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Phase III study of ^{18}F-PSMA-1007 versus ^{18}F-fluorocholine PET/CT for localization of prostate cancer biochemical recurrence: a prospective, randomized, cross-over, multicenter study

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ABSTRACT

Objective: To compare ^{18}F-PSMA-1007 and ^{18}F-fluorocholine PET/CT for localization of prostate cancer (PCa) biochemical recurrence.

Methods: This prospective, open-label, randomized, cross-over, multicenter study, included prostate cancer patients with prior definitive therapy and suspicion of PCa recurrence. All men underwent both ^{18}F-PSMA-1007 and ^{18}F-fluorocholine PET/CT (102 received ^{18}F-PSMA-1007 first and 88 received ^{18}F-fluorocholine PET/CT first). All images were assessed independently by three readers blinded to all clinical information using a 3-point qualitative scale (0-no-recurrence; 1-undetermined; 2-recurrence). Patients were followed for approximately 6 months. An independent panel with a urologist, radiologist, and nuclear physician reviewed all clinical data, including imaging and response to therapy but blinded to PET/CT information, and acting in consensus, determined a patient-based and region-based composite standard of truth for PCa lesions. The "correct detection rate" of PCa lesions on a patient-basis for each radiopharmaceutical was compared for the three readers individually and for the average reader. Secondary objectives included determining if PET/CT findings impact diagnostic thinking (impact of a test result on post-test versus pre-test probability of a correct diagnosis), therapeutic decision making (description and quantification of impact of diagnostic information gained with both radiopharmaceuticals on patient management), and adequacy of management changes.

Results: A total of 190 patients were included. The primary endpoint was met. Overall correct detection rate of ^{18}F-PSMA-1007 was 0.82 vs 0.65 for ^{18}F-fluorocholine ($p<0.0001$) when considering undetermined findings as positive for malignancy, and 0.77 vs 0.57 respectively ($p<0.0001$) when considering undetermined findings as negative for malignancy. A change in diagnostic thinking due to PET/CT was reported in 149 patients among whom ^{18}F-PSMA-1007 contributed more than ^{18}F-fluorocholine in 93. In 122 patients, PET/CT led to an adequate

diagnosis which benefited the patient, among whom ^{18}F-PSMA-1007 contributed more than ^{18}F-fluorocholine in 88 patients.

Conclusions: ^{18}F-PSMA-1007 PET/CT is superior to ^{18}F-fluorocholine PET/CT in localization of PCa recurrence. Decision making was more adequate when based on ^{18}F-PSMA-1007 PET/CT results.

Keywords: positron emission tomography/computed tomography, prostatic neoplasms, prostate-specific antigen, decision making

INTRODUCTION

Prostate cancer (PCa) is the most prevalent cancer in men with approximately 473,000 new diagnoses and over 108,000 deaths in Europe in 2020(*1*). Although long-term outcomes are good for most men, recurrence after definitive therapy is common. One study found that 37% of patients with radical prostatectomy and 48% of patients with radiation therapy had biochemical recurrence within 15 years of the initial definitive treatment; for both, the majority of relapses occurred within the first 5 years(*2*). The diagnosis of PCa recurrence after prior definitive therapy is based on an increase in serum prostate-specific antigen (PSA); the threshold level varies by treatment, being higher for patients treated with radiation than those treated by radical prostatectomy(*3*). PET/CT imaging is the recommended modality for localization of PCa recurrence(*3*). ^{18}F-fluorocholine has been recommended for PET/CT imaging of PCa recurrence since a marketing authorization was granted in France in 2010. The development of radiopharmaceuticals that directly target the extracellular domain of the prostate-specific membrane antigen (PSMA) resulted in an improvement in the detection of PCa lesions and is now recommended for PET/CT imaging of PCa recurrence.

A recent meta-analysis evaluated the diagnostic efficacy of all PSMA-directed PET agents and reported an overall detection rate of 74.1% with no notable differences among the various tracers(*4*). The authors concluded that PSMA-directed PET agents were preferable to choline PET, particularly in patients with a serum PSA of less than 1 ng/mL(*4*). However, to date, only single-center studies with limited number of patients have compared ^{18}F-fluorocholine to a radiolabeled PSMA ligand for PET/CT imaging for PCa recurrence localization and large randomized controlled trials were lacking(*5*).

^{18}F-PSMA-1007 was developed by Cardinale and Giesel *et al.* in Heidelberg in 2016 as a PSMA targeting ligand with low urinary excretion(*6,7*). The compound showed a high detection

rate at low PSA values and high sensitivity and specificity in both biochemical recurrence and primary staging(*8*,*9*). In some patients, nonspecific bone uptake may be a confounding factor(*10*).

The ABX-CT-301 study (NCT04102553) aimed to compare ^{18}F-PSMA-1007 and ^{18}F-fluorocholine PET/CT for the detection of PCa lesions in patients with biochemical recurrence. Secondary objectives were to compare the detection rate of the clinical investigator for both radiopharmaceuticals on a patient-based analysis; to assess diagnostic performance of both radiotracers for PCa lesions on a region-based analysis; to assess the impact on diagnostic thinking, therapeutic decision making, and adequacy of therapy changes for both radiotracers; and to assess the safety profile of ^{18}F-PSMA-1007.

MATERIALS AND METHODS

Population

This study was a prospective, open-label, randomized, two-armed cross-over study conducted in 6 study centers in France. Men aged at least 18 years old, diagnosed with PCa and with prior definitive therapy were considered for enrollment. Eligible patients presented with suspicion of PCa recurrence, defined by 3 consecutive PSA increases and/or a PSA rise of ≥2.0 ng/mL above nadir after radiotherapy (external-beam radiation and/or brachytherapy) or cryotherapy and/or a PSA rise of ≥0.2 ng/mL after prostatectomy. The main exclusion criteria were participation in another therapeutic clinical trial within 5 days of enrollment into the present study and a life expectancy less than 6 months.

The study protocol was approved by a national ethical committee certified by the French Ministry of Health (Institutional Review Board:IORG0009855). All patients gave written informed consent before randomization.

Intervention

All men underwent both ^{18}F-PSMA-1007 and ^{18}F-fluorocholine PET/CT using a standardized imaging protocol (Supplement 1). Patients were randomized using a computer-generated block-randomized sequence, stratified by center, to receive either ^{18}F-PSMA-1007 PET/CT or ^{18}F-fluorocholine PET/CT first. Patients underwent both PET/CT examinations within a minimum of 24 hours and a maximum of 240 hours; depending on the individual site preferences, either low-dose or diagnostic CT could be used, but the use of contrast agents was not permitted. At each PET/CT visit, vital signs were recorded before and after injection of the study drug and again at the end of the PET/CT examination. Laboratory samples, including serum PSA, were obtained prior to the administration of each study drug. Patients were followed for adverse events

for 24 hours after the second PET/CT examination (Supplement 2). Patients were then followed for 6 months, during which all treatments, additional diagnostic methods including biopsy confirmation of detected foci if feasible, and PSA values were collected.

Image Reading and Standard of Truth

PET images were read on-site the day of acquisition by investigators who were not blinded to clinical data and were transferred to a core imaging laboratory where they were evaluated by three independent blinded readers (Supplement 3). ^{18}F-PSMA-1007 and ^{18}F-fluorocholine images were read on separate days, at least one week apart. The results of an "average reader" were determined statistically from the three reader independent results and not by consensus read.

The composite standard of truth (recurrence, no recurrence or undetermined) at the time of imaging was determined by an independent expert panel, who considered all available clinical patient data from pre-inclusion to the end of the follow-up period, excluding all information from the PET/CT (Supplement 4). The expert panel consisted of a urologist, a radiologist, and a nuclear physician; they reached their conclusions by consensus.

Outcomes

The primary objective was to compare ^{18}F-PSMA-1007 to ^{18}F-fluorocholine regarding the "correct detection rate" of recurrent PCa lesions on a patient-basis, as determined by 3 independent readers and confirmed by an independent expert panel based on a composite standard of truth (Supplement 4).

Secondary objectives were to compare the "correct detection rate" of the clinical investigators; to assess "correct detection rate" of both radiotracers for PCa lesions on a region-based analysis; to report the impact on diagnostic thinking (impact of PET/CT result on post-test versus pre-test

probability of a correct diagnosis), therapeutic decision making (impact on the comprehensive process in which physicians make decision to response PCa), and adequacy of management changes by the investigator at three time points (before PET, immediately after both PET studies, and at the end of follow-up) and by the expert panel (only at the end of follow-up), using 3 dedicated forms (Supplement 5); to compare the blinded intra and inter-reader agreement; and to assess the safety profile of ^{18}F-PSMA-1007.

Statistical Analysis

Analysis was performed using SAS 9.4 or higher (SAS Institute, Cary, NY, USA), detailed in Supplement 6. A p-value ≤0.05 was considered statistically significant. Descriptive statistics were calculated for quantitative variables; frequency counts by category were given for qualitative variables. 95% confidence intervals (CI) or interquartile ranges were given where appropriate. The intention-to-treat (ITT) population was the primary population for the analyses of efficacy endpoints and all baseline characteristics. The correct detection rate was determined for each reader individually. Generalized estimation equations were used to account for the correlations between readers' assessments and to summarize the overall reader results ("average reader"). Patients in whom the expert panel could assess the true disease state on a patient level, but for whom the affected region could not be identified by the expert panel, were included as correct assessment on a patient-basis. If on a region-basis there was no region with a correct detection of recurrence compared to the standard of truth, the patient was regarded as false negative. If at least in one region the reader and expert panel detected a recurrence, independent of the other regions, then this was classified true positive. Subgroup analyses were performed based on the PSA-level at baseline: <0.5 ng/mL, 0.5 ng/mL to <1.0 ng/mL, ≥1.0 ng/mL to <2.0 ng/mL and ≥2.0 ng/mL. For the primary analysis on a patient level, two distinct analyses were performed by considering undetermined

results as positive or negative for PCa recurrence. For sub-group and secondary analyses, undetermined results were considered negative for PCa recurrence. Intra- and inter-reader agreement was evaluated using pairwise and multiple Cohen's kappa. Each blinded reader read 10% of the images twice (on separate occasions). Inter-reader agreement was assessed pairwise and across all three readers. The degree of agreement was defined according to Landis & Koch(*11*).The sample size was selected to provide a power of at least 80% to detect a 10% difference in correct detection rate between the two products.

RESULTS

Population

From March 5, 2019 to October 8, 2020, 200 patients consented to this study; 195 were randomized and 189 completed all follow-up (Figure 1). One patient ended study participation prematurely as he died 3.5 months after PET imaging but was included in the ITT population. Most of the patients had previously undergone prostatectomy, and the median serum PSA was 1.7 ng/mL. Study population characteristics are summarized in Table 1.

The median follow-up period for the ITT population was 8.3 months (range: 2.9-16.1), as its duration was extended because of the COVID-19 pandemic.

Primary Objective

Per-patient and per-region PET findings are detailed in Supplement 7. At the patient level, the blinded readers found evidence for PCa recurrence in 145 - 162 patients (76.3-85.3%) for ^{18}F-PSMA-1007 and 99 - 128 patients (52.1-67.4%) for ^{18}F-fluorocholine. Findings remained undetermined in 6 - 12 patients (3.2-6.3%) for ^{18}F-PSMA-1007 and 10 - 21 patients (5.3-11.1%) for ^{18}F-fluorocholine (Supplement 7). The expert panel confirmed PCa recurrence according to the standard of truth in 179/190 cases (94%).

The overall proportion of patients with correct detection rates of PCa lesions by ^{18}F-PSMA-1007 was 0.82 (95%CI: 0.78-0.86) and 0.77 (95%CI: 0.72-0.82) when undetermined results were considered positive or negative for malignancy, respectively, statistically superior to that of 0.65 (95%CI: 0.60-0.71) and 0.57 (95%CI: 0.51-0.62) by ^{18}F-fluorocholine when undermined results were considered as positive or negative for PCa, respectively (Table 2) ($p<0.0001$). Thus, the primary endpoint was reached.

For both study drugs, the "correct detection rate" of PCa recurrence was higher for patients with higher PSA values. For all examined PSA-level subgroups, the "correct detection rate" was statistically higher for ^{18}F-PSMA-1007 (Table 3).

Blinded intra and inter-reader agreement for detection of metastases (patient-level) ranged from 0.24 - 0.73 and 0.30 - 0.36 for ^{18}F-PSMA-1007 and from 0.48 - 0.72 and 0.34 - 0.40 for ^{18}F-fluorocholine, respectively (Supplement 8).

Secondary Objectives

Comparison of Patient-based Correct Detection Rates According to Investigator Findings. Using the clinical investigators' overall findings, the correct detection rate was 0.80 (95%CI=0.74-0.86) for ^{18}F-PSMA-1007, compared to 0.50 (95%CI=0.42-0.57) for ^{18}F-fluorocholine ($p<0.0001$).

Comparison of Region-based Correct Detection Rates According to Blinded Readers' Findings. Of the 72 patients for whom one or more regions could be assessed by the expert panel, there was a total of 78 regions with confirmed PCa lesions. The most common sites for PCa lesions being the pelvis (59 patients) and the spine (6 patients) (Supplement 9). Among the patients considered to have a positive PET more suspicious lesions were detected using ^{18}F-PSMA-1007 than ^{18}F-fluorocholine, especially for patients with 3 lesions or more.

Overall composite region-level sensitivity for ^{18}F-PSMA-1007 PET was 0.77 (95%CI= 0.69-0.84), compared to 0.57 (95%CI= 0.48-0.67) for ^{18}F-fluorocholine PET ($p<0.0001$).

Impact on Diagnostic Thinking, Therapeutic Decision Making, and Adequacy of Therapy Changes. The investigator assessments on the change in diagnostic thinking after both PET/CTs and at the end of follow-up are summarized in Tables 4&5 and Supplement 5. Treatment plans

before and after PET/CTs were available in 187 patients. The treatment plan was changed in 100 patients, 89 being major changes (Supplement 10). A change in diagnostic thinking due to PET/CT was reported in 149 patients. Diagnostic thinking was unchanged in 41 patients (including 3 with no reported answer). Of 149 patients with a change in diagnostic thinking, ^{18}F-PSMA-1007 contributed more in 93 (62%), both tracers contributed equally in 49 (33%), and ^{18}F-fluorocholine contributed more in 4 (3%).

In 122 patients, PET/CT led to a more adequate diagnosis which benefited the patient. In 11 patients, PET/CT was not to the benefit of the patient, and in 45 patients PET/CT did not exert a positive or negative influence. Of the 122 patients with a more adequate diagnosis after PET/CT that benefited the patient, ^{18}F-PSMA-1007 contributed more in 88 patients, ^{18}F-fluorocholine contributed more in only 6, and both contributed equally in 27.

Safety Profile of ^{18}F-PSMA-1007. There were no serious adverse events. No patient discontinued study participation because of an adverse event. Four patients had four events (toothache, diarrhea, chest discomfort, arterial hypertension) after the administration of ^{18}F-PSMA-1007 and one patient had one event (shoulder pain) after the administration of ^{18}F-fluorocholine. None were considered to be attributable to the study drug.

DISCUSSION

This study was the first multicenter, cross-over, randomized study to compare ^{18}F-PSMA-1007 and ^{18}F-fluorocholine for localization of biochemical recurrence. The correct detection rate was significantly higher with ^{18}F-PSMA-1007 PET/CT than ^{18}F-fluorocholine PET/CT. Results were similar for the population as a whole and for the 72 patients for whom individual lesions could be verified, either by biopsy or response to local treatment. The difference was especially pronounced in patients with lower serum PSA levels, allowing earlier, targeted, salvage treatment. Our results with ^{18}F-PSMA-1007 are in agreement with those reported in the literature for ^{68}Ga-PSMA-11 (*4,12–18*). In a meta-analysis, Treglia et al.(*19*) also found similar results comparing a PSMA tracer (^{68}Ga-PSMA-11 or ^{64}Cu-PSMA-617) and radiocholine. Because the results with the various PSMA ligands are generally similar, it is generally accepted that the PSMA ligands are interchangeable for this indication. PSMA ligands radiolabeled with fluorine-18 have wider accessibility than with gallium-68.

The investigator assessments after PET/CT and at the end of follow-up demonstrate the superiority of ^{18}F-PSMA-1007 over ^{18}F-fluorocholine in identifying sites of recurrence. The impact of ^{18}F-PSMA-1007 was benefit of the patient" in the majority of cases. These results are likely linked to the higher correct detection rate of ^{18}F-PSMA-1007. In previous studies with ^{18}F-Fluorocholine (*13,20*) and 68-Ga-PSMA-11 (5, *21*), an impact rate of 39% - 58% on patient management was reported. Our study is consistent with published data on ^{18}F-fluorocholine and demonstrates higher impact of ^{18}F-PSMA-1007 on patient management.

The strengths of our study are its prospective, multicenter, randomized cross-over design. Limitations include the lack of histopathology for most lesions. Because obtaining histopathology is often ethically questionable or medically impractical, our standard of truth was a composite based on biopsy, response to local therapy, imaging, and change in serum PSA during 6 months of

follow-up established by an independent panel of experts. The use of the independent panel removed potential bias in determining "truth" while modeling what is done in "real-life" practice.

In this work, we found that ^{18}F-PSMA-1007 has an impact on diagnostic thinking and therapeutic decision making, and that therapy changes are more adequate when based on ^{18}F-PSMA-1007 PET/CT findings compared to ^{18}F-fluorocholine PET/CT (Figure 2). However, we did not make statistical comparison of these data because the study was not powered for this purpose.

CONCLUSION

This prospective, multicenter, open-label, cross-over randomized study demonstrates that ^{18}F-PSMA-1007 PET/CT localizes PCa recurrence in significantly more patients than ^{18}F-fluorocholine PET/CT, especially in patients with low PSA serum levels. ^{18}F-PSMA-1007 PET/CT also demonstrates a higher impact on diagnostic thinking, therapeutic decision making, and therapy changes compared to ^{18}F-fluorocholine PET/CT.

CONFLICT OF INTEREST AND FINANCIAL DISCLOSURE

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KEY POINTS

QUESTION: Is ^{18}F-PSMA-1007 superior to ^{18}F-fluorocholine PET/CT for the localization of biochemical recurrence in prostate cancer patients?

PERTINENT FINDINGS: In this prospective, open-label, randomized, cross-over, multicenter study that included 190 patients with prostate cancer biochemical recurrence, we demonstrated that ^{18}F-PSMA-1007 PET/CT localizes significantly more prostate cancer lesions than ^{18}F-fluorocholine PET/CT, especially when PSA serum levels are low.

IMPLICATION FOR PATIENT CARE: More accurate staging of recurrent prostate cancer might lead to more adequate decision-making and patient management.

A theranostic use of PSMA radioligands be considered in recurrent prostate cancer.

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Figure 1:Trial chart

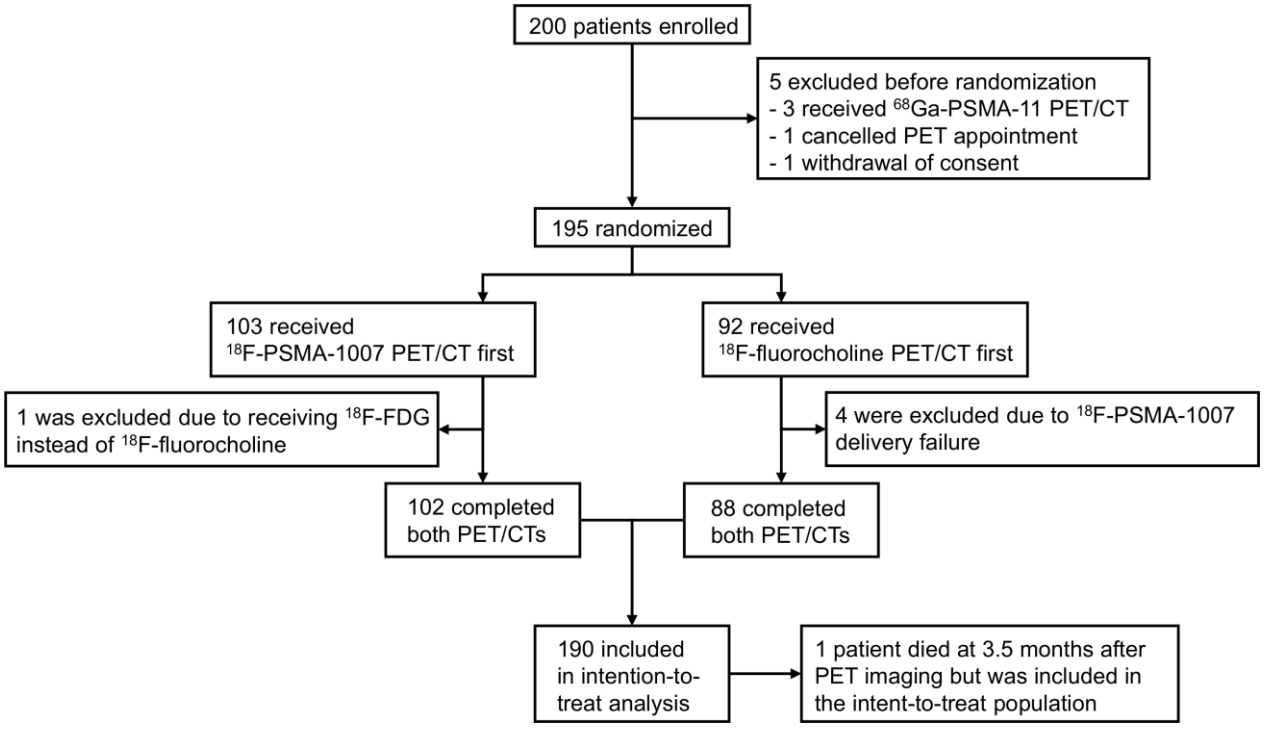


Figure 2: 62-year-old patient with history of prostate cancer (ISUP 3, PSAi 5.7ng/ml), initially treated with prostatectomy (pT3N0R0), prostate bed radiation therapy, and 6 months androgen deprivation therapy (ADT) presenting with PSA recurrence (0.72 ng/ml). ^{18}F-PSMA-1007 PET/CT detected pelvic lymph nodes (red arrows) and bone metastases (green arrows) that were not detected by ^{18}F-fluorocholine PET/CT. Therapeutic management changed from targeted radiation therapy before PET to ADT after PET leading to a drop in PSA to 0.1 ng/ml at 6 months.

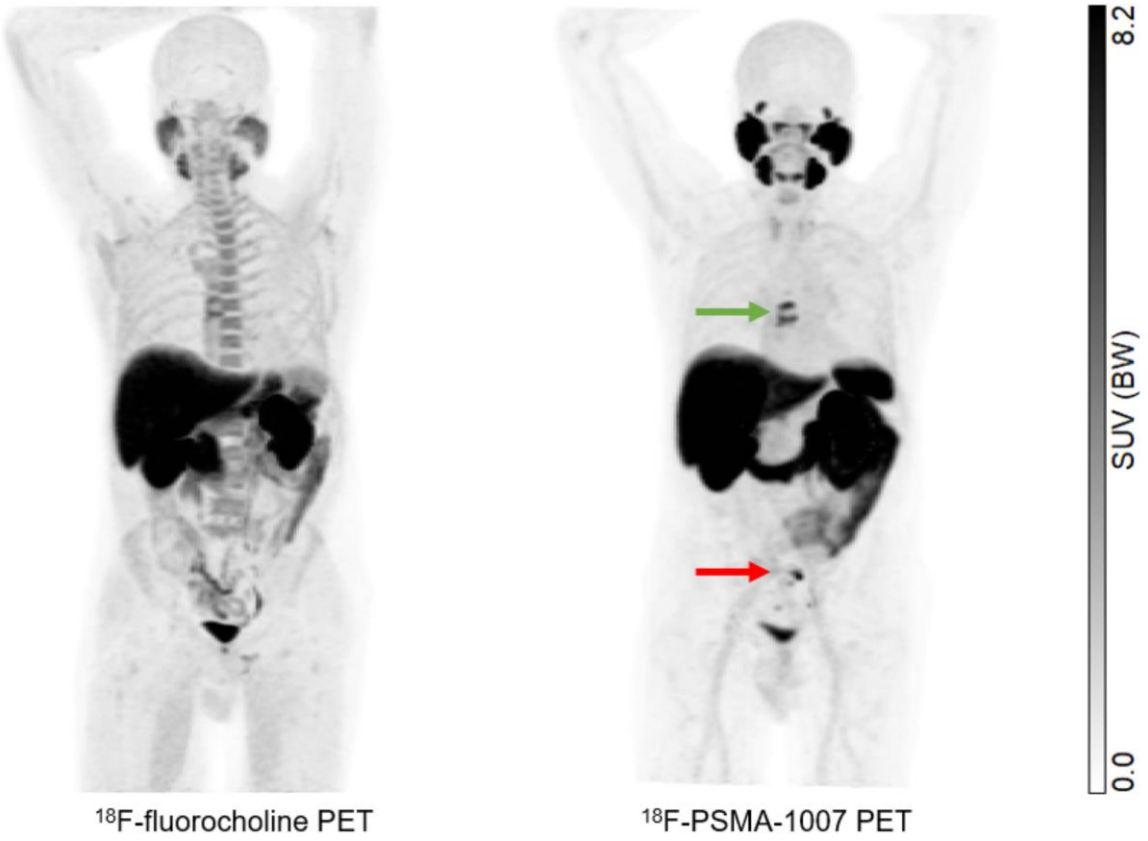


Table 1: Patient characteristics (intention-to-treat population)

	All patients (n=190)	^{18}F-PSMA-1007 first (n=102)	^{18}F-fluorocholine first (n=88)
Median age in years (range)	69 (49-84)	68 (49-81)	70 (51-84)
Initial ISUP group grade at prostate cancer diagnosis (%)			
1	29 (15.3%)	12 (11.8%)	17 (19.3%)
2	64 (33.7%)	32 (31.4%)	32 (36.4%)
3	55 (29.0%)	33 (32.4%)	22 (25%)
4	14 (7.4%)	8 (7.8%)	6 (6.8%)
5	21 (11.1%)	13 (12.8%)	8 (9.1%)
Unknown	7 (3.7%)	4 (3.9%)	3 (3.4%)
Prior prostatectomy	154 (81%)	80 (78%)	74 (84%)
With pelvic lymph node dissection	93	51	42
Serum PSA in ng/ml prior to the first PET (median with IQR)			
Overall	1.7 (0.6-4.2)	2.0 (0.9-5.5)	1.3 (0.6-3.1)
In patients with prior prostatectomy	1.3 (0.5-3.2)	1.7 (0.6-3.5)	0.9 (0.4-2.5)
In patients without prior prostatectomy	4.5 (2.3-9.9)	6.3 (2.8-10.9)	3.0 (2.1-9.0)
Serum PSA doubling time in months	6.3 (3-12.1)	6.4 (3.0-11.6)	5.9 (2.7-12.6)
Prior to the first PET examination			
(median with IQR)			
PSA doubling time ≤ 6 months	49%	47%	51%
PSA doubling time ≤ 12 months	74%	76%	70%

ISUP: International Society of Urological Pathology; PSA: Prostate-Specific Antigen; PET: Positron emission tomography; IQR: Interquartile Range

Table 2: Patient-level overall proportion of patients with correct detection rate of recurrent prostate cancer according to the standard of truth and positive predictive value; ITT population (n=190); [95% confidence interval]

	^{18}F-PSMA-1007	^{18}F-fluorocholine	
Undetermined lesions considered as **positive** for prostate cancer recurrence in the analysis			
Proportion	0.82 [0.78-0.86]	0.65 [0.60-0.71]	
Difference in proportion	0.16 [0.11-0.22]		p<0.0001
Odds ratio	2.40 [1.79-3.21]		p<0.0001
Positive predictive value	0.96 [0.93-0.99]	0.96 [0.93-0.99]	
Difference in positive predictive value	0.002 [0.031-0.035]		p=0.90
Odds ratio	0.95 [0.42-2.15]		p=0.90
Undetermined lesions considered as **negative** for prostate cancer recurrence in the analysis			
Proportion	0.77 [0.72-0.82]	0.57 [0.51-0.62]	
Difference in proportion	0.21 [0.15-0.26]		p<0.0001
Odds ratio	2.61 [1.97-3.46]		p<0.0001
Positive predictive value	0.95 [0.92-0.99]	0.97 [0.95-1.00]	
Difference in positive predictive value	0.02 [0.01-0.05]		p=0.25
Odds ratio	0.58 [0.22-1.55]		p=0.27

Table 3: Patient-level proportion of patients with correct detection rate of PCa lesions by PSA level at baseline; ITT population (n=190); [95% confidence interval]

	^{18}F-PSMA-1007	^{18}F-fluorocholine	
PSA < 0.5 ng/ml			
Number of patients with recurrence detected by SOT = 43			
Proportion	0.57 [0.45-0.68]	0.39 [0.28-0.50]	
Odds radio	2.10 [1.13-3.89]		p=0.002
0.5 ng/ml ≤ PSA < 1.0 ng/ml			
Number of patients with recurrence detected by SOT = 25			
Proportion	0.83 [0.72-0.93]	0.43 [0.28-0.58]	
Odds radio	6.88 [3.35-14.13]		p<0.0001
1.0 ng/ml ≤ PSA < 2.0 ng/ml			
Number of patients with recurrence detected by SOT = 33			
Proportion	0.81 [0.72-0.89]	0.50 [0.37-0.62]	
Odds radio	4.31 [2.26-8.24]		p<0.0001
PSA ≥ 2.0 ng/ml			
Number of patients with recurrence detected by SOT = 78			
Proportion	0.85 [0.79-0.91]	0.74 [0.66-0.82]	
Odds radio	2.01 [1.27-3.19]		P=0.003

Table 4: Change in diagnostic thinking after both PET/CTs; ITT population (n = 190)

Change in diagnostic thinking after both PET/CTs					
		^{18}F-fluorocholine contributed more	^{18}F-PSMA-1007 contributed more	Both PET contributed equally	missing
YES	PET identified a site of recurrence not known before	3 (1.6%)	80 (42.1%)	29 (15.3%)	3 (1.6%)
	PET confirmed a site of recurrence that was suspected before	1 (0.5%)	6 (3.2%)	3 (1.6%)	
	Other		4 (2.1%)	15 (7.9%)	
	Missing		3 (1.6%)	2 (1.1%)	
NO		38 (20%)			
Missing					3 (1.6%)

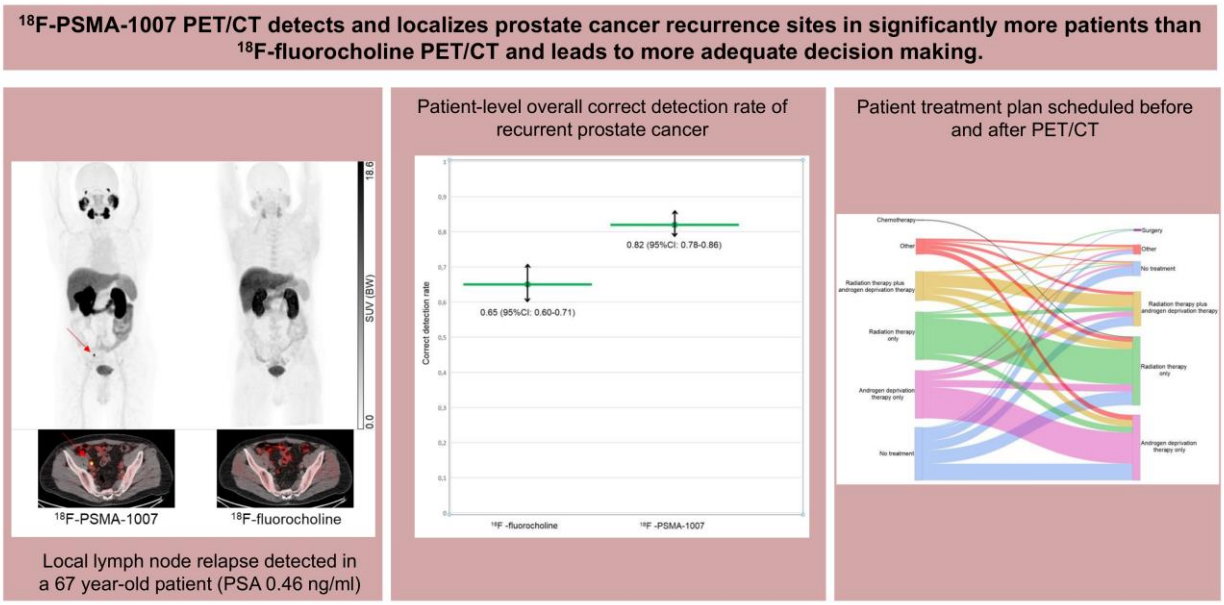
PET: Positron Emission Tomography

Table 5: Change in diagnostic thinking after both PETs and influence at the end of follow-up; ITT population (n = 190)

		The influence was			
		To the benefit of the patient	Not to the benefit of the patient	Neither to the benefit nor the disadvantage of the patient	Missing
^{18}F-fluorocholine contributed more	More accurate diagnosis	6 (3.3%)	0	0	0
	Diagnostic thinking was misled by PET	0	0	0	0
	PET had no influence	0	1 (0.6%)	1 (0.6%)	0
	Missing	0	0	0	0
^{18}F-PSMA-1007 contributed more	More accurate diagnosis	88 (48.4%)	2 (1.1%)	10 (5.5%)	2 (1.1%)
	Diagnostic thinking was misled by PET	1 (0.6%)	1 (0.6%)	2 (1.1%)	0
	PET had no influence	0	0	1 (0.6%)	0
	Missing	0	0	0	0
Both PET contributed equally	More accurate diagnosis	27 (14.8%)	0	13 (7.1%)	0
	Diagnostic thinking was misled by PET	0	5 (2.8%)	1 (0.6%)	0
	PET had no influence	5 (2.8%)	2 (1.1%)	16 (8.8%)	0
	Missing	0	0	1 (0.6%)	0
Missing	More accurate diagnosis	1 (0.6%)	0	0	0
	Diagnostic thinking was misled by PET	0	0	0	0
	PET had no influence	0	0	0	0
	Missing	0	0	0	4 (2.1%)

PET: Positron Emission Tomography

Graphical Abstract



Supplemental Information:

Phase III study of ^{18}F-PSMA-1007 versus ^{18}F-fluorocholine PET/CT for localization of prostate cancer biochemical recurrence: a prospective, randomized, cross-over, multicenter study

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Contents

1 Supplement 1: Imaging protocols 3
2 Supplement 2: Safety profile 5
3 Supplement 3: PET reading 7
4 Supplement 4: Standard of truth 9
5 Supplement 5: Diagnostic thinking 11
6 Supplement 6: Statistical and analytical plans 16
7 Supplement 7: PET findings per patient and per region 20
8 Supplement 8: Readers' agreement 26
9 Supplement 9: Distribution of prostate cancer recurrence location 27
10 Supplement 10: Patient treatment plan scheduled 28

1 Supplement 1: Imaging protocols

Study drugs

^{18}F-PSMA-1007 is composed of the PSMA-specific pharmacophore and fluorine-18, a synthetic positron emitting isotope of fluorine. ^{18}F-PSMA-1007 was administered as a single intravenous injection of 3-4 MBq/kg.

Any authorized ^{18}F-fluorocholine was permitted in this study if indicated for use with positron emission tomography in patients with suspicion of prostate cancer recurrence. ^{18}F-fluorocholine was similarly administered with an activity of 200-400 MBq according to summary of product characteristics.

Image Acquisition and Post-Processing

All PET/CT equipment and the related software modules were commercially available and approved for clinical patient studies. PET/CT was performed using a protocol comprising a topogram (scout scan), a low dose CT scan for attenuation correction (AC-CT) and anatomical correlation, and the PET scan. A fully diagnostic CT scan was acceptable instead of a low dose CT if this was local practice, but iodinated contrast agents were not permitted. AC-CT was performed while the patient continued tidal or shallow breathing. In the case of CT systems with six or fewer rings, a protocol using breath-hold in normal expiration was permitted for the duration of scanning of the thorax and upper abdomen. The low-dose CT protocol was obtained at 100–140 kV depending on patient weight, automatic definition of the mAs product with acceptable maximum of 40 mAs, and pitch 1–1.75.

The PET scan with ^{18}F-PSMA-1007 was acquired in 3D mode with 3–5 min per bed position, with coverage from mid-thigh to the skull vertex. The field of view was large, including the cross section of the whole body and avoiding truncation. One static whole-body image starting at 90 minutes post-injection was obtained.

For ^{18}F-fluorocholine, three separate PET scans were obtained:

- Dynamic imaging including the prostate bed and pelvis for 8 min (starting 1 min p.i.); if this was not possible, one static 2 min image at 1 min p.i. was obtained.
- Whole-body PET (from skull vertex through mid-thigh), starting 10–20 min p.i.
- A second whole-body PET was obtained at 1 hour p.i.

The PET data was corrected for geometrical response and detector efficiency (normalization), system dead time, random coincidences, scatter and attenuation. All system corrections necessary to obtain quantitative image data were applied during the reconstruction process. When available, time-of-flight information was used during reconstruction. Reconstruction was done with an ordered-subset expectation maximization (OSEM) algorithm (e.g., 2 iterations and 21 subsets), followed by a post reconstruction smoothing gaussian filter (e.g., 5 mm at full width at half maximum). Both, attenuation corrected (AC-PET) and non-attenuation-corrected PET (NAC-PET) axial images were reconstructed for interpretation. Slice thickness of the reconstructed axial PET images was between 2 and 5 mm. Slice thickness of the reconstructed axial CT images was 2 to 5 mm, according to the slice thickness of the PET images.

2 Supplement 2: Safety profile

Vital signs (heart rate, respiratory rate, and blood pressure) were obtained before and after injection of each radiopharmaceutical, and after completion of PET image acquisition.

Blood chemistry, hematology and urinalysis were collected before each PET examination. The following parameters were obtained:

- Biochemistry (before 1st PET and before 2nd PET):
    - AST, ALT, GGT, alkaline phosphatase
    - Total bilirubin, direct bilirubin
    - Cholesterol, LDL-cholesterol, triglycerides
    - Creatinine, urea, BUN, albumin, globulin, potassium, sodium, calcium, chloride, bicarbonate, glucose, phosphate
    - CK, LDH
    - CRP
- Hematology / coagulation:
    - Hb, Hct, RBC, WBC, platelets, MCHC, MCV
    - prothrombin time, INR, APTT
- Urinalysis
    - pH, glucose, proteins, ketones, bilirubin, urobilinogen, nitrite, RBC, WBC

Adverse events (AE): that occurred after the administration of study drugs until 24 hours after the second PET examination were reported as adverse events. Serious AEs were those that resulted in death, were life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability / incapacity, or was a

congenital anomal/birth defect. Because there was no formal washout period in this cross-over study, any AE that occurred after the administration of ^{18}F-PSMA-1007 was temporally related to that product, even if ^{18}F-fluorocholine had been administered after the administration of ^{18}F-PSMA-1007. That is, the only events that were temporally related to ^{18}F-fluorocholine were in those patients in whom ^{18}F-fluorocholine was administered first and ^{18}F-PSMA-1007 had not yet been administered. This approach was taken as the most conservative assessment of the safety of ^{18}F-PSMA-1007.

Standard summary and/or analysis techniques were used for the evaluation of AEs, vital sign measurements, and clinical laboratory results. All AEs were assessed and documented by the investigator according to the seriousness, intensity, main pattern, concomitant medications, causal relationship to study drug, causal relationship to study conduct and outcome.

3 Supplement 3: PET reading

Central reading performed by three independent readers

The independent readers were blinded to all clinical data. Images for ^{18}F-PSMA-1007 and ^{18}F-fluorocholine were read separately, readings being scheduled at least one week apart to reduce recall bias. The order of image presentation was randomized but not blinded, because of differences in study drug biodistribution the readers implicitly knew the radiotracer. The blinded readers each independently evaluated the PET images for the presence of prostate cancer lesions in 12 predefined body regions (prostate bed including seminal vesicles, pelvic lymph nodes, retroperitoneal lymph nodes, sub and supraclavicular lymph nodes, other supradiaphragmatic lymph nodes, pelvic skeleton, spine, ribs, limbs and shoulders, skull and facial skeleton, liver, lung), using a 3-point qualitative scale: 0-no-recurrence; 1-undetermined; 2-recurrence. CT images were used for anatomic correlation of suspicious foci and to ease diagnosis. The blinded readers also assessed overall image quality and the mean, maximum, and standard deviation of the standardized uptake value (SUV) of the largest lesion present in any body region. The results of an "average reader" was determined statistically from the three readers' independent results and not by consensus read.

Local reading performed by the investigators

The investigators, who were not blinded to clinical data, evaluated the PET images for the presence of prostate cancer lesions the day of image acquisition. They assessed uptakes across the same 12 predefined anatomic regions described above, but instead used a 5-point qualitative scale: 0-surely benign/no lesion present; 1-probably benign; 2-equivocal; 3-probably malignant; 4-surely

malignant. The investigators also provided a final diagnosis based on all available images with ^{18}F-PSMA-1007 and ^{18}F-fluorocholine, including all body regions and at the patient level.

4 Supplement 4: Standard of truth

The composite standard of truth (recurrence, no recurrence or undetermined) at the time point of imaging with the study drugs was determined by an independent expert panel, who considered all available clinical patient data from pre-inclusion to the end of the follow-up period. The expert panel consisted of a urologist, a radiologist, and a nuclear medicine physician; they reached their conclusions by consensus. Clinical information that was provided to the expert panel included: medical history at study entry and PSA values, relevant concomitant medications, results from follow-up including results from additional imaging (excluding any follow-up PET imaging with ^{18}F-fluorocholine or ^{18}F-PSMA-1007) and other diagnostic tests, biopsy, tumor treatment, especially targeted procedures such as surgery or radiotherapy, and follow-up PSA values. The expert panel assessed each of 10 predefined anatomic regions for the presence of PCa recurrence: pelvis (prostate bed, pelvic lymph nodes and pelvic skeleton), paraaortic lymph nodes, supraclavicular lymph nodes, other supradiaphragmatic lymph nodes, spine, ribs, limb and shoulders, skull and facial skeleton, liver, lung. A region was positive for recurrence if at least one of the following conditions were true: 1- histology positive; 2- imaging modality other than study drugs positive; 3-local therapy effective. If the panel could not make a definitive conclusion, the region was considered “undetermined”. A region could be called “no recurrence” only if there was diagnostic data, such as imaging results, to prove that the region did not contain recurrence. If the region-based analysis was not possible (for example, because the patient received systemic therapy), the expert panel specified the disease state in a patient-based analysis instead. The patient-based analysis was based on the following criteria:1- PSA continued to rise→recurrence; 2- patient had systemic therapy during follow-up and PSA was stable or decreasing→recurrence; 3- patient

did not have any anti-cancer therapy during follow-up and PSA was stable or decreasing→no recurrence; 4- no PSA follow-up available, no other diagnostic results available→undetermined.

5 Supplement 5: Diagnostic thinking

This study was developed and conducted according to the Food and Drug Administration (Developing Medical Imaging Drug and Biological Products) and European Medicine Agency (Guideline on clinical evaluation of diagnostic agents) guidelines.

The impact on diagnostic thinking refers to the impact of a test result on post-test versus pre-test probability of a correct diagnosis, in relation to a well-defined clinical context (patient characteristics, prior diagnostic procedures). It aims to demonstrate that the diagnostic test provides information on the prognosis that is independent from other data of the conventional work-up or may replace independent prognostic factors which are more demanding to obtain.

The impact on patient management refers to a description and quantification of impact of diagnostic information gained with the diagnostic agent on patient management. A major impact was defined as a change in management intent or modality. A minor impact was defined as a change in delivery of modality, but not intent. The consequences and adequacy of the changes to the scheduled management are assessed by using follow-up data.

The investigators prospectively asked the patient's referring physician to complete a dedicated questionnaire to provide an assessment of diagnostic thinking and therapeutic options on 3 occasions: at baseline (Figure 1), after PET images with both study drugs had been obtained (Figure 2), and again at the end of patient follow-up (Figure 3). Each questionnaire stated the current diagnosis (no recurrence, recurrence and if so, local, regional, distant, or unknown) and the current treatment plan (hormone therapy associated with radiotherapy, hormone therapy, surgery, radiotherapy, chemotherapy, no treatment, or other). Questionnaires 2 and 3 questioned if ^{18}F-PSMA-1007 or ^{18}F-fluorocholine contributed to a change in diagnostic thinking, if both study drugs contributed equally, or if none of the study drugs contributed. At the end of clinical follow-up, both

the investigator and the expert panel were again asked to consider the impact of PET imaging on diagnostic thinking and patient management.

The expert panel was trained with a video presentation that explained the study objectives, definition of standard of truth, available data and required analysis. Panelists had to complete a multiple-choice test after watching the video. At least 4 of the 5 questions had to be answered correctly with a maximum of 2 attempts. After a successful test, a training certificate was issued.

Training was completed before start of the patient analysis. In addition, study protocol and blank paper case report form were shared with the panelists beforehand. The focus of the expert panel training was the determination of the true disease state on the patient level, as well as the true disease state in predefined body regions, which served as the standard of truth for both PET examinations. Instructions related to diagnostic thinking and patient management were the following:

"After concluding the region (or patient) based analysis, panel will additionally see the site investigators' PET lesion analysis. Panel is then asked to answer questions about diagnostic thinking and therapeutic decision making, such as:

• How did the PET results affect the diagnostic thinking

• Was the influence of PET to patient management beneficial or not

• Was the patient treated adequately during follow-up?

• and if not, panel needs to give their own suggestion and explain why this would have been a better treatment option"

No specific definition of a "not beneficial" PET was given to the panelists.

Figure 1: Questionnaire 1

Study No. ABX –CT-301	
Patient no.: |___|___|-|___|___|___|	
BASELINE/VISIT 1 Questionnaire on diagnostic thinking and therapeutic decisions (no. 1)	
Date and time of assessment	|___|___|/|___|___|/|___|___|___|___| day month year |___|___| : |___|___| hrs min
Investigator Name:	_____
Specialty	❑ Urology ❑ Oncology ❑ other, specify: _____
What is the current diagnostic thinking (before PET)?	☐ No prostate cancer recurrence ☐ Prostate cancer recurrence if recurrence, please specify: ☐ local ☐ regional ☐ distant ☐ don't know
Which management is currently planned?	❑ Hormone therapy associated with radiotherapy, specify: _____ ❑ Hormone therapy, specify: _____ ❑ Surgery, specify: _____ ❑ Radiotherapy, specify: _____ ❑ Chemotherapy, specify: _____ ❑ No treatment ❑ Other, specify: _____
Please provide (a) reason(s) for the planned management:	_____

Figure 2: Questionnaire 2

VISIT 3 / IMAGING Questionnaire on diagnostic thinking and therapeutic decisions (no. 2)	
Date and time of assessment	|__|__|/|__|__|/|__|__|__|__| day month year |__|__| : |__|__| hrs min
Investigator Name:	_____
Specialty	❑ Urology ❑ Oncology ❑ other, specify: _____
Did PET imaging change diagnostic thinking?	❑ no ❑ yes, specify below
if change in diagnostic thinking (select all that apply):	❑ ... PET identified a site of recurrence that was not known before ❑ ... PET confirmed a site of recurrence that was suspected before ❑ ... other, specify: _____
if change in diagnostic thinking (select the one that is most correct):	❑ ... F-18 Fluorocholine PET contributed more than F-18 PSMA-1007 PET ❑ ... F-18 PSMA-1007 PET contributed more than F-18 Fluorocholine PET ❑ ... both PET examinations contributed equally
Which management do you propose for the patient?	❑ Hormone therapy associated with radiotherapy, specify: _____ ❑ Hormone therapy, specify: _____ ❑ Surgery, specify: _____ ❑ Radiotherapy, specify: _____ ❑ Chemotherapy, specify: _____ ❑ No treatment ❑ Other, specify: _____
Did your management approach change after PET?	❑ yes ..... ❑ no if yes, provide details: _____ if yes, provide reason(s): _____

Figure 3: Questionnaire 3

VISIT 4 / FOLLOW-UP Questionnaire on diagnostic thinking and therapeutic decisions (no. 3)	
Date and time of assessment	|___|___|/|___|___|/|___|___|___|___| day month year |___|___| : |___|___| hrs min
Investigator Name	_____
Specialty	❑ Urology ❑ Oncology ❑ other, specify: _____
Retrospectively, considering what happened to the patient, select one statement regarding diagnostic thinking that is most correct	❑ PET led to a more accurate diagnosis of patient state ❑ diagnostic thinking was misled by PET results ❑ .. PET had no influence on diagnostic thinking
Select one statement that is most correct	❑ F-18 Fluorocholine PET contributed more than F-18 PSMA-1007 PET ❑ F-18 PSMA-1007 PET contributed more than F-18 Fluorocholine PET ❑ ..both PET examinations contributed equally
Retrospectively, should PET have influenced therapeutic decision making	❑ no ❑ yes, specify: _____
A change occurred in patient's management, independently of PET results	❑ no ❑ yes, specify: _____
Retrospectively, considering what happened to the patient, how do you evaluate the influence of PET on patient's management	❑ the influence was to the benefit of the patient ❑ the influence was NOT to the benefit of the patient ❑ the influence was neither to the benefit nor to the disadvantage of the patient

6 Supplement 6: Statistical and analytical plans

The patient characteristics will be evaluated using the following parameters:

- ⇨ Demographic characteristics
- ⇨ Baseline data

Descriptive statistics will be performed on demographic data. Baseline data will be listed and summarized descriptively where appropriate.

There were four study populations:

1-Safety population: all patients who received either study drug

2-Full analysis set (FAS): all patients who received at least one injection of ^{18}F-PSMA-1007 and for whom any images were provided. The expert panel received data for all patients in the FAS

3-Intention-to-treat (ITT) population: all patients who underwent both PET examinations and completed at least 4 weeks follow-up

4-Per protocol (PP) population: all patients who had no major protocol deviations.

Statistical Analysis of Efficacy

Analysis of the Primary Efficacy Variable

The primary efficacy variables are planned to be the detection rate of all lesions with ^{18}F-fluorocholine and ^{18}F-PSMA-1007 on a patient basis. For the evaluation of the diagnostic value of [^{18}F]PSMA-1007 compared to ^{18}F-fluorocholine PET, the detection rate will be tested with following hypotheses and a z test based on generalized estimation equations (GEEs) at a one-sided level of significance of 2.5% each. GEEs will be used to account for the correlations between readers' assessments.

H0 = “The detection rate of ^{18}F-PSMA-1007 vs. [^{18}F]fluorocholine shows an odds ratio equal or below 1” vs. H1 = “The detection rate of ^{18}F-PSMA-1007 vs. ^{18}F-fluorocholine shows an odds ratio above 1”.

The null hypothesis H0 can be rejected if the two-sided 95% confidence interval (CI) for the difference in detection rates is completely above 1 for the odds ratio.

Analysis of the Secondary Efficacy Variables

The detection rate on a segment level will be analyzed analogously to the primary analysis but will also take into account the correlation of segments within a patient.

For all secondary efficacy variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated for each quantitative variable. Absolute and relative frequencies will be given for categorical data.

Image quality and diagnostic confidence will be assessed descriptively.

Statistical Analysis of Safety

All safety analyses will be done by study drug. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated for each quantitative variable; frequency counts by category will be made for each qualitative variable. The frequencies of adverse events will be reported by study group and treatment arm. Tabulations will be provided for body systems, severity, seriousness, intensity, main pattern, study drug or device action, causal relationship to study drug or device, causal relationship to study conduct, and outcome of the adverse event. Any withdrawals from the study due to adverse events will be reported. Further safety assessments will determine frequencies and percentages of relevant changes in results of

physical examinations and vital signs. For pre-treatment events summary tables and listings will be provided.

Determination of sample size

A simulation study was performed to assess the sample size for an overall power of >80%. The primary analysis of the primary efficacy variable will be done with generalized estimating equations with compound symmetry working correlation matrix taking into account the correlations between the three blinded readers and between modalities through robust variance estimates. Random numbers were generated introducing correlation between the readers and between the modalities with 1000 runs. The comparison of detection rates was performed with appropriate contrasts. ^{18}F-PSMA-1007 and ^{18}F-fluorocholine were assumed to show a detection rate as displayed below.

The following settings and assumptions were used to estimate the sample size: Power (overall)=89%; Alpha (1-sided)=2.5%; Detection rate for ^{18}F-PSMA-1007=70%; Detection rate for [^{18}F]fluorocholine=60%; Number of blinded readers=3; Statistical test based on the odds ratio. Overall, 150 patients with expert panel (SOT) assessment were required for the primary efficacy analysis. With a drop-out rate of 20%, the study planned to enroll a total of 188 patients. Missing values were not imputed. Dropouts were excluded from any statistical analyses and observed values for dropouts were listed only.

Randomization/Stratification

The sequence of the two imaging modalities within the patient were randomized. A randomization list by study site was created using SAS (Version 9.4) and a paper document was

provided to the sites. The randomization list was computer-generated and included stratification by center. For each center, a separate randomization list was provided.

7 Supplement 7: PET findings per patient and per region

Table 1: PET findings per-patient and per-region from the independent read by reader; Intention-to-treat population

	Reader	^{18}F-PSMA-1007 PET/CT	^{18}F-fluorocholine PET/CT
Patient-based results (n=190)			
Recurrence	Reader 1	151 (79.5%)	111 (58.4%)
	Reader 2	162 (85.3)	128 (67.3%)
	Reader 3	145 (76.3%)	99 (52.1%)
No Recurrence	Reader 1	30 (15.8%)	58 (30.5%)
	Reader 2	16 (8.4%)	52 (27.4%)
	Reader 3	39 (20.5%)	73 (38.4%)
Undetermined	Reader 1	9 (4.7%)	21 (11.1%)
	Reader 2	12 (6.3%)	10 (5.3%)
	Reader 3	6 (3.2%)	18 (9.5%)
Region-based results (=72)			
Pelvis			
Recurrence	Reader 1	52	38
	Reader 2	57	47
	Reader 3	54	34
No Recurrence	Reader 1	16	26
	Reader 2	12	22
	Reader 3	16	33
Undetermined	Reader 1	4	8
	Reader 2	3	3
	Reader 3	2	5
Paraaortic lymph nodes			

Recurrence	Reader 1	8	8
	Reader 2	4	5
	Reader 3	3	2
No Recurrence	Reader 1	64	59
	Reader 2	67	67
	Reader 3	69	67
Undetermined	Reader 1	0	5
	Reader 2	1	0
	Reader 3	0	3
Supraclavicular lymph nodes			
Recurrence	Reader 1	1	1
	Reader 2	2	0
	Reader 3	1	2
No Recurrence	Reader 1	71	71
	Reader 2	69	71
	Reader 3	70	69
Undetermined	Reader 1	0	0
	Reader 2	1	1
	Reader 3	1	1
Other supradiaphragmatic lymph nodes			
Recurrence	Reader 1	3	1
	Reader 2	3	1
	Reader 3	3	3
No Recurrence	Reader 1	69	70
	Reader 2	69	71
	Reader 3	67	65
Undetermined	Reader 1	0	1

	Reader 2	0	0
	Reader 3	2	4
Spine			
Recurrence	Reader 1	4	5
	Reader 2	15	5
	Reader 3	7	4
No Recurrence	Reader 1	68	67
	Reader 2	57	67
	Reader 3	65	68
Undetermined	Reader 1	0	0
	Reader 2	0	0
	Reader 3	0	0
Ribs			
Recurrence	Reader 1	4	4
	Reader 2	6	4
	Reader 3	4	3
No Recurrence	Reader 1	68	68
	Reader 2	64	68
	Reader 3	68	69
Undetermined	Reader 1	0	0
	Reader 2	2	0
	Reader 3	0	0
Limb and shoulders			
Recurrence	Reader 1	2	2
	Reader 2	4	2
	Reader 3	3	2
No Recurrence	Reader 1	69	70

	Reader 2	68	70
	Reader 3	69	70
Undetermined	Reader 1	1	0
	Reader 2	0	0
	Reader 3	0	0
Skull and facial skeleton			
Recurrence	Reader 1	2	2
	Reader 2	2	2
	Reader 3	2	2
No Recurrence	Reader 1	70	70
	Reader 2	70	70
	Reader 3	70	69
Undetermined	Reader 1	0	0
	Reader 2	0	0
	Reader 3	0	1
Liver			
Recurrence	Reader 1	0	0
	Reader 2	0	0
	Reader 3	0	0
No Recurrence	Reader 1	72	72
	Reader 2	72	72
	Reader 3	72	72
Undetermined	Reader 1	0	0
	Reader 2	0	0
	Reader 3	0	0
Lung			
Recurrence	Reader 1	2	0

	Reader 2	3	2
	Reader 3	2	0
No Recurrence	Reader 1	70	72
	Reader 2	68	70
	Reader 3	69	70
Undetermined	Reader 1	0	0
	Reader 2	1	0
	Reader 3	1	2

Patient-based results from the independent read and agreement with the standard of truth defined by the expert panel

Table 2: Patient-based results from the independent read (by reader)

Evaluation	Reader	^{18}F-PSMA-1007 (n=190)	^{18}F-fluorocholine (n=190)
Recurrence	Reader 1	151 (79.5%)	111 (58.4%)
	Reader 2	162 (85.3%)	128 (67.3%)
	Reader 3	145 (76.3%)	99 (52.1%)
No recurrence	Reader 1	30 (15.8%)	58 (30.5%)
	Reader 2	16 (8.4%)	52 (27.4%)
	Reader 3	39 (20.5%)	73 (38.4%)
Undertermined	Reader 1	9 (4.7%)	21 (11.1%)
	Reader 2	12 (6.3%)	10 (5.3%)
	Reader 3	6 (3.2%)	18 (9.5%)

Patient-based results from the independent read (by reader); the table shows patients in whom the expert panel confirmed the presence of a malignant lesion (correct detection rate; this table excludes 5 patients who were rated as undetermined by expert panel, and 6 patients rated as "no recurrence" by the expert panel)

Table 3: Patient-based results confirmed by expert panel

Evaluations agree with expert panel (recurrence)	^{18}F-PSMA-1007 (n=179)	^{18}F-fluorocholine (n=179)
Reader 1	135 (75.4%)	97 (54.2%)
Reader 2	146 (81.6%)	118 (65.9%)
Reader 3	132 (73.3%)	88 (49.2%)

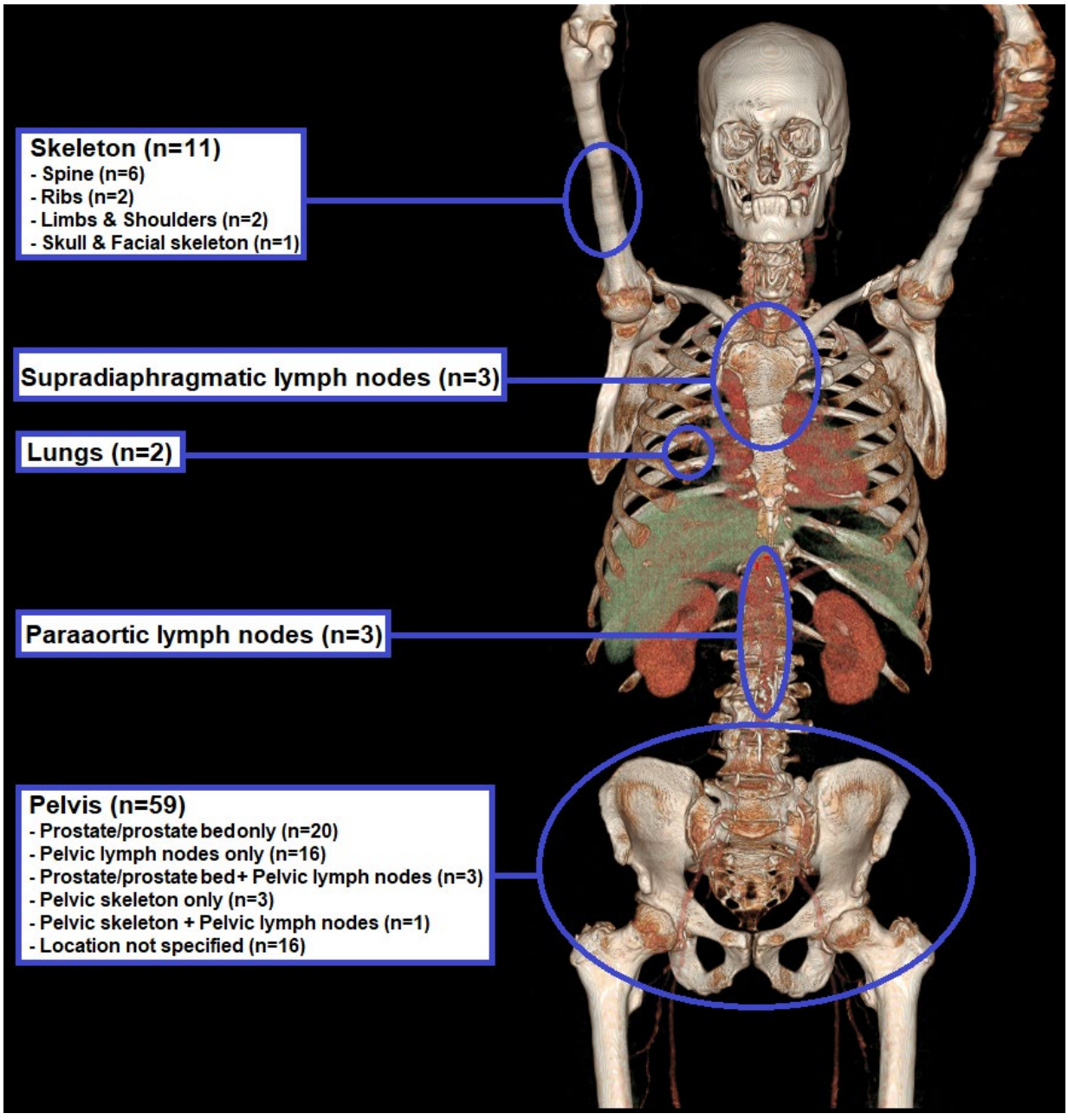
8 Supplement 8: Readers' agreement

Table 4: Intra- and inter-reader categorical agreement; Intention-to-treat population (N=190)

	^{18}F-PSMA-1007	^{18}F-fluorocholine
Intra-reader agreement		
Detection of metastases on patient-level	Kappa	Kappa
Reader 1	0.24 / fair (n=19)	0.63 / substantial (n=19)
Reader 2	0.73 / substantial (n=19)	0.48 / moderate (n=19)
Reader 3	0.59 / moderate (n=19)	0.72 / substantial (n=19)
Detection of metastases on region-level		
Reader 1	0.62 / substantial (n=190)	0.76 / substantial (n=190)
Reader 2	0.70 / substantial (n=190)	0.68 / substantial (n=190)
Reader 3	0.72 / substantial (n=190)	0.68 / substantial (n=190)
Inter-reader agreement		
Detection of metastases on patient-level	Kappa	Kappa
Reader 1	0.36 / fair (n=190)	0.34 / fair (n=190)
Reader 2	0.30 / fair (n=190)	0.40 / fair (n=190)
Reader 3	0.35 / fair (n=190)	0.35 / fair (n=190)
Multiple readers	0.33 / fair (n=190)	0.36 / fair (n=190)
Detection of metastases on region-level		
Reader 1	0.70 / substantial (n=1900)	0.64 / substantial (n=1900)
Reader 2	0.75 / substantial (n=1900)	0.61 / substantial (n=1900)
Reader 3	0.70 / substantial (n=1900)	0.63 / substantial (n=1900)
Multiple readers	0.72 / substantial (n=1900)	0.63 / substantial (n=1900)

9 Supplement 9: Distribution of prostate cancer recurrence location

Figure 4: Distribution of prostate cancer recurrence location according to the standard of truth (n=78)



10 Supplement 10: Patient treatment plan scheduled

Table 5: Patient treatment plan scheduled before and after ^{18}F-PSMA-1007 and ^{18}F-fluorocholine PET/CT

		After PET						
		ADT only	Radiation therapy only	Radiation therapy plus ADT	No treatment	Other	Surgery	Total
Before PET	No treatment	**16**	**13**	**9**	9	**3**	**1**	51
	ADT only	30	**7**	**5**	**2**	**2**	0	46
	Radiation therapy only	**6**	34	4	**1**	0	**1**	46
	Radiation therapy plus ADT	**6**	7	12	**1**	**2**	0	28
	Other	**5**	**4**	**3**	**1**	2	0	15
	Chemotherapy	0	**1**	0	0	0	0	1
	Total	63	66	33	14	9	2	187

PET: positron emission tomography; ADT: androgen deprivation therapy. Major changes are bold and underlined.

Patient treatment plan data missing for 3 patient