning the order of the PET scans, half of the patients will be first scanned (= 1st period) with [18F]PSMA-11 and subsequently (=2nd period, maximum three weeks later) with [68Ga]PSMA-11. The scan order in the remaining group of patients will be reversed. Identity of the PET scans will be blind to the patients, the recruiting physicians, and the nuclear medicine physicians interpreting the images. Therefore, after PET/CT reconstruction, raditracer identity details are deleted.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ga-PSMA / F-PSMA

Arm description:

1st PET CT scan: 68Ga-PSMA-11
2nd PET CT scan: 18F-PSMA-11

Arm type	comparator followed by experimental
Investigational medicinal product name	68Ga-PSMA-11
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

2.0 +- 0.2 MBq/kg (single bolus intravenous injection)

Investigational medicinal product name	18F-PSMA-11
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

2.0 + 0.2 MBq/kg body weight (single intravenous bolus injection)

Arm title	F-PSMA / Ga-PSMA

Arm description:

1st PET CT: F-PSMA
2nd PET CT: Ga-PSMA

Arm type	experimental followed by comparator
Investigational medicinal product name	18F-PSMA-11
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

2.0 + 0.2 MBq/kg body weight (single intravenous bolus injection)

Investigational medicinal product name	68Ga-PSMA-11
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

2.0 +- 0.2 MBq/kg (single bolus intravenous injection)

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: clinical trial coordinators and nuclear department secretary are not blinded as they participate in the randomisation process
For safety reasons, the staff members that prepare the individual patient radiotracer dose (syringe) and the staff members that administer the dose are also not blinded. These staff members are not involved in the data analysis process

Number of subjects in period 1	Ga-PSMA / F-PSMA	F-PSMA / Ga-PSMA
Started	48	48
Completed	43	42
Not completed	5	6
Consent withdrawn by subject	5	6

Baseline characteristics

End points

End points reporting groups

Reporting group title	Ga-PSMA / F-PSMA
Reporting group description: 1st PET CT scan: 68Ga-PSMA-11 2nd PET CT scan: 18F-PSMA-11	
Reporting group title	F-PSMA / Ga-PSMA
Reporting group description: 1st PET CT: F-PSMA 2nd PET CT: Ga-PSMA	

Primary: Evaluation of the non-inferiority of [18F]PSMA-11 compared to [68Ga]PSMA-11 with respect to the number of positive PET scans. Hereby, a positive PET scan is defined as a scan showing at least one suspected lesion.

End point title	Evaluation of the non-inferiority of [18F]PSMA-11 compared to [68Ga]PSMA-11 with respect to the number of positive PET scans. Hereby, a positive PET scan is defined as a scan showing at least one suspected lesion.
End point description: The non-inferiority of [18F]PSMA-11 will be investigated based on a Tango's score two-sided 95% confidence interval (CI) for a difference of proportions of positive scans of [18F]PSMA-11 compared to [68Ga]PSMA-11 with matched pairs. Non-inferiority will be concluded if the lower limit of this CI is larger than 0.10 (non-inferiority limit).	
End point type	Primary
End point timeframe: 0 to 100 minutes post injection for both [18F]PSMA-11 and [68Ga]PSMA-11	

End point values	Ga-PSMA / F-PSMA	F-PSMA / Ga-PSMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: confidence interval	42	42		

Statistical analyses

Statistical analysis title	Tango's score two-sided 95% confidence interval (C
Statistical analysis description: Non-inferiority of 18F-PSMA-11 was investigated based on a Tango's score two-sided 95% confidence interval (CI) for a difference of proportions of positive scans of 18F-PSMA-11 compared to 68Ga-PSMA-11 with matched pairs. Non-inferiority was concluded if the lower limit of this CI is larger than -0.10 (non-inferiority limit).	
Comparison groups	F-PSMA / Ga-PSMA v Ga-PSMA / F-PSMA

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	confidence interval
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.045
upper limit	0.045

Notes:

[1] - 82 patients included in the trial. (period 1 Ga-PSMA and period 2 F-PSMA comprise the same group of patients; period 1 F-PSMA and period 2 Ga-PSMA comprise the same group of patients)

Secondary: Evaluation of the superiority of [18F]PSMA-11 compared to [68Ga]PSMA-11 with respect to the number of positive PET scans. Hereby, a positive PET scan is defined as a scan showing at least one suspected lesion

End point title	Evaluation of the superiority of [18F]PSMA-11 compared to [68Ga]PSMA-11 with respect to the number of positive PET scans. Hereby, a positive PET scan is defined as a scan showing at least one suspected lesion

End point description:

Superiority of 18F-PSMA-11 compared to 68Ga-PSMA-11 with respect to the number of positive PET scans was statistically assessed by applying a McNemar's test on the proportions of positive PET scans in each group. Hereby, superiority was defined as a difference of minimum 10% in the proportions of positive PET scans (18F-PSMA-11 > 68Ga-PSMA-11).

End point type	Secondary

End point timeframe:

0 to 100 minutes post injection for both [18F]PSMA-11 and [68Ga]PSMA-11]

End point values	Ga-PSMA / F-PSMA	F-PSMA / Ga-PSMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: p-value				
number (not applicable)	42	40		

Statistical analyses

Statistical analysis title	McNemar's test

Statistical analysis description:

McNemar's test on the proportions of positive PET scans in each group. Hereby, superiority is defined as a difference of minimum 10% in the proportions of positive PET scans (18F-PSMA-11 > 68Ga-PSMA-11).

Comparison groups	Ga-PSMA / F-PSMA v F-PSMA / Ga-PSMA

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	confidence interval
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.045
upper limit	0.045

Secondary: Evaluation of the superiority of [18F]PSMA-11 compared to [68Ga]PSMA-11 with respect to the total number of suspected prostate cancer lesions in corresponding ([68Ga]PSMA-11 vs [18F]PSMA-11) scans

End point title	Evaluation of the superiority of [18F]PSMA-11 compared to [68Ga]PSMA-11 with respect to the total number of suspected prostate cancer lesions in corresponding ([68Ga]PSMA-11 vs [18F]PSMA-11) scans

End point description:

The Wilcoxon signed rank test was applied to investigate differences (number of suspected prostate cancer lesions and scoring of corresponding suspected lesions) between 18F-PSMA-11 and 68Ga-PSMA-11 scans. Hereby, the superiority was defined as a difference of minimum 10% (18F-PSMA-11 > 68Ga-PSMA-11).

End point type	Secondary

End point timeframe:

0 to 100 minutes post injection for both [18F]PSMA-11 and [68Ga]PSMA-11

End point values	Ga-PSMA / F-PSMA	F-PSMA / Ga-PSMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: p-value				
number (not applicable)	42	40		

Statistical analyses

Statistical analysis title	Wilcoxon signed rank

Statistical analysis description:

The Wilcoxon signed rank test was applied to investigate differences with regard to the number of suspected prostate cancer lesions between 18F-PSMA-11 and 68Ga-PSMA-11 scans. Hereby, the superiority was defined as a difference of minimum 10% (18F-PSMA-11 > 68Ga-PSMA-11).

Comparison groups	Ga-PSMA / F-PSMA v F-PSMA / Ga-PSMA

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.431 [2]
Method	Wilcoxon Signed rank

Notes:

[2] - no statistical difference was found

Secondary: Evaluation of the superiority of [18F]PSMA-11 compared to [68Ga]PSMA-11 with respect to the scoring of corresponding ([68Ga]PSMA-11 vs [18F]PSMA-11) suspected lesions

End point title	Evaluation of the superiority of [18F]PSMA-11 compared to [68Ga]PSMA-11 with respect to the scoring of corresponding ([68Ga]PSMA-11 vs [18F]PSMA-11) suspected lesions

End point description:

The Wilcoxon signed rank test was applied to investigate differences (number of suspected prostate cancer lesions and scoring of corresponding suspected lesions) between 18F-PSMA-11 and 68Ga-PSMA-11 scans. Hereby, the superiority was defined as a difference of minimum 10% (18F-PSMA-11 > 68Ga-PSMA-11).

End point type	Secondary

End point timeframe:

0 to 100 minutes post injection for both [18F]PSMA-11 and [68Ga]PSMA-11

End point values	Ga-PSMA / F-PSMA	F-PSMA / Ga-PSMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: p-value				
number (not applicable)	42	40		

Statistical analyses

Statistical analysis title	Wilcoxon signed rank

Statistical analysis description:

The Wilcoxon signed rank test was applied to investigate differences with regard to scoring of corresponding suspected lesions between 18F-PSMA-11 and 68Ga-PSMA-11 scans. Hereby, the superiority was defined as a difference of minimum 10% (18F-PSMA-11 > 68Ga-PSMA-11).

Comparison groups	Ga-PSMA / F-PSMA v F-PSMA / Ga-PSMA
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024 [3]
Method	Wilcoxon Signed rank

Notes:

[3] - as p< 0.05 --> statistically significant result

Secondary: Descriptive evaluation of [18F]PSMA-11 compared to [68Ga]PSMA

End point title	Descriptive evaluation of [18F]PSMA-11 compared to [68Ga]

	PSMA

End point description:

Descriptive evaluation of the results of the scan analysis (number of lesions, impact on TNM score, ...)

End point type	Secondary

End point timeframe:

Time Frame: 0 to 100 minutes post injection for both [18F]PSMA-11 and [68Ga]PSMA-11

End point values	Ga-PSMA / F-PSMA	F-PSMA / Ga-PSMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: number of lesions, miTNM score				
number (not applicable)	42	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of the diagnostic specificity of [18F]PSMA-11 compared to [68Ga]PSMA-11

End point title	Evaluation of the diagnostic specificity of [18F]PSMA-11 compared to [68Ga]PSMA-11

End point description:

This endpoint will be evaluated in a descriptive way, more specifically by a description of the number of positive scans (and/or positive lesions) that can be confirmed via an anatomopathological diagnosis, changes in PSA concentration or via MRI, and by comparison of these numbers between [18F]PSMA-11 and [68Ga]PSMA-11.

End point type	Secondary

End point timeframe:

0 to 180 days post [18F]PSMA-11 and [68Ga]PSMA-11 administration

End point values	Ga-PSMA / F-PSMA	F-PSMA / Ga-PSMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: sensitivity				
number (not applicable)	42	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of the safety of [18F]PSMA-11 administration: CTCAE 4.0

criteria

End point title	Evaluation of the safety of [18F]PSMA-11 administration: CTCAE 4.0 criteria

End point description:

Adverse events will be reported and scored (CTCAE 4.0 criteria) between the first dose administration of trial medication and the last trial related activity. From the time of radiotracer injection till completion of the PET/CT scan (for both [18F]PSMA-11 and [68Ga]PSMA-11), the site staff will visually observe and actively ask the patient whether or not he has observed any adverse effects. Although [18F]PSMA-11 is totally eliminated from the body within 9 hours post injection (= 10 x half-life of 47 ± 5 minutes), AE's occurring up to 24h after the second PET/CT scan will also be handled as such if spontaneously reported by the patient to the investigator.

End point type	Secondary

End point timeframe:

0 to 24 h post [18F]PSMA-11 and [68Ga]PSMA-11 administration

End point values	Ga-PSMA / F-PSMA	F-PSMA / Ga-PSMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: CTCAE 4.0				
number (not applicable)	42	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the interobserver variability with regard to the evaluation of the [18F]PSMA-11 and [68Ga]PSMA-11 PET scans

End point title	Assessment of the interobserver variability with regard to the evaluation of the [18F]PSMA-11 and [68Ga]PSMA-11 PET scans

End point description:

This endpoint will be evaluated by determining a Light's kappa value

End point type	Secondary

End point timeframe:

0 to 100 minutes post injection for both [18F]PSMA-11 and [68Ga]PSMA-11

End point values	Ga-PSMA / F-PSMA	F-PSMA / Ga-PSMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: light's kappa value				
number (not applicable)	42	40		

Statistical analyses

Statistical analysis title	Light's kappa value

Statistical analysis description:

For the interobserver variability with regard to the evaluation of the 18F-PSMA-11 and 68Ga-PSMA-11 PET scans, a Light’s Kappa value was determined.

Comparison groups	Ga-PSMA / F-PSMA v F-PSMA / Ga-PSMA
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.00326
Method	light's kappa
Parameter estimate	lights kappa
Point estimate	0.6375
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4587
upper limit	0.8162

Adverse events

Adverse events information

Timeframe for reporting adverse events:

0 to 24 h post [18F]PSMA-11 and [68Ga]PSMA-11 administration

Adverse event reporting additional description:

AE's will be reported and scored between the first dose administration of trial medication and the last trial related activity. Active questioning for AE's during period that patient is at clinical trial site. Passive follow-up of AE's reported by the patient until 24 hours after 2nd PET/CT scan.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Nausea

Reporting group description:

Nausea after CT contrast

Serious adverse events	Nausea		
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	Nausea		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 85 (1.18%)		
Gastrointestinal disorders			
Nausea	Additional description: Nausea and vomiting tendencies after administration of CT contrast (grade 1 CTCAE)		
subjects affected / exposed	1 / 85 (1.18%)		
occurrences (all)	86		

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.

11 drop-outs : 9 drop-outs before any study related handlings, 2 drop-outs after the first PET/CT scan (transport issue and loss of interest) scans of 2 patients not included in the analysis due to motion artefacts and technical issues

Notes: