CLINICAL TRIAL PROTOCOL

Title: Fully hybrid 18F-PSMA PET/MRI as one-stop approach for the diagnosis of clinically significant prostate cancer

Protocol Acronym/Number	RF-2021-12372278
EudraCT number	2022-003905-31
Other Protocol Identifiers	NA
Version	v2.0
Date	30 GEN 2023

Sponsor	IRCCS Ospedale San Raffaele
Authorized Sponsor Representative	Arturo Chiti, Prof Director U.O. of Nuclear Medicine
Funding Sponsor or Source(s)	Italian Ministry of Health
Principal Investigator	Maria Picchio, MD Professor U.O. of Nuclear Medicine

VERSION HISTORY

Protocol version n.	Reason of changes	Date issued
v1.0	First Version submitted to the OSR Ethics Committee (EC) and AIFA	23 NOV 2022

PROTOCOL SIGNATURE PAGE

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Protocol Version and Date: v2.0 30 GEN 2023

The undersigned has read and understood all the aspects of the protocol detailed within this document and agrees to supervise and conduct the trial in accordance with the protocol, Guideline for Good Clinical Practice ICH E6 (R2), Declaration of Helsinki, and all applicable regulatory requirements.

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Authorized Sponsor Representative Name	**Signature**	**Affiliation**	**Date**

Maria Picchio		U.O. of Nuclear Medicine	
Principal Investigator Name	**Signature**	**Affiliation**	**Date**

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1. KEY TRIAL CONTACTS

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2. SYNOPSIS

Trial Title	Fully hybrid 18F-PSMA PET/MRI as one-stop approach for the diagnosis of clinically significant prostate cancer	
Protocol Acronym/Number	RF-2021-12372278	
Protocol Version and Date	v2.0, 30 GEN 2023	
EudraCT number	NA	
Sponsor	IRCCS Ospedale San Raffaele Via Olgettina 60 – 20132, Milan, Italy	
Funding Source(s)	Italian Ministry of Health	
Principal Investigator	Maria Picchio, U.O. of Nuclear Medicine	
Trial Description	This project aims to evaluate the role of fully hybrid PET/MRI with 18F-PSMA and multiparametric MR imaging (mpMRI) as one-stop approach for the diagnosis of clinically significant prostate cancer (csPCa). Our main hypothesis is that adding 18F-PSMA PET to mpMRI prior to biopsy, will reduce the number of false negative findings, while at the same time, allowing also to reduce the number of unnecessary prostate biopsies in patients with low-risk, clinically indolent PCa.	
	Primary	**Secondary**
Objectives	To assess the accuracy and the predictive value of fully hybrid 18F-PSMA PET/MRI for the diagnosis of csPCa	1) To compare the proportion of csPCa missed by 18F-PSMA PET scan or mpMRI alone 2) To report the reduction in the detection of clinically insignificant PCa when combining mpMRI and 18F-PSMA PET, and consequently the proportion of unnecessary biopsies potentially spared.
Endpoints	Diagnostic accuracy measured with sensitivity, specificity, positive and negative predicted value	1) The number of csPCa missed by PET and MR imaging when read independently **2)** Only in patients with positive mpMRI and negative 18F-PSMA PET: The proportion of clinically insignificant PCa
Time point(s)	day 0: 18F-PSMA PET/MRI day 90 (+/- 90): prostate biopsy	
Phase	Phase II	
Trial Design	Monocentric, single-arm, prospective	

Trial Population	Men with clinical suspicion of csPCa.
Inclusion Criteria	1) Men at least 18 years of age referred with clinical suspicion of prostate cancer candidate for prostate biopsy 2) Feasibility to undergo all procedures listed in protocol 3) Ability to provide written informed consent
Exclusion Criteria	1) Prior diagnosis of prostate cancer 2) Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR lower or equal to 50mls/min) 3) Contraindication to prostate biopsy
Intervention(s)	
IMP(s)	18F-PSMA, 4 MBq/Kg, intravenous administration
NIMP(s)	Not applicable.
Other intervention(s)	Prostate biopsy guided by imaging findings
Comparator	Not applicable.
Safety Criteria	Patients' compliance.
Efficacy Criteria	Diagnostic accuracy
Sample Size	167 patients, all enrolled at OSR
Statistical Design	Diagnostic accuracies of 18F-PSMA PET and mpMRI will be calculated by means of sensitivity: true positive/(true positive + false negative); specificity: true negative/(false positive + true negative); PPV: true positive/(true positive + false positive); and NPV: true negative/(true negative + false negative) using the prostate biopsy result as reference standard
List of Enrolling Sites (if applicable)	Not applicable.
Duration of the Trial	Duration of enrollment: 27 months Duration of treatment: two hours per patient (over 27 months)

	Duration of total follow-up: NA (after biopsy there will not be further visits) Duration of total trial period: 36 months

3. ABBREVIATIONS AND DEFINITIONS

3.1. Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
CIOMS	Council for International Organization of Medical Science
CRF	Case Report Form
CRO	Contract Research Organization
CTA	Clinical Trial Application
DSMB	Data and Safety Monitoring Board
DSUR	Development Safety Update Report
EC	Ethics Committee
GCP	Good Clinical Practice
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
LVSL	Last Visit of Last Subject
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	Non-Investigational Medicinal Product
PeIMP	Products equivalent to the IMP
PI	Principal Investigator
QP	Qualified Person
ReTNIMP	Regardless to Trial NIMP
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDR	Serious Drug Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
csPCa	clinically significant prostate cancer
PSA	prostate specific antigen
EAU	European Association of Urology

mpMRI	multiparametric magnetic resonance imaging
PSMA	prostate specific membrane antigen
PET	positron emission tomography
ROI	region of interest
OSR	Ospedale San Raffaele
ROC	Receiver operating characteristics

3.2. Definitions

Not applicable.

4. BACKGROUND AND RATIONALE

Prostate cancer (PCa) is the second most common cancer in men, with 1,414,259 new cases in 2020, accounting for 15.1% of all cancer diagnoses within the male population (1). The current EAU Guidelines for PCa recommend performing mpMRI before prostate biopsy in men with clinical suspicion of PCa (2). However, the accuracy of mpMRI in detecting csPCa remains suboptimal and a significant proportion of unnecessary biopsies are performed in men with suspicious lesions on mpMRI (3). Several efforts were made to identify new diagnostic strategies to implement mpMRI performances. The use of PSMA PET, widely implemented for clinical management of PCa both in recurrent and primary setting, has recently gained interest for diagnostic purposes. In 296 men with suspicion of PCa, the combined use of ^{68}Ga-PSMA PET and mpMRI for PCa diagnosis showed improved sensitivity and negative predicted value for csPCa (4). Based on these results, the combination of mpMRI and ^{68}Ga-PSMA PET might reduce the number of prostate biopsies required to diagnose csPCa. In this prior study, mpMRI and ^{68}Ga-PSMA PET have been acquired and interpreted separately, with the risk of introducing potential confounders. Moreover, imaging-guided targeted biopsies were not systematically performed.
In this project, the role of hybrid PET/MRI with ^{18}F-PSMA will be evaluated in PCa diagnosis. The major advantages of this innovative technology are the simultaneous acquisition of PET and mpMR imaging by using a fully hybrid PET/MRI scan and the use of ^{18}F-PSMA with improved spatial resolution compared to ^{68}Ga-PSMA, due to its lower positron energy.

5. RISK/BENEFIT ASSESSMENT

5.1. Known Potential Risks

A potential risk of this study is patients' compliance regarding the execution of a PET exam in addition to the standard of care MRI and the prolonged scan time. The scan will be performed simultaneously on a dedicated hybrid PET/MRI whole body scanner and additional data regarding potential disease extension will be collected concomitantly. Longer execution time, though, will offer added value for describing disease both to the patient as well as for the scope of this study. The side effects of contrast medium for MRI are very low (standard of care), as are those documented by internal unpublished data on the use of ^{18}F-PSMA. Our goal is also to optimize these dedicated PET/MRI acquisition protocols in terms of duration, hopefully increasing patient compliance. The interventions proposed in this trial are aligned with what suggested by the EAU Guidelines for prostate cancer diagnosis. Specifically, all patients will undergo mpMRI as recommended by EAU guidelines. In addition to mpMRI, all patients will undergo a concomitant ^{18}F-PSMA PET whose results will be evaluated jointly with those of the mpMRI during the same diagnostic session. Therefore, participants will be offered the diagnostic gold standard plus additional ^{18}F-PSMA PET, whose use in the diagnostic pathway has been already proposed (4,5). Regarding the toxicity and radioactive exposure associated with the use of radionuclides PSMA, several studies have demonstrated the low exposure to radiation and showed no adverse effects or toxicity (6). All patients will then undergo a 12-core SBx as also recommended by the EAU guidelines plus TBx in case of either ^{18}F-PSMA PET or mpMRI would show suspicious lesion/s, adverse events (AE) will be recorded by a member of the research team or clinical team on an AE report form. All serious AE (SAE) will be recorded on a SAE report form. Both AE and SAE should be recorded in the medical notes.

5.2. Known Potential Benefits

In this study we will implement and assess a novel ^{18}F-PSMA PET targeted software-assisted fusion biopsy method to accurately target ^{18}F-PSMA PET ROIs and to provide reliable data on ^{18}FPSMA PET diagnostic accuracy. We will develop an efficient and time-effective one-stop session ^{18}F-PSMA PET/mpMRI examination for PCa diagnosis by using a fully hybrid PET/MRI. The simultaneous acquisition of PET using a new radiotracer such as ^{18}F-PSMA and mpMRI provides metabolic structural and functional information regarding PCa status in a whole-body single session examination, thus representing an improvement and innovation for PCa staging. Data provided by this study will have potential clinical implications such as the improvement of csPCa detection and the reduction of clinically indolent PCa diagnosis, thus overdiagnosis and overtreatment.

5.3. Assessment of Risks and Benefits ratio

The prolonged acquisition time that characterizes fully hybrid PET/MRI is necessary to provide a one-stop-shop for the diagnosis of csPCa. Furthermore, PSMA PET, despite obviously entailing a low radiation exposure to patients, is a safe procedure already recommended for the characterization of PCa both in the staging and restaging phase by international guidelines (2). The low risk that this protocol entail is therefore justified by its potential clinical implications such as the improvement of csPCa detection and the reduction of clinically indolent PCa diagnosis, thus overdiagnosis and overtreatment.

6. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints	Time point(s)
Primary Objective To assess the accuracy and the predictive value of fully hybrid ^{18}F-PSMA PET/MRI for the diagnosis of csPCa	**Primary Endpoint** Diagnostic accuracies of 18F-PSMA PET and mpMRI will be calculated by means of sensitivity: true positive/(true positive + false negative) and specificity: true negative/(false positive + true negative) using the prostate biopsy result as reference standard.	PET/MRI examination at day 0, and biopsy at day 1-30 (within a month from imaging study)
Secondary Objectives To compare the proportion of csPCa missed by 18F-PSMA PET scan or mpMRI alone	**Secondary Endpoints** The proportion of csPCa (defined by analysis of prostate biopsy cores, ISUP grade equal or higher than 2) missed by PSMA PET scan or mpMRI alone will be calculated.	PET/MRI examination at day 0, and biopsy at day 1-30 (within a month from imaging study)
Exploratory Objectives To assess the proportion of unnecessary biopsies potentially spared	**Other** Number of clinically insignificant PCa (ISUP grade 1) identified combining mpMRI and ^{18}F-PSMA PET.	PET/MRI examination at day 0, and biopsy at day 90 (+/-90)

7. EFFICACY AND SAFETY CRITERIA

7.1. Efficacy Criteria

Diagnostic accuracies of 18F-PSMA PET and mpMRI will be calculated by means of sensitivity: true positive/(true positive + false negative); specificity: true negative/(false positive + true negative); PPV: true positive/(true positive + false positive); and NPV: true negative/(true negative + false negative) using the prostate biopsy result as reference standard

7.2. Safety Criteria

A large amount of evidence shows that ^{18}F-PSMA is well tolerated, and it is not associated with serious adverse events (SAE) (6). Drug's reaction could occur, in a very small percentage of the population as it is reported in the normal clinical practice. Patients presenting contraindication to PET/MRI examination will be excluded from the study a priori. More details on this can be found in the section "Exclusion criteria" of this protocol.

8. TRIAL DESIGN

In this single-arm phase II, prospective, monocentric study we will test whether addition of 18F-PSMA PET scan to mpMRI helps improving the diagnostic pathway efficiency in identifying those men who should necessarily undergo TBx, because of high-risk to harbor csPCa.
Furthermore, the combined use of 18F-PSMA PET and mpMRI for the diagnosis of PCa may also result in a reduced number of follow-up procedures in those patients who can safely avoid a prostate biopsy given the very low risk of harboring csPCa using a single, one-stop approach with both imaging modalities. A more efficient pre-biopsy triage test using the fully hybrid 18F-PSMA PET/MRI might result in the reduction of the total number of biopsies for men with a clinical suspicion of PCa, reducing also patient discomfort combining two different diagnostic procedures in one single step and avoiding, whenever possible, the biopsy-related side effects.

A total of 167 consecutive patients with a clinical suspicion of csPCa (defined as the presence of PCa with ISUP grade equal or higher to 2), referred to simultaneous 18F-PSMA PET/MRI with mpMRI, will be identified and enrolled. PET/MRI images will be qualitatively and quantitatively evaluated by an experienced Nuclear Medicine and an experienced Radiologist physicians. In particular, for qualitative evaluation, lesions classified as PI-RADS higher or equal to 3 on mpMRI images and/or showing pathologically increased 18F-PSMA uptake on PET images, will be considered as positive for csPCa. All men will then receive a prostate biopsy (12-core random systematic prostate biopsy plus eventual targeted biopsy) as back-up histology according to the results of PET/MR imaging.

Specifically, patients with both positive mpMRI and 18F-PSMA PET, defined as the presence of one or more lesions with PI-RADS higher or equal to 3 and an increased uptake of 18F-PSMA, will receive a 12-core random systematic prostate biopsy (TRUS-Bx) in addition to MRI targeted biopsy (MRI-TBx) and 18F-PSMA PET targeted biopsy (PSMA PETTBx).

Patients with both negative mpMRI and 18F-PSMA PET scan will receive a 12-core TRUS-Bx. Patients with only positive mpMRI will receive MRI-TBx and 12-core TRUSBx. Patients with only positive 18F-PSMA PET will receive 18FPSMA PET-TBx and 12-core TRUSBx. MRI-TBx will be performed by means of a fusion software-assisted approach using the Biojet system taking 4 cores in any mpMRI suspicious areas. PSMA PET-TBx will be performed taking 4 cores in the area of the prostate showing an increased tracer uptake. All prostate biopsy specimens will be evaluated by fully dedicated uro-pathologist.
In order to calculate accuracy, sensitivity, specificity, positive predictive value and negative predictive value of 18F-PSMA PET/MRI for the identification of csPCa, 18F-PSMA PET/MRI findings will be correlated with histopathological samples gathered with prostate biopsy.
The proportion of csPCa missed by PSMA PET scan or mpMRI alone will be then calculated.
In order to study the proportion of unnecessary biopsies that could be spared by adding 18F-PSMA PET to mpMRI in the triage phase, only patients with positive mpMRI and negative 18F-PSMA PET scan will be considered for the analysis and the proportion of clinically insignificant PCa detected in this subset of patients will be assessed. In this way we will identify proportion of unnecessary prostate biopsies that could have been spared, thus reducing overdiagnosis.
Furthermore, the potential role of quantitative PET and mpMRI parameters in identifying csPCa will be investigated. Specifically, recently emerging radiomic features will be evaluated, together with PET- and MRI-derived quantitative conventional imaging parameters, and regression analyses will be used for evaluating their role in predicting histopathological data. To assess the diagnostic performance of PET and MRI parameters, ROC curve analysis will be performed to select optimal cut-offs in predicting the presence of csPCa as defined by cytological examination and the corresponding diagnostic accuracy will be computed (more detailed information in the section “Statistics” of this protocol). No interim analyses are planned.

The following measures will be taken in order to minimize the risk of bias:
MpMRI is the standard of care diagnostic tool for staging and restaging in patients with Pca. The high expertise of the Center in prostate MRI has shown negligible inter-reader variability. All MRIs will be analysed by an experienced Radiologist (6 years of experience in prostate mpMRI). All PET exams will be analysed by an expert Nuclear Medicine physician (>10 years of experience in prostate PET). Furthermore, to avoid bias in the qualitative image anlaysis, PET and mpMR scans will be evaluated blind to the results of the other imaging modality. For efficacy analyses that require complete patient data, missing values during the treatment period will be replaced, for all variables, with the LOCF technique (Last Observation Carried Forward). Imputed values will be included in the analysis set(s), but will not change the original clinical database. For subjects who interrupt prematurely the trial due to the "adverse event", the BOCF technique (Basal Observation Carried Forward) will be used instead of the LOCF, in order to avoid the allocation of a positive result to patients to be considered treatment failures.

8.1. Study duration

Duration of enrollment: The enrolment will start on April 30th 2023 and will end before July 2025.
Duration of treatment: PET/MRI examination takes about two hours. Then patients will undergo prostate biopsy (90 days +/- 90 days after imaging)
Duration of total follow-up: A follow-up is not planned
Duration of total trial period: Three years (36 months)

9. TRIAL POPULATION

9.1. Trial Participants

Participants with clinical suspicion of clinically significant prostate cancer (defined by ISUP grade equal or higher than 2) referred for simultaneous 18F-PET/MR, with mpMRI, examination.

9.2. Inclusion Criteria

1) Men at least 18 years of age referred with clinical suspicion of prostate cancer candidate for prostate biopsy
2) Feasibility to undergo all procedures listed in protocol
3) Ability to provide written informed consent

9.3. Exclusion Criteria

1) Prior treatment for prostate cancer
2) Prior diagnosis of prostate cancer
3) Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR lower or equal to 50mls/min)
4) Contraindication to prostate biopsy
5) Men in whom artifact would reduce the quality of the MRI (e.g. hip replacement)
6) Unfeasibility to undergo any procedures listed in protocol

9.4. Screening Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. Minimal information including demography, screening failure details, eligibility criteria, and any serious adverse event (SAE) experienced by the patients will be reported.

10. TRIAL INTERVENTIONS

10.1. Investigational Medicinal Product(s) (IMP) Description

18F-PSMA synthesis is performed using an automatic synthesis module (NEPTIS) through the incorporation of 18F (produced by the IBA 18 MeV cyclotron) in a PSMA 1007 precursor molecule; after formulation and sterilization on a 0.22 um filter membrane, quality control is performed to evaluate the chemical, radiochemical, radionuclidic and microbiological purity of the final product in compliance with the monograph of Eu. Ph. 3116

10.2. Treatment Schedule

Experimental drug	Dosage	Route	Day
18F-PSMA	Approximately 4 MBq/Kg	Intravenous	0

10.3. Method for Assigning Subjects to Treatment Groups

Not applicable

10.4. Blinding of IMPs

Not applicable

10.5. Receiving and Storage of IMP

Not applicable. The IMP is produced by the radio-pharmacy of Ospedale San Raffaele and used immediately due to its short half-life.

10.6. Preparation, Administration and Accountability of the Trial Treatments

Radiotracer synthesis: 18F-PSMA synthesis is performed using an automatic synthesis module (NEPTIS) through the incorporation of 18F (produced by the IBA 18 MeV cyclotron) in a PSMA 1007 precursor molecule; after formulation and sterilization on a 0.22 um filter membrane, quality control is performed to evaluate the chemical, radiochemical, radionuclidic and microbiological purity of the final product in compliance with the monograph of Eu. Ph. 3116.
PET/MR acquisition protocol: PET/MRI will start approximately 90 minutes after intravenous administration of 4 MBq/Kg of 18F-PSMA. A PET/MR total body acquisition and a high statistics pelvic PET simultaneously acquired to mpMRI will be performed. Using 3 Tesla PET/MR system the endorectal coil is not needed for the MR acquisition thus increasing patient compliance.
MpMRI protocol will follow ESUR guidelines: axial T2 weighted sequence with large field of view (FOV), axial and sagittal T2 weighted sequence with small FOV, DWI sequence with small FOV b= 50, 800, 1400; 2000s/mm2 and ADC maps, T1-Lava Flex sequence of the pelvic region pre-contrast and post-contrast, a high temporal resolution T1 perfusion sequence after IV injection of 0.1 mmol/kg bolus of gadobutrol at a flow rate of 3.5 mL/s.
PET/MRI qualitative analysis: images will be evaluated by expert Nuclear Medicine and Radiologist physicians blinded to each other on the Advantage Workstation (AW, General Electric Healthcare, Waukesha, WI, USA) where PET, MRI and fused PET/MRI images can be visualized in axial, coronal and sagittal planes. Focal uptake of 18F-PSMA higher than background and not associated with physiologic uptake was considered positive. For mpMRI, T2W morphological, diffusion (DWI) and perfusion (DCE) sequences will be used to define lesions according to PIRADS v. 2.1 classification (7). Lesions classified as PI-RADS >= 3 on mpMRI images and/or showing increased 18F-PSMA uptake on PET, will be considered positive for csPCa.
Biopsy protocol: Each patient will receive a 12-core random systematic biopsy (TRUSBx) and mpMRI targeted biopsy as standard clinical procedure. MpMRI software assisted targeted biopsy will be performed using the BioJetTM fusion system (D&K Technologies, Barum, Germany) (8,9). Before biopsy both the prostate and each mpMRI suspicious lesion will be contoured and superimposed with the transrectal (TR) ultrasound image. TR ultrasound will be performed using a Flex Focus 500 machine with a biplanar transducer (BK Medical, Herlev, Denmark) (10). In

addition, 18F-PSMA PET targeted biopsy will be also performed, using the BioJetTM fusion system relying on PET images co-registered with mpMRI images for a correct contouring of both prostate and 18F-PSMA PET ROIs and superimposition with ultrasound images. Each mpMRI and 18F-PSMA PET ROI will be biopsied with a 4-cores targeted biopsy. Prostate biopsies will be carried out using a 18-gauge needle and a biopsy gun providing a specimen size of 18-22 mm.
PET/MR quantitative analysis: ROIs on primary tumour showing 18F-PSMA uptake will be semi-automatically defined on transaxial PET images and the following semi-quantitative parameters will be extracted: maximum standardised uptake value (SUVmax), mean SUV (SUVmean, using different thresholds and metabolic tumour volume (MTV) calculated at different thresholds. ROIs on the MR images, ADC and DCE maps will be drawn to measure MR parameters related to the lesions detected by MRI.
Radiomic analysis: Volumes of interest (VOIs) will be manually segmented on 18F-PSMA PET, T2w-images and ADC maps by expert Nuclear Medicine and Radiologist physicians in correspondence of the intra-prostatic findings referable to the site of primary tumour. IBSI compliant radiomic features (11) will be extracted from VOIs and features reduction and selection procedures will be used to define a smaller set of radiomic features showing the best discrimination between csPCa and clinically insignificant PCa or healthy tissue.
Remaining radio-pharmaceutical will be stored in a bunker at Ospedale San Raffaele and after radioactivity decay will be destroyed in accordance with the hospital and the applicable local, federal and national regulations.

10.7. Compliance with Trial Treatment

All patients that will complete PET/MRI examination and will undergo prostate biopsy will be considered compliant with the clinical trial. A through database containing all relevant information for this study will be generated and patients that fail to complete the study procedures will be annotated. PET/MRI acquisition protocol will be optimized to ensure, as much as possible, patients' compliance.

10.8. Concomitant Medication

Only prior medication for PCa and concomitant medication that entail contraindication for PET/MR examination or biopsy will not be allowed, and therefore patients showing these characteristics will be excluded from the study (see section "Exclusion criteria").

10.9. Rescue Therapy

Not applicable.

10.10. Post-trial Treatment

There will be not provision of the IMP beyond the rial period.

10.11. Other Treatments (NIMPS: PeIMP - ReTNIMP)

Not applicable.

10.12. Other Interventions

Not applicable.

11. TRIAL PROCEDURES

	Enrollment	Screening	Baseline	Study Visit	Final Study Visit
Day **Procedures**	-20 (+/- 20 days)	-20 (+/- 20 days)	0 (+/- 0 days)	+90 (+/-90 days)	+90 (+/-90)
Informed consent	x				
Demographics		x			
Medical history		x			
Eligibility assessment		x			
Urological visit, including physical examination		x			
Performance status		x			
Study drug administration			x		
Compliance evaluation			x		
Radiologic/Imaging assessment			x		
Prostate biopsy				x	
Adverse event assessments		x	x	x	x

11.1. Informed Consent

Consent forms describing in detail the study procedures, and risks, are given to the participant and written documentation of informed consent is required prior to starting to administer 18F-PSMA. The following consent materials are submitted with this protocol “Consenso informato v2.0”.

Informed consent is a process that is initiated prior to the individual’s agreeing to participate in the study and continues throughout the individual’s study participation. Consent forms will be EC-approved, and the participant will be asked to read and review the document. The investigator (according to applicable regulatory requirements) or a person designated by the investigator, and under the investigator's responsibility, will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant’s comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant MUST signed the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.2. Subject Recruitment and Screening

A total of 167 consecutive patients with a clinical suspicion of csPCa (defined as the presence of PCa with ISUP grade equal or higher to 2), referred to simultaneous 18F-PSMA PET/MRI with mpMRI, will be identified and enrolled. The sample size was computed based on sensitivity analysis for the detection of clinically significant PCa. Assuming an average prevalence of clinically significant PCa of 56%, a total sample size of 167 patients is sufficient for evaluating a sensitivity of 96% with an absolute precision of 4% (at 95% confident level). Patients will be identified and enrolled by the department of Urology at OSR following standard procedures for the evaluation of suspected csPCa, including prostate specific antigen (PSA) examination.

11.3. Subject Identification

Starting from the signature of the informed consent by the patient or patient’s legal tutor, the subjects is considered enrolled in the clinical trial.

A subject identification code will be assigned consecutively (i.e.: csPCa_XXX; where csPCa is the abbreviation of the acronym, XXX is the progressive subject number in increasing order starting from 001).

A patient identification list will be kept.

11.4. Randomization and Blinding

Not applicable.

11.5. Baseline Assessments

At the screening visit the urologist will evaluate the risk of csPCa, according to the normal clinical practice.

11.6. Visits and Follow Up

The protocol does not include a follow-up. At Day 0 patients undergo 18F-PSMA PET/MRI examination. Then patients undergo prostate biopsy. Analysis of prostate biopsy cores is necessary to validate imaging findings and to diagnose csPCa. No further time points are considered. The patients will then continue to be monitored according to the normal clinical practice regardless of their participation in this study.

11.7. Definition of End of Study

According to the study design, the end of the study is defined as the date on which the last patient completes the last visit (Day 90 ± 90 days).

11.8. Premature termination or suspension of a trial

This study may be temporarily suspended or prematurely terminated by the PI if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to funding agency and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the EC and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and informed of the closure of the study
Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, EC, and/or Competent Authority.
In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

12. DISCONTINUATION AND WITHDRAWAL

Participants can withdraw from the study at any time. Patients that decide to withdraw from the study will undergo mpMRI, as for clinical practice, before prostate biopsy.

12.1. Discontinuation of Trial Intervention

Patients can decide to withdraw from PET/MRI examination at any time. Patients that decide to discontinue from study intervention will be treated according to the normal clinical practice. However, data of patients that did not complete the PET/MR intervention will be discarded from the analyses.

12.2. Participant Discontinuation/Withdrawal from the Trial

Participants can withdraw from the study at any time upon request. In addition, the Investigator may discontinue or withdrawal a participant from the trial for the following reason:

- Significant protocol deviation
- Significant non-compliance with treatment regimen or trial requirements
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

The reason for participant discontinuation or withdrawal from the study will be recorded on the clinical records and in Case Report Form (CRF). Subjects who sign the informed consent form but do not perform 18F-PSMA PET/MRI examination may be replaced. Subjects who sign the informed consent form and performed 18F-PSMA PET/MRI examination, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

12.3. Lost to Follow-Up

The protocol does not include a follow-up. At Day 0 patients undergo 18F-PSMA PET/MRI examination. Then patients undergo prostate biopsy. Analysis of prostate biopsy cores is necessary to validate imaging findings and to diagnose csPCa. No further time points are considered.

13. SAMPLE HANDLING

Not applicable.

14. PATIENT SAFETY

adverse events (AE) will be recorded by a member of the research team or clinical team on an AE report form. All serious AE (SAE) will be recorded on a SAE report form. Both AE and SAE should be recorded in the medical notes.

14.1. Safety profile of the IMP

The known side effects for the IMP are reported with the relative frequencies. The safety profile of the IMP is based on the Summary of Product Characteristics and/or IB are reported below.

14.2. Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered, a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Reference: GCP ICH E6(R2)
Adverse Drug Reaction (ADR)	In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function. Reference: GCP ICH E6(R2)
Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)	Any untoward medical occurrence that at any dose: – results in death, – is life-threatening, – requires inpatient hospitalization or prolongation of existing hospitalization, – results in persistent or significant disability/incapacity, or – is a congenital anomaly/birth defect. Reference: GCP ICH E6(R2)
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. ‘‘Unexpected,’’ as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation. CFR Title 21

14.3. Adverse Event Severity Grading Scale

Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated

Grade 2	Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
Grade 4	Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5	Death	Death related to AE
Reference: Common Terminology Criteria for Adverse Events (CTCAE) version 5.0		

14.4. AE Attribution Scale

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to investigational agent/intervention	Unrelated	The AE is ***clearly NOT*** related to the intervention.
	Unlikely	The AE is ***doubtfully related*** to the intervention.
Related to investigational agent/intervention	Possible	The AE ***may be related*** to the intervention.
	Probable	The AE is ***likely related*** to the intervention.
	Definite	The AE is ***clearly related*** to the intervention.
Reference: NCI Guidelines: Adverse Event Reporting Requirements		

14.5. Procedures for Reporting Adverse Events

All AEs occurring during the safety window for the trial as defined above that are observed by the Investigator or reported by the participant will be reported in the trial CRF.
The following information will be reported in the CRF: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.
The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.
Non-serious AEs considered related to the trial medication as judged by a medically qualified investigator will be followed up either until resolution or until the event is considered stable.
It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

14.6. Reporting Procedures for Serious Adverse Events

All SAEs, defined as serious using the MedDRA (Medical Dictionary for Regulatory Activities) terms, will be reported. Using the SAE Reporting Form, the PI must communicate the SAEs to the OSR Clinical Trial Pharmacy (farmacia.trialsclinici@hsr.it) within 24 hours of becoming aware of the event.
All deaths that occur during the course of the study must always be reported to the ethics committee.

14.7. Follow-up of AE / SAE / ADR

The Investigator should take all appropriate measures to ensure the safety of the patients. Notably, they should follow up on the outcome of any event (clinical signs, laboratory values, etc.) until resolution or until the event is considered stable.
In the case of any **Serious Adverse Event or Serious Adverse Drug Reaction**, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study and that the Ethics Committee may request additional investigations.

14.8. SUSAR Reporting

SUSARs related to the IMP(s) or PeIMP(s) will be reported by the PI to the OSR Clinical Trial Pharmacy (farmacia.trialsclinici@hsr.it), within 24 hours of becoming aware of the event, using the CIOMS (Council for International Organizations of Medical Sciences) form.
Subsequently, the Clinical Trial Pharmacy will report the SUSARs to the relevant Competent Authority (via Eudravigilance) and the EC. For fatal and life-threatening SUSARS, the Pharmacy must report the SUSAR within 7 calendar days. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.
Treatment codes will be un-blinded for specific participants.
Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

14.9. Development Safety Update Reports

As part of the annual report and in accordance with IOG 226 “Farmacovigilanza negli studi clinici interventistici farmacologici no-profit promossi da OSR”, the PI will prepare the DSUR in collaboration with the Clinical Trial Pharmacy.

14.10. Unblinding Procedures

Not applicable

15. DATA MANAGEMENT

15.1. Definition of source data and source documents

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified

copies). Any data recorded directly on the CRFs (i.e., no prior written or electronic record of data), is considered to be source data.
Source Documents: Original documents, data, and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subjects' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, or records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).
All parameters asked for in the case report form (CRF) should be documented in the source documents.

A record of patient screen failures will be maintained for patients who do not qualify for enrollment, including the reason for the screen failure.

15.2. Documentation of data Case Report Forms (CRFs)

All relevant data collected during the study for all of the patients enrolled in the study shall be entered in the CRF by the responsible investigator or someone authorized by the investigator in a timely manner (as soon as possible after the information is collected) to ensure that they are clear and legible. The physician shall confirm the completeness, correctness, plausibility, and compliance with the ICH guidelines and the institutional SOPs of the data by dated signature. An explanation must be provided for any and all missing data. The entries shall be made with black ballpoint pen.
The properly filled in CRF will remain in the trial site; in case of electronic CRF, a copy of all pages will be conserved in the trial site.

15.3. Data Recording and Record Keeping

The investigator shall arrange for the retention of Essential Documents for the Conduct of a Clinical Trial (according to Chapter 8 of GCP ICH E6(R2) (e.g., patient files, other source data, and the Trial Master File) for at least 25 years after the completion or discontinuation of the study.

15.4. Data Protection

The researcher will have to keep the patient's original data and a copy of the signed written informed consent. The files will be kept in a locked closet in Nuclear Medicine Unit.

16. STATISTICS

16.1. Description of Statistical Methods

Diagnostic accuracies of 18F-PSMA PET and mpMRI will be calculated by means of sensitivity: true positive/(true positive + false negative); specificity: true negative/(false positive + true negative); PPV: true positive/(true positive + false positive);
and NPV: true negative/(true negative + false negative) using the prostate biopsy result as reference standard.

- The assessment of quantitative imaging parameters, including radiomic features and conventional parameters, characterizing regions of csPCa will be performed by generalized Linear Mixed Models for binary responses. Logistic regression will be used for evaluating PET and MRI parameters and texture features in predicting the presence of csPCa, as defined by biopsy results. To assess the diagnostic performance of PET and MRI parameters, ROC curve analysis will be performed to select optimal cut-offs in predicting the presence of csPCa, as defined by cytological examination, and the corresponding diagnostic accuracy values will be computed.
- McNemar test will be used to compare the proportion of csPCa missed by 18F-PSMA PET or mpMRI alone (12).
- All statistical analyses and data processing will be performed using the R statistical package or the SPSS software. All p-value will be rounded to three decimal places. Statistical significance will be declared if the rounded p-value will be less than 0.050. Two-sided 95% confidence intervals will be calculated.

16.2. Sample Size Determination

The sample size was computed based on sensitivity analysis for the detection of clinically significant PCa. Assuming an average prevalence of clinically significant PCa of 56%, a total sample size of 167 patients is sufficient for evaluating a sensitivity of 96% with an absolute precision of 4% (at 95% confident level).

16.3. Analysis Populations

Participants with clinical suspicion of clinically significant prostate cancer (defined by ISUP grade equal or higher than 2) referred for simultaneous 18F-PET/MR, with mpMRI, examination.

16.4. Interim Analysis

No interim analyses are planned.

16.5. Stopping Rules

Not applicable.

17. ETHICAL AND REGULATORY CONSIDERATIONS

This clinical trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments established by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice.
This clinical trial will be conducted in compliance with all international laws and regulations; national laws and regulations of the country in which the clinical trial is performed; as well as any other applicable guidelines.

17.1. Responsibilities of the Investigator(s)

The Investigator(s) undertake(s) the responsibility to perform the study in accordance with this Protocol, Good Clinical Practice, and the applicable regulatory requirements. The Investigator is required to ensure compliance with the investigational product schedule, visits schedule, and procedures required by the protocol. The Investigator agrees to provide all information requested in the Case Report Form (CRF) in an accurate and legible manner. The investigator may

implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior EC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted. The investigator must have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

17.2. Ethics Committee (EC) Approvals

This clinical trial protocol as well as the Informed Consent are to be submitted to the appropriate Ethics Committee, and it is mandatory to obtain the written and dated approval, signed by the chairman with Ethics Committee(s) composition.
The clinical trial the documents reviewed, the list of voting members and their qualifications, and the date of the review should be clearly stated on the written Ethics Committee approval.

17.3. Other Ethical Considerations

There are no additional ethical considerations to be made.

18. QUALITY ASSURANCE AND QUALITY CONTROL

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations, and standard operating procedures. A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities. Investigators involved in the study will permit study-related monitoring, audits, EC review, and regulatory inspections by providing direct access to all study records.
The Investigator should notify the CTC promptly of any inspection scheduled by any regulatory authorities and will promptly forward copies of any inspection reports received.

18.1. Monitoring

Regular monitoring will be performed, according to the Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted, and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

18.2. Deviation from study protocol

A deviation from the protocol is an unintended departure from the procedures or processes approved by the Sponsor and the EC.
The Investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The Investigator may implement a deviation from the protocol to eliminate an immediate hazard to study patients without prior IEC approval. As soon as possible after such an occurrence, the implemented deviation, the reasons for it, and any proposed protocol amendments should be submitted to the EC for review and approval, and to the regulatory authorities, if required.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Investigators will be notified in writing by the monitor of deviations. As required by local regulatory authorities, the Investigator will notify the EC of any applicable protocol deviations in a timely manner.
Every deviation from the trial protocol must be specified and documented separately for each patient. The investigator must consult with the monitor and discuss the type and extent of deviation as well as the possible consequences for further participation of the patient in the study. If the evaluability of a patient is questionable, the coordinating investigator will be consulted.

18.3. Data and Safety Monitoring Board

Not applicable.

18.4. DSMB roles and responsibilities

Not applicable.

19. FINANCE AND INSURANCE

19.1. Funding

The Italian Ministry of Health funded this study with 450000 euros. Please, refer to the project “bando ricerca finalizzata, number: RF-2021-12372278, page: 25” attached to this protocol for detailed information regarding funding.

19.2. Patient Insurance

We note that an insurance coverage, which guarantees any damage to the person deriving from the experimentation, according to the indications provided by the Ministerial Decree of Health 14 July 2009, will be activated for the entire duration of the trial. Please, refer to the attached document “Patient insurance” for details.

19.3. Contractual arrangements

Not applicable.

20. END OF CLINICAL TRIAL

In accordance with applicable regulation, ICH GCP and SOPs, the PI shall notify the end of the clinical trial within 15 days from the end of the clinical trial.
The PI shall notify a temporary halt of a clinical trial for reasons not affecting the benefit-risk balance within 15 days from the temporary halt of the clinical trial and shall include the reasons for such action. When a temporarily halted clinical trial is resumed the PI shall notify within 15 days from the restart of the temporarily halted clinical trial. If a temporarily halted clinical trial is not

resumed within two years, the expiry date of this period or the date of the decision of the PI not to resume the clinical trial shall be deemed to be the date of the end of the clinical trial. In the case of early termination of the clinical trial, the date of the early termination shall be deemed to be the date of the end of the clinical trial. In the case of early termination of the clinical trial for reasons not affecting the benefit-risk balance, the PI shall notify the reasons for such action and, when appropriate, follow-up measures for the subjects.

Upon completion or termination of the study, the study monitor will conduct site closure activities with the Investigator or site staff (as appropriate).

20.1. SUMMARY OF THE RESULTS OF THE CLINICAL TRIAL

Irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial, the PI shall submit a summary of the results of the clinical trial. The content of that summary is set out according to Annex IV of the EU regulation N° 536/2014. It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of that summary is set out in according to Annex V of the EU regulation N° 536/2014.

21. INTELLECTUAL PROPERTY

Not applicable.

22. PUBLICATION POLICY

Due to the high relevance and originality of the proposed project, the planned and developed methodology, together with the obtained results, will be objective of scientific dissemination (scientific paper in peer reviewed journals and/or presentation at medical conferences) for the scientific community in the field of Imaging, and particularly PET/MR imaging, in the field of radiomics and Urology.

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24. APPENDIX A: AMENDMENT HISTORY

Not applicable.

25. APPENDIX B: LIST OF CLINICAL SERVICES / LABORATORIES

Not applicable.