Statistical Analysis Plan

Version 3.0 07 October 2021

Protocol Title: A prospective, Phase 3, multi center, single-arm, imaging study investigating the safety and diagnostic performance of rhPSMA-7.3 (^{18}F) PET ligand in men with suspected prostate cancer recurrence based on elevated PSA following prior therapy

Protocol Number: BED-PSMA-302

Compound Number: Flotufolastat (18F) injection

Short Title: SPOTLIGHT

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Parexel International

Blue Earth Diagnostics Ltd

BED-PSMA-302

A prospective, Phase 3, multi center, single-arm, imaging study investigating the safety and diagnostic performance of rhPSMA-7.3 (^{18}F) PET ligand in men with suspected prostate cancer recurrence based on elevated PSA following prior therapy

Statistical Analysis Plan

Version: 3.0

Parexel Project Number: 245597

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Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

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TABLE OF CONTENTS

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

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Version No.	Effective Date	Summary of Change(s)
1.0	03Jul2020	Finalized document
1.1		Updated to CSP Amendment 4. Added BMI and display of amount of medication in both MBq and mCi. Removed formal hypothesis testing at interim analysis, exploratory objective and endpoint number 3. Renamed the majority decision of blinded readers from 'consensus' to 'majority'. Clarified that for Gleason score the surgery score is preferred to be used for summaries, with biopsy to be used when no surgery score available. Clarified that for TNM stage the clinical stage is preferred to be used for summaries, with pathological to be used when no clinical stage available.
2.0	22Jul2021	Updated to CSP Amendment 4. In particular, removed formal hypothesis testing at interim analysis, exploratory objective and endpoint number 3. Updates in Invicro document versions. Added BMI and display of amount of medication in both MBq and mCi. Renamed the majority decision of blinded readers from 'consensus' to 'majority'. Clarified that for Gleason score the surgery score is preferred to be used for summaries, with biopsy to be used when no surgery score available. Clarified that for TNM stage the clinical stage is preferred to be used for summaries, with pathological to be used when no clinical stage available. Added in listings for SoT and summaries concerning SoT. Added in summaries of lesion size by reader. Added in listings for rhPSMA reads and SoT reads for blinded readers who did not complete all reads. Added text stating for PPV CI and hypothesis testing asymptotic normal is used with formulas and SAS code for it. In addition added logit transform using the delta method for additional CI ensuring the whole CI will be within interval 0-1. Textual updates improving flow of text. Added Analysis Population: Evaluable PET Scan Population (EPSP)

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		Updated analysis of patient management plans. Updated that 'Other' changes in patient management plan will be classified manually by sponsor. Added Cohen's Kappa at region level. Changed the analysis for AEs with missing CTCAE grading to be summarized as missing. Added more detail on incomplete start dates for AE. Added display of lesion size. Added shift table heart rate. Added handling of missing start date of recurrence, for calculation of duration since recurrence. Clarified other region: bones, extra pelvic lymph nodes and soft tissues/parenchyma. Specified that for PSAdt only the last three measurements will be used.
3.0	Date of last signature	Imputation rule for partial missing dates for time from initial diagnosis extended to all history of current disease. Durations which hence become negative will become missing. A month is 30.4375 Days. Complete rebuild of changes of patient management plan section. Plots of PSA against Study Day will cut-off at two years. Updated errors in calculation of PSA doubling time, natural log PSA to be used in regression. Negative slopes to be missing in summaries. Values with less than sign to be imputed by removing the '<'. Added non estimable in PSAdt category. Clarified rule for SoT determination: The imaging SoT will be matched with the blinded PET reader based on the lesion ID for each reader as identified by the SoT panel, and the histopathology finding by the investigator (as recorded on CRF) will be matched with the blinded PET reader finding based on the anatomical location of the lesion, provided the histopathology is within 60 days from the PET scan. Clarified that blinded PET reader location and region will be used in analysis. Clarified that upstaging outputs concern patients with negative baseline. Updated TEAE definition from on or before Visit 3 to on or before Day 7. Changed summaries of TEAE leading to death, serious adverse events, and discontinuation will only display TEAE.

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LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
BCR	Biochemical recurrence
BED	Blue Earth Diagnostics
BMI	Body Mass Index
CDR	Correct Detection Rate
COVID19	Coronavirus disease 2019
CI	Confidence interval
CSP	Clinical Study Protocol
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DRM	Data Review Meeting
eCRF	electronic Case Report Form
EAP	Efficacy Analysis Population
FAS	Full Analysis Set
FN	False Negative
FP	False Positive
FSP	Full Safety Population
ICF	Informed consent form
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
PCa	Prostate Cancer
PET	Positron emission tomography
PLND	pelvic lymph node dissection
PP	Per Protocol Population
PPV	Positive Predictive value
PSA	Prostate-specific antigen

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Abbreviation / Acronym	Definition / Expansion
PSAdt	PSA doubling time
PSMA	Prostate-specific membrane antigen
PT	Preferred Term
RP	Radical prostatectomy
RT	Radiation therapy
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard Deviation
SOC	System Organ Class
SoT	Standard of Truth
TEAE	Treatment-emergent adverse event
TN	True Negative
TP	True Positive
WHO-DD	WHO Drug Global

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1 INTRODUCTION

Prostate Cancer (PCa) is the most prevalent cancer in men in the developed world and the third leading cause of death (Jemal 2011). It is most commonly diagnosed in men aged 65 years and over and diagnosis is often made following the detection of elevated Prostate-specific antigen (PSA) and/or an abnormal digital rectal examination, with confirmation of this diagnosis by prostate biopsy. PSA is used as a tumor marker and serum levels of PSA positively correlated with the risk of metastatic disease or subsequent disease recurrence or progression.

rhPSMA-7.3 (^{18}F) injection, is a positron emission tomography (PET) ligand for the detection of PCa. Several hundred patients with PCa have been imaged clinically, which has informed the design of this study.

As described in Clinical Study Protocol (CSP) Section 1.2, the detection rate of rhPSMA-7.3 (^{18}F) varies depending on the PSA level at scanning. The findings at Technical University of Munich are consistent with the recently published paper (Fendler 2019), describing the use of gallium-68 (^{68}Ga)-PSMA-11 in 635 patients with biochemical recurrence (BCR) of prostate cancer irrespective of the results of other imaging. They reported an overall detection rate of 75%, but stratifying for PSA levels, the detection rates were 45%, 84%, 86%, and 97% for patients with PSA levels of <1 ng/mL, 1 to <2 ng/mL, 2 to <5 ng/mL and ≥5 ng/mL, respectively.

One of the major disadvantages of the (mostly retrospective) studies to date is the lack of standard of truth confirmation for Prostate-specific membrane antigen (PSMA) PET images. Although the detection rates (defined as the number of positive scans/all included patients) are reported, it is not known if every positive scan is a True Positive (TP) scan. Ideally, both the positive predictive value (PPV) and the *Correct* Detection Rate (CDR) of PET findings should be known. The CDR is defined as the percentage of all patients scanned who have at least one **TP** lesion (localized correspondence between rhPSMA-7.3 (^{18}F) PET imaging and the reference standard) regardless of any coexisting False Positive (FP) findings.

Most trials investigating diagnostic PSMA ligands have thus far focused on those patients with prior negative conventional imaging. Going forward in routine clinical care, given the low sensitivities of these conventional imaging procedures, it is difficult to continue to support subjecting patients to two or three non-sensitive imaging procedures before the patient may receive a more sensitive one. Based on the retrospectively determined high sensitivity of PSMA ligands, this study is designed to establish the performance of rhPSMA-7.3 (^{18}F) PET irrespective of the findings of conventional imaging in order to support the use of rhPSMA-7.3 (^{18}F) as an imaging option during the initial workup of these patients. This study by Blue Earth Diagnostics (BED) will do so acknowledging the limitations of obtaining proof of true-positivity of the PSMA-positive lesions given the difficulties of obtaining histopathology in all patients and the relative insensitivity of other imaging modalities. Therefore, CDR and PPV are set at reasonable threshold levels, accounting for the limitations of the Standard of Truth (SoT) and considering the significant influence of the PSA level on the scan's performance.

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP). In case of discrepancies between Study Protocol and SAP the SAP supersedes the Study Protocol.

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The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 4.0 (23 Oct, 2020)
- Electronic Case Report Form (eCRF), Version 3.0 (17 Aug, 2020)
- Invicro Independent Review Charter (IRC), Version 3.0 (21 April , 2021)
- Invicro Technical Operations Manual Version 2.0 (04 Aug, 2020)
- Invicro Review Session Methodology: Conventional Imaging Version 2.0 (21 Apr 2021)

The following guidance document has been used:

- Guidance for Industry and FDA Staff - Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests (13 March 2007)

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of the study is to assess the patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET for BCR of PCa using histopathology or imaging as a SoT. The CDR is defined as the percentage of all patients scanned who have at least one TP lesion (localized correspondence between rhPSMA-7.3 (^{18}F) PET imaging and the reference standard) regardless of any coexisting FP findings. When determining the region level PPV, all rhPSMA-7.3 (^{18}F) PET-positive regions will be categorized as TP or FP regions using histopathology or imaging.

2.2 Secondary Objective(s)

The secondary objectives of the study are to:

1. Assess the patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET in the subgroup of patients who have negative baseline conventional imaging (classified at the site level).
2. Assess the patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET separated into subgroups of patients with reference standard histopathology available and unavailable.
3. Assess the patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET stratified by PSA level.
4. Assess the CDR of rhPSMA-7.3 (^{18}F) PET on a region level.
5. Assess the impact of rhPSMA-7.3 (^{18}F) results on the intended clinical management of study participants using a clinician survey.
6. Assess the inter- and intra-reader agreement of rhPSMA-7.3 (^{18}F) scan interpretation by the blinded independent readers.
7. Assess the safety of rhPSMA-7.3 (^{18}F) injection in patients.

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2.3 Exploratory Objective(s)

The exploratory objectives of the study are to:

1. Assess the overall detection rate (without SoT confirmation) on a patient level and including detection rate subgroup analyses of patients: a) who have negative baseline conventional imaging, b) with reference standard histopathology available and unavailable, and detection rate stratified by PSA level and assessed by region.
2. Assess the patient level PPV in which a TP patient is defined as having at least one TP region, regardless of any coexisting FP regions.
3. Assess the impact of rhPSMA-7.3 (^{18}F) PET on upstaging patients with BCR of PCa a) post-Radical prostatectomy (RP) or b) post-Radio therapy (RT) compared to conventional imaging.
4. Assess patient and regional level detection rates of rhPSMA-7.3 (^{18}F) PET.
5. Assess patient and regional level detection rates of rhPSMA-7.3 (^{18}F) PET as a function of PSA, prior Gleason score, and PSA doubling time (PSAdt) in a) post-RP or b) post-RT patients.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a prospective, Phase 3, multicenter, single-arm, diagnostic imaging study designed to evaluate the safety and diagnostic performance of rh-PSMA7.3 (^{18}F) PET ligand for imaging in men with suspected BCR of PCa based on elevated PSA following prior therapy.

Given the observed difference in performance of PSMA ligands in patients with PSA levels <1 ng/mL versus ≥1 ng/mL, the patient population will be weighted to prevent over-representation of patients with a PSA <1 ng/mL. The proportion of patients with a PSA <1 ng/mL will be capped at approximately 40% of total study population, which is consistent with the study population studied by Fendler (2019). Once 60% of the planned 190 positive cases have PSA level recorded in the eCRF , the proportion of included patients with a PSA <1 ng/mL will be assessed. If this proportion exceeds 60% then investigators will be told to stop further enrolment of this cohort.

Patients with a diagnosis of BCR of PCa being worked up for re-staging and eligible for potential salvage treatment will be consented and enrolled. Patients who meet all the inclusion criteria and none of the exclusion criteria will be entered into the study. Participation in this study does not replace conventional imaging required for staging as per local guidelines/standard of care. If not already completed within 90 days before Visit 1, standard of care conventional imaging will be performed following Visit 1 and up to 2 weeks after Visit 2 (Optional Visit 2(a)). Conventional images that have been obtained at non-participating institutions will be accepted as historical or baseline. After enrollment (either before or after conventional imaging if not already completed), patients will receive an administered activity of 8 mCi (296 MBq) ± 20% of rhPSMA-7.3 (^{18}F), delivered as an intravenous (IV) bolus injection with a 10 mL fast 0.9% sodium chloride flush, followed by a PET/CT scan.

Note: Due to the COVID-19 pandemic, the screening/eligibility evaluation can (if necessary) take place on the same day as rhPSMA-7.3 (^{18}F) administration (with pre-screening via telephone) after

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obtaining written informed consent to ensure the safety of subjects (see Visit 1 and 2 combined; Section 10.3). Alternatively, the time interval from Visit 1 (initial screening) to Visit 2 (rhPSMA-7.3 (^{18}F) PET scan) may be extended up to 45 days due to the COVID-19 pandemic if preferred by the site investigator.

Up to 45 days following rhPSMA-7.3 (^{18}F) PET imaging and if feasible, the patient will undergo image-guided biopsy of any PET-positive lesion(s) suspicious for confirming recurrence of PCa (this may be extended up to 60 days due to the COVID-19 pandemic, see Section 3.2.1 and CSP Section 10.5, Appendix 1).

If necessary, confirmatory (for SoT) imaging will be performed within 45 days following rhPSMA-7.3 (^{18}F) PET imaging or attempted biopsy according to the algorithm in Figure 1 (may be extended up to 60 days due to the COVID-19 pandemic). If necessary, additional confirmatory imaging may be performed up to 90 days after rhPSMA-7.3 (^{18}F) PET. Note: in patients with multiple PET-positive regions, confirmation of at least one PET positive lesion in each region is required either by biopsy/surgical resection or confirmatory imaging. Patients may receive salvage treatment following further consultation with their physician (outside the scope of this study). The salvage treatment prescribed will be recorded. If treatment consists of a surgical resection, any histology obtained will be correlated with rhPSMA-7.3 (^{18}F) PET imaging. Follow-up confirmatory imaging performed for the SoT assessment should not delay the patient's treatment.

For the primary endpoint rhPSMA-7.3 (^{18}F) PET images will be blinded, randomized, and read by three trained independent central PET readers who have received specific training on rhPSMA-7.3 (^{18}F) scans and are blinded to results of the patient's conventional and /or confirmatory imaging. The Invicro Independent Review Charter Version V3.0 (April 21 2021) and Review Session Methodology: Conventional Imaging V2.0 (April 21 2021) specify the image review process and data flow for both conventional and rhPSMA-7.3 (^{18}F) PET images. PET positive lesions, as determined by the blinded, central read, will be subjected to the SoT algorithm to determine the patient level CDR and region level PPV. The patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET will be compared to set values, see Section 4.16, with study success based upon exceeding the pre-specified thresholds for both CDR and PPV.

PET scan reads by additional independent central PET readers who do not complete the full set of reads will be listed only. Results of SoT based on PET scan results from readers who did not complete will be listed only.

Adverse events (AEs) were monitored throughout the study. Vital sign assessments were conducted at screening (Visit 1) and pre- and post-rhPSMA-7.3 (18F) administration on the day of injection (Day 1; Visit 2).

The full schedule of activities is given in Section 6.2 (Appendix).

3.2 Standard of Truth

Any one of the following will determine SoT: If a positive lesion on PET is confirmed by one of the Steps (1 to 4) listed below, the lesion will be considered TP.

When determining the PPV on a region level, a region will be categorized as a TP if there is at least one TP lesion confirmed in that body region (prostate bed, pelvic lymph nodes, or other (bones, extra-pelvic lymph nodes, and soft tissue/parenchyma), regardless of any other co-existing FP lesions in that region.

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When determining the CDR on a patient level, a patient will be categorized as a TP if there is at least one TP lesion confirmed in at least one body region (prostate bed, pelvic lymph nodes, or other sites [bones, , extra pelvic lymph nodes and soft tissues/parenchyma]) on rhPSMA-7.3 (^{18}F) PET, regardless of any other co-existing FP lesions. For the primary analysis, pelvic lymph nodes will include the right and left external iliac, obturator, hypogastric (internal iliac), perirectal and presacral lymph node groups.

Notes:

a. In patients with multiple PET-positive regions, confirmation of at least one PET positive lesion in each region is required either by biopsy/surgical resection or confirmatory imaging in order to calculate the region level PPV for the efficacy analyses.

b. In patients with multiple lesions in a specific region, the presence of one TP lesion determines truth for the region regardless of any concurrent FP findings in the same region. Therefore, multiple PET positive lesions can be evaluated in a specific region in order to confirm at least one TP.

3.2.1 **Step 1: Histological SoT**

Histological confirmation should be obtained whenever possible:

a) Of PET-positive lesion.

b) Of biopsy or surgically removed sample.

Re-biopsy (in case of inconclusive histology) or biopsy of a second lesion will be allowed.

If histology is not available or determined non-diagnostic (and re-biopsy not possible) then proceed with imaging confirmation as described below (Steps 2 to 4). If biopsy histology is negative, then images acquired during the procedure will be reviewed by local readers to ensure the targeted tissue was sampled. If local readers determine the biopsy placement was correct, then the biopsy results will stand. If local readers determine the targeted tissue was missed during the biopsy procedure, then either a re-biopsy will be performed, or the following steps will also be undertaken to verify rhPSMA-7.3 (^{18}F) images.

3.2.2 **Steps 2 to 4: Imaging as Standard of Truth**

Imaging as SoT should include a longitudinal assessment of all available historical, baseline and confirmatory imaging scans. Any change over time at the PET-positive site (upon review of all available imaging) suggestive of the presence of cancer will be accepted as the SoT. A change suggesting the disappearance of disease at the PET-positive site following treatment will also be accepted as the SoT (objective criteria defined in the study Independent Review Charter).

3.2.2.1 Step 2: Historical and Baseline Conventional Imaging SoT

If historical conventional images (as defined in CSP Section 9.1.5.2) had been acquired prior to acquisition of the baseline conventional images as part of the patient's PCa management, then these images can be used along with baseline to establish the SoT.

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Where historical conventional images (e.g. Computed tomography [CT], Magnetic resonance imaging [MRI], bone scan, PET) are available that could be relevant to confirmation of an identified rhPSMA-7.3 (^{18}F) PET-positive lesion then as many prior imaging series as practical (from approximately the last 2 years) should be made available to the central reviewers.

In cases where historical imaging and baseline conventional images are deemed sufficient (by local site reader) for SoT determination, then this will be acceptable, and follow-up confirmatory imaging (Steps 3 and 4) will not be needed.

3.2.2.2 Step 3: Confirmatory Imaging SoT (up to 45 Days Post-rhPSMA-7.3 (^{18}F) PET)

In cases where, in the opinion of the local site reader, historical conventional images are not available or are inconclusive in comparison to baseline imaging, rhPSMA-7.3 (^{18}F) directed (for confirmation of lesion location only) follow-up confirmatory imaging of the site(s), will be acquired. Confirmatory imaging will be acquired at the discretion of the local investigator(s), with reference to the Technical Operations Manual.

3.2.2.3 Step 4: Additional Confirmatory Imaging SoT (up to 90 Days Post-rhPSMA-7.3 (^{18}F) PET)

If in the opinion of the local investigator(s) the above imaging Steps 2 or 3 do not allow SoT verification, then a final follow-up, rhPSMA-7.3 (^{18}F) PET directed (for confirmation of lesion location only) confirmatory imaging scan can be obtained up to 90 days post rhPSMA-7.3 (^{18}F) PET.

Reading of conventional and confirmatory imaging to determine the next steps in the confirmation process will be performed locally.

Both the rhPSMA-7.3 (^{18}F) PET scans and all available conventional (historical and baseline) and confirmatory imaging scans acquired under Steps 2 to 4 above will be read centrally for the primary endpoint assessment, according to Table 1 and Figure 1 below. Reads of the conventional and confirmatory imaging as SoT will be directed by rhPSMA-7.3 (^{18}F) PET findings (for confirmation of lesion location only) and performed by different readers than the blinded, independent rhPSMA-7.3 (^{18}F) interpretations. Three central reviewers will review all submitted images and reach consensus on the nature of the PET positive target lesion(s). A brief summary of clinical information will be made available to the readers (e.g. 67-year-old male post-RP with pelvic lymph node dissection (PLND) and adjuvant pelvic RT 5 years before; PSA rising to 1.2 ng/mL prior to rhPSMA-7.3 (^{18}F) scan; PSAdt 9 months). Readers will be blinded to all other information. Further details are given in the study Independent Review Charter.

rhPSMA-7.3 (^{18}F) positive lesions will be categorized by the consensus central SoT read as positive, negative or indeterminate using all available conventional and confirmatory imaging. Indeterminate classifications will be categorized as False Positives for the primary analysis. Further details are given in the study Independent Review Charter.

If a positive lesion on rhPSMA-7.3 (^{18}F) PET is confirmed by SoT, the lesion will be considered TP. For the primary efficacy analysis, a region will be categorized as a TP if at least one rhPSMA-7.3 (^{18}F) PET positive lesion is confirmed in that body region (prostate bed, pelvic lymph nodes or other [bone, extra-pelvic lymph nodes and soft tissues/parenchyma] sites), regardless of any coexisting FP lesions in that region. For the primary analysis, pelvic lymph nodes will include the right and left external iliac, obturator, hypogastric (internal iliac), perirectal and presacral lymph node groups.

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If all above SoT techniques fail to positively confirm the PET-positive lesion(s), the rhPSMA-7.3 (^{18}F) PET lesion will be deemed FP.

Table 1: Central Reading Plan

Imaging	Modalities	Image Interpretation	# Readers	Read Criteria
rhPSMA-7.3 (^{18}F)	rhPSMA-7.3 (^{18}F) PET	Blinded, independent, central reads	3	Further details are given in the Study Independent Review Charter
Conventional (Baseline and Historical) and Confirmatory Imaging as SoT	Conventional: Pelvic CT or MRI, bone scan, chest CT, Axumin. Confirmatory: Examples include: specific body region MRI (including functional or multi-parametric MRI), CT, Axumin, NaF PET, etc.	rhPSMA-7.3 (^{18}F) directed, consensus image reads. A brief summary of clinical information will be available to the readers (e.g. 67 year old male post-RP with PLND and adjuvant pelvic RT 5 years before; PSA rising to 1.2 ng/mL prior to rhPSMA scan; PSAdt 9 months). Readers will be blinded to all other information.	3 via consensus	Longitudinal assessment of all available conventional and confirmatory imaging scans per standard of care / society guidelines. Further details are given in the study Independent Review Charter. Specifically allowing, for example: a) sub-cm changes in LN size on CT during progression/therapy response to be indicative of cancer or b) small bone CT scleroses to be indicative of cancer

CT=computed tomography; ^{18}F=fluorine-18; LN=lymph node; MRI=magnetic resonance imaging; NaF=sodium fluoride; PET=positron emission tomography; PLND=pelvic lymph node dissection; PSA=prostate-specific antigen; PSAdt=prostate specific antigen doubling time; rhPSMA=radiohybrid prostate-specific membrane antigen; RP=radical prostatectomy; RT=radiation therapy.

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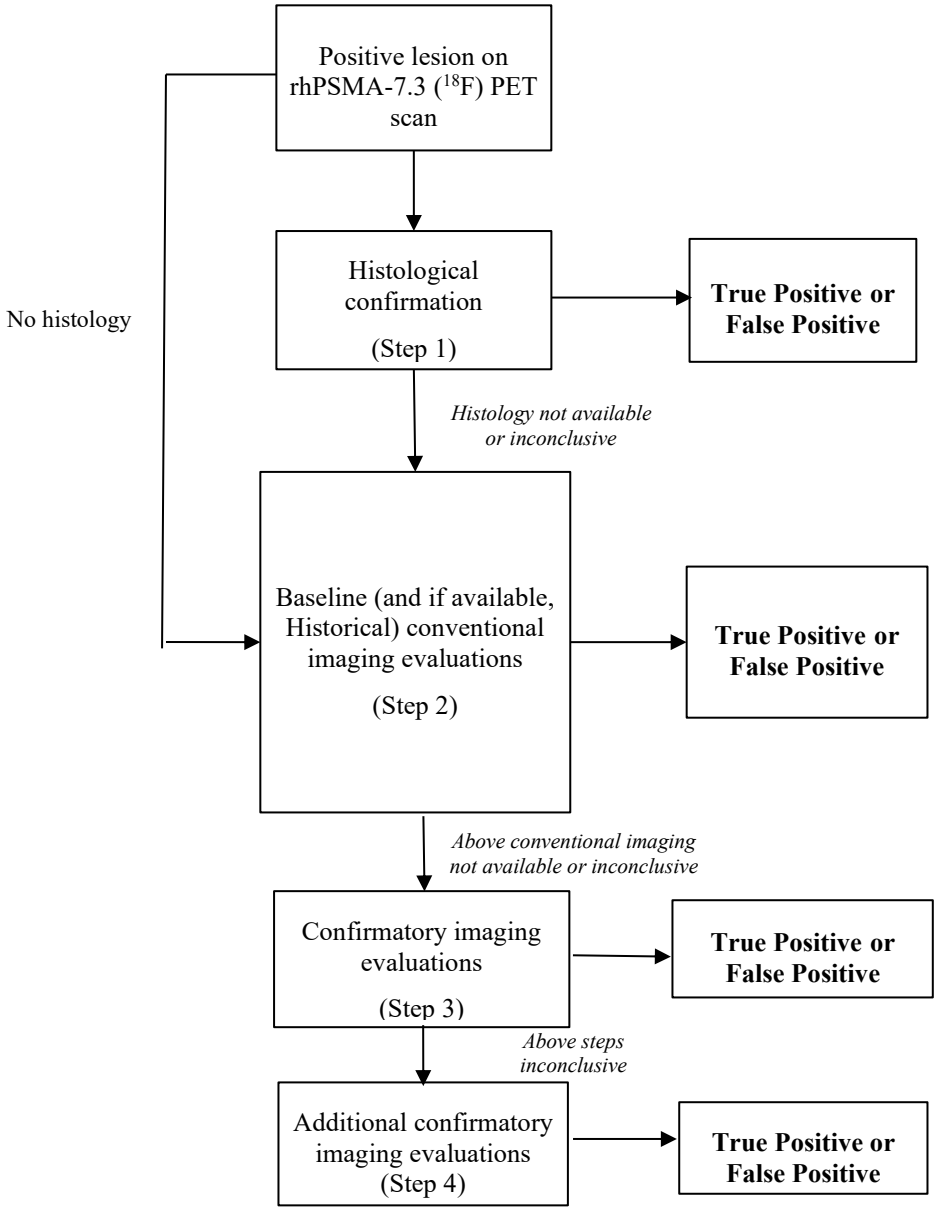
Figure 1: Standard of Truth Algorithm (to be applied for each PET-positive region)



18F=fluorine-18; FP=False Positive; PET=positron emission tomography; PPV=Positive predictive value; rhPSMA=radiohybrid prostate-specific membrane antigen; TP=True Positive.
Notes:
a) In patients with multiple PET-positive regions, confirmation of at least one PET positive lesion in each region is required either by biopsy/surgical resection or confirmatory imaging in order to calculate the region level PPV for the efficacy analyses.
b) In patients with multiple lesions in a specific region, the presence of one TP lesion determines truth for the region regardless of any concurrent FP findings in the same region. Therefore, multiple PET positive lesions can be evaluated in a specific region in order to confirm at least one TP.

3.3 Endpoints

3.3.1 Primary Efficacy Endpoint

The co-primary endpoints for the study are the (1) patient level CDR defined as the percentage of all patients scanned who have at least one TP lesion (localized correspondence between rhPSMA-7.3 (18F) PET imaging and the reference standard) regardless of any coexisting FP findings and (2) region level PPV (defined as TP/{TP+FP}) of rhPSMA-7.3 (18F) PET. Histopathology (preferred method)

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or imaging will be utilized as the SoT (see Section 3.2.1). A lesion that is deemed positive for PCa based on rhPSMA-7.3 (^{18}F) PET will be assessed using the algorithm described in Figure 1.

3.3.2 **Secondary Endpoints**

The secondary endpoints for this study will be:

3.3.2.1 Efficacy Variables

1. Patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET in the subgroup of patients who have negative baseline conventional imaging.
2. Patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET for recurrence in those patients with and without reference standard histopathology available.
3. Patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET stratified by PSA level.
4. CDR of rhPSMA-7.3 (^{18}F) PET in the following regions: local recurrence, pelvic lymph nodes, other.
5. Percentage of patients in whom rhPSMA-7.3 (^{18}F) PET imaging results changed the intended patient management (major and other changes).
6. Reader kappa statistics of rhPSMA-7.3 (^{18}F) scan interpretation by the blinded independent readers.

3.3.2.2 Safety Variables

1. Safety (AEs and vital signs) of rhPSMA-7.3 (^{18}F) injection in patients.

3.3.3 **Exploratory Endpoints**

The exploratory endpoints for this study will be:

1. The overall patient level detection rate (without SoT confirmation), including detection rate subgroup analyses of patients: a) who have negative baseline conventional imaging, b) with reference standard histopathology available and unavailable, and detection rate stratified by PSA level and assessed by region.
2. Patient level PPV in which a TP patient is defined as having at least one TP region, regardless of any coexisting FP regions.
3. The number of positive rhPSMA-7.3 (^{18}F) scans compared to conventional imaging in defined regions, leading to upstaging of the patient a) post-RP; b) post--RT.
4. Patient and regional level detection rates of rhPSMA-7.3 (^{18}F) PET.
5. Patient and regional level detection rates of rhPSMA-7.3 (^{18}F) PET as a function of PSA, prior Gleason score and PSAdt in a) post--RP; b) post--RT patients.

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

'Baseline' is defined as the last available pre-IP administration assessment, with the exception of baseline imaging which may be performed up to 2 weeks following IP administration if conventional imaging has not been performed within 90 days prior to enrolment.

'End of Study' is defined as the last available post-treatment assessment.

'Study Day' will be calculated relative to the date of rhPSMA-7.3 (^{18}F) injection day, and is equal to:

- Assessment Date – IP Administration Date + 1 if the assessment date is on or after IP administration date.
- Assessment Date – IP Administration Date, if the assessment date is before IP administration date.

(i.e. rhPSMA-7.3 IP Administration Date = Study Day 1, the day before IP administration date = Study Day –1))

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. Continuous data (e.g. counts) that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic, irrespective of the previous rules.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Confidence intervals (CI) will be presented to one more decimal place than the raw data, CI for percentages will be to one decimal place.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

4.3 Software

All report outputs will be produced using SAS® version 9.3 or a later version in a secure and validated environment.

4.4 Study Subjects

4.4.1 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion as per CONSORT guidance.

The following summaries will be made.

- A summary of the number of subjects screened for entry into the study and the number and percentage of subjects excluded prior to IP administration by major reason and overall (Analysis set: All Enrolled Subjects)
- A summary of the number of subjects enrolled per center, and per country (Analysis set: Full Analysis Set (FAS))
- A summary of the number of subjects who received IP, number of subjects who had an evaluable PET scan following IP administration, and the number and percentage of subjects withdrawing from the study and completing each phase. (Analysis set: FAS).
- A summary of withdrawals from the study and from IP administration by major reason (Analysis set: FAS).

By-subject listings of center, eligibility details, visit dates (including impact of COVID-19 on visit), and withdrawal/study completion details (including reason for discontinuation and time since IP administration prior to discontinuation), informed consent form (ICF) date will be provided using the FAS.

4.4.2 Protocol Deviations

Protocol deviations will be handled in accordance with Parexel Standard Operating Procedures (SOPs).

Protocol deviations occur when the patient, investigator, or Sponsor fails to adhere to significant protocol requirements or where there is a significant non-compliance to ICH-GCP, affecting patient safety or the scientific value of the trial.

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. The impact of major protocol deviations on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by major protocol deviations.

Major protocol deviations and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification which

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

is agreed and signed off before analysis. All deviations and implication on inclusion of analysis populations are discussed prior to study lock in a data review meeting (DRM).

Major protocol deviations which lead to withdrawal and replacement of the subject include:

- Failure to meet inclusion/exclusion criteria (see CSP Sections 6.2 and 6.3).
- IP administration but no subsequent PET scan.
- Significant non-compliance with IP administration,

The initiation of any targeted or systemic therapy prior to definitive pathology for satisfying the SoT assessment may also be deemed a major protocol deviation (depending on patient specifics); these will be assessed on a patient by patient basis by the medical and statistical teams.

Deviations due to COVID-19 will be listed separately.

4.5 Analysis Sets

All enrolled patients: all patients who signed the informed consent form.

Full Analysis Set (FAS): all patients who were scheduled to receive the rhPSMA-7.3 (^{18}F) injection having met the inclusion/exclusion criteria or have received rhPSMA-73 (^{18}F) injection.

Full Safety Population (FSP): all patients who received the rhPSMA-7.3 (^{18}F) injection.

Efficacy Analysis Population (EAP): all patients who received rhPSMA-7.3 (^{18}F) injection followed by a PET/CT scan and for whom sufficient data are available to permit a clear classification following the SoT algorithm.

Per Protocol Population (PP): All evaluable patients in the EAP population without major protocol deviations which could affect the primary endpoint.

Evaluable PET Scan Population (EPSP): All patients who received the rhPSMA-7.3 (^{18}F) injection with a PET scan.

All safety analyses will be performed using the FSP. The primary analysis of CDR and PPV will be based on the EAP.

A summary of patients in each population will be given, including a breakdown of populations by center.

Upon database release, protocol deviation and analysis set outputs will be produced and will be sent to BED for review. An analysis set classification meeting will be arranged to discuss the outputs and to decide which subjects and/or subject data will be excluded from certain analyses. Decisions made regarding the exclusion of subjects and/or subject data from analyses, and the agreement of population inclusion for each patient, will be made prior to locking the database and will be documented and approved by BED.

A summary of the number and percentage of subjects entering and completing each phase of the study for each analysis set will be provided. Analysis set used: FAS.

A by-subject listing of analysis set details will be provided. This listing will include center, subject identifier, and inclusion/exclusion flag for each set and reason for exclusion from each set. All

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

subjects screened appear on this listing. If subject data has been partially excluded, visit will also appear on this listing.

4.6 Demographic and Other Baseline Characteristics

The demographics and baseline characteristics will be summarized using the FAS.

The following summaries will be provided:

- Demographics: age at informed consent (including age groups of <65, ≥65 and the subgroup of ≥75), sex, ethnicity, race and height. Weight at screening and weight and Body Mass Index (BMI) on Day 1 will be in the summary.
  - BMI will be calculated as $BMI(kg/m^2) = \frac{weight\ (kg)}{height\ (m)^2}$
- History of current disease:
  - Time (months) from initial diagnosis of prostate cancer to informed consent Time (months) since diagnosis of biochemical recurrence.
  - Time (months) since Start date of prior curative intent treatment with or without adjuvant therapy
  - Time (months) since End date of prior curative intent treatment with or without adjuvant therapy
  - Duration (months) of prior curative intent treatment with or without adjuvant therapy
  - For each of these durations, Dates with missing day will be imputed with 15th, dates with missing month and day will be imputed with 01 Jul to obtain the duration. If this results in a negative duration, duration will be missing.
  - A month is assumed to take 30.4375 days.
- Medical history

By subject listings of demographics and baseline characteristics will be provided

4.7 Patient management plans

Patient intended treatment at baseline (before rhPSMA-7.3 (^{18}F) PET imaging) and post rhPSMA-7.3 (^{18}F) PET imaging will be listed by subject and time point. The listing will show planned treatments and include details on therapy as applicable, by Subject, Center and Visit. A summary of planned treatment at baseline and post PET imaging (but before confirmatory imaging) by Center and overall will be provided using the FAS.

The options in the intended management plan are:

- Watchful Waiting / Active Surveillance
- Androgen-Deprivation Therapy
- Radiotherapy
- Cryotherapy
- Brachytherapy
- HIFU
- Prostatectomy
- Lymph Node dissection

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

- Other

The options in the revised management plan are:

- Watchful Waiting / Active Surveillance
- Androgen-Deprivation Therapy
- Radiotherapy
- Cryotherapy
- Brachytherapy
- HIFU
- Prostatectomy
- Targeted treatment of PSMA positive extra-pelvic / bony areas
- Chemotherapy / Immunotherapy
- Lymph Node dissection
- Other

The intended management plan and revised management plan will be compared, and assigned to one of the following categories, for each patient:

- No Change
- Major Change
- Other Change
- Additional Information Required
- Intended Plan Not Valid

The assignment of the category and sub-category in change in management plan to each subject will be performed manually by Blue Earth Diagnostics team, using the SDTM data on the intended and revised management plans provided by Parexel as the source data. An Excel file containing the unique subject ID, category and sub-category in change in management plan.

Patients who have intended management plan but no revised management plan will be considered as having no change in management plan. This is because the question “Is the management plan revised after PSMA scan results available:” is ambiguous – when the site selects “no” as the answer, it is unclear whether this means there is no revision to the management plan, or the management plan after PSMA scan results is not available.

The use of the phrase “revised management plan” for the management plan after the PSMA scan results can be confusing also, because the management plan is not “revised” as such if it is the same as the intended management plan. Therefore the “intended management plan” and the “revised management plan” will be reworded to “pre-PSMA management plan” and “post-PSMA management plan”, to clearly indicate that the analysis is to compare the management plans before and after PSMA respectively.

The pre-PSMA management plan and post-PSMA management plan will be compared, and assigned to one of the following categories in Table 2, for each patient with both pre-PSMA and post-PSMA plans.

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

Table 2: Changes in Management Plan

Change in Management Plan Category	Definition
No Change	When there is no change from the pre-PSMA management plan to the post-PSMA management plan, because: • The options selected in the pre-PSMA management plan are equivalent to the options selected in the post-PSMA management plan, or • There is a pre-PSMA management plan, and the post-PSMA management plan leading question "Is the management plan revised after PSMA scan results available:" is answered as "no", or there is no post-PSMA management plan.
Major Change	When the main options in the pre-PSMA management plan are different from the main options selected in the post-PSMA management plan, and the post-PSMA management plan is clearly a treatment plan.
Minor Change	When the main options in the pre-PSMA management plan and post-PSMA management plan are the same, but there are some differences in the details (e.g. different radiation fields for radiotherapy)
Additional Information Required	When the main options in the pre-PSMA management plan are different from the main options selected in the post-PSMA management plan, but the post-PSMA management plan indicates additional diagnostic procedures to be performed (e.g. MRI or biopsy before a decision on treatment plan is taken), or the post-PSMA management plan does not contain clear choice of treatment plan.
Intended Plan Not Valid	When the pre-PSMA plan does not contain sufficient or clear information on the treatment plan prior to PSMA, or the pre-PSMA plan date is after day 1 (PSMA administration date)

The subcategories in "major change" will be assigned manually using Table 3.

Table 3: Subcategories for Major Change

"Major Change" Subcategories	Definition of the subcategory
Salvage or non-curative systemic therapy to watchful waiting	Pre-PSMA Management Plan: Any categories other than "Watchful Waiting / Active Surveillance" Post-PSMA Management Plan: "Watchful Waiting / Active Surveillance" only

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

"Major Change" Subcategories	**Definition of the subcategory**
Salvage therapy to non-curative systemic therapy	Pre-PSMA Management Plan: Any categories other than "Watchful Waiting / Active Surveillance", "Androgen-Deprivation Therapy", "Chemotherapy / Immunotherapy" or any other therapies which are not considered as non-curative systemic therapy Post-PSMA Management Plan: "Androgen-Deprivation Therapy" or "chemotherapy/immunotherapy" or any other therapies which are considered as non-curative systemic therapy
Watchful Waiting to Salvage or non-curative therapy	Pre-PSMA Management Plan: "Watchful Waiting / Active Surveillance" only post-PSMA Management Plan: Any categories other than "Watchful Waiting / Active Surveillance"
Alternative major change	Major change that does not meet the definition of the above subcategories.

"Minor change" is defined as a change in therapy within the same category from the pre-PSMA management plan to the post-PSMA management plan. The following subcategories in "minor change" will be assigned manually upon review of the data using Table 4

Table 4: Subcategories for Minor Change

"Minor Change" Subcategories	**Definition of the subcategory**
Modified RT field plan	Pre-PSMA Management Plan and post-PSMA Management Plan both contain Radiotherapy (may include other therapy/therapies, as long as there is no change in these therapies)
Modified Androgen-Deprivation Therapy Regimen	Pre-PSMA Management Plan and post-PSMA Management Plan both contain Androgen-Deprivation Therapy only
Alternative other change	Pre-PSMA Management Plan and post-PSMA Management Plan have the same category / categories selected, but the details within the categories have changed.

4.8 Medication and Prostate Cancer Surgical Procedure history

Medication and/or procedure start and stop dates will be compared to the date of IP administration to allow medications/procedures to be classified as either Prior only, both Prior and Concomitant, or

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

Concomitant only. Medications and/or procedures starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications/procedures that start and stop prior to the date of dose of IP administration will be classified as Prior only. If a medication/procedure starts before the date of IP administration and stops on or after the date of IP administration, then the medication/procedure will be classified as both Prior and Concomitant. Medications/procedures will be classified as Concomitant only if they have a start date on or after the date of first dose of study medication.

If medication/procedure start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of IP administration. Medications/procedures will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication/procedure started prior to the IP administration. If there is clear evidence to suggest that the medication/procedure started prior to the IP administration, the medication/procedure will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication/procedure stopped prior to the IP administration. If there is clear evidence to suggest that the medication/procedure stopped prior to the IP administration, the medication will be assumed to be Prior only.

Medications will be coded using WHODrug Global Dictionary and summarized by ATC code (levels 2 and 4) and Preferred term and listed by subject using the FAS. In case of missing level 4 coding the level 3 coding will be used.

Medications for prostate cancer will be summarized and listed separately.

Procedures will be summarized by System Organ Class (SOC) and Preferred Term (PT) using MedDRA dictionary and listed by subject.

For some endpoints subjects with Radical Prostatectomy (RP) and Prior Radiotherapy (RT) will be selected. The identification of subjects with RP or RT will be derived from the Procedures (PR) eCRF page:

- A subject is considered to have had RP if PT contains the phrase “Radical prostatectomy” or “Prostatectomy”.
- A subject is considered to have had RT if PT contains the phrase “Radiotherapy”, or equal to “Brachytherapy” or “Brachytherapy to prostate”

Concomitant medication will be coded using WHODrug Global (WHODD) WHODD_Global_01Sep2019_B3.

Procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA) 22.1.

All summaries will be performed using the FSP

4.9 Staging, Gleason score and Gleason Grade Group

Staging, Gleason score and categorization will be analyzed using the FAS.

TNM staging at baseline (pathological or clinical if no pathological available) will be summarized by type. In addition, a summary by center will be provided.

TNM staging will be listed by patient and center.

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

Frequency of total Gleason score will be summarized, using score from surgery as primary result and biopsy if no surgery available. Scores below 6 will be combined to a score of ⩽6 in summary tables. Primary, secondary and total Gleason scores will be listed by patient and center.

Gleason Grade Group is defined by the International Society of Urological Pathologists, and the categories are as follow:

- Grade Group 1 is defined as Total Gleason score ⩽6
- Grade Group 2 is defined as Gleason score 3+4=7
- Grade Group 3 is defined as Gleason score 4+3=7
- Grade Group 4 is defined as Total Gleason score of 8
- Grade Group 5 is defined as Total Gleason scores 9-10

Gleason Grade group (using surgery or biopsy if no surgery is available) will be summarized.

For any analysis by TNM stage, pathologic will be used, while clinical will be used if no pathologic is available. For any analysis by Gleason Grade group or Gleason Score the surgery Gleason will be used while biopsy will be used if no surgery is available. TNM staging will be displayed at observed level and combined at levels T2, T3, T4, M0, M1, MX, where each of these contain underlying categories (i.e. T2 -All contains subjects with observed at T2, T2a, T2b, T2c)

4.10 PSA

PSA will be analyzed using the FAS.

Most recent PSA level will be summarized as a continuous variable.

An additional summary of PSA level will be by prior therapy based on PT. Each patient will be in one category only.

- Prior Prostatectomy (as defined in section 4.8). This includes all patients who had other therapies (including radiotherapy), as long as they had prostatectomy.
- Prior Radiation Therapy (as defined in section 4.8). This excludes patients with previous prostatectomy.
- Other: Neither Radiation Therapy nor Prostatectomy.

A plot (spaghetti plot) showing subject PSA against Study Day (relative to PET scan) by center. PSA will be listed by patient date, and study day, with a cut-off of two years (day -730).

In addition, PSA will be categorized using the categories: PSA<0.5, 0.5≤ PSA<1.0, 1.0≤PSA<2.0, 2.0≤PSA<5.0, 5.0≤PSA<10.0, 10.0≥PSA (ng/mL). A frequency table of the categories with proportion will be provided overall. These same categories will be used for analysis of subgroups on PSA level. In case of categories with low counts a category may be merged with an adjacent category in order to have at least five patients in each category.

The PSA doubling time will be calculated by first doing regression of historical natural log PSA on date of PSA measurement and subsequently division of natural log 2 (0.693) by the slope, using the last 3 values in the 2 years prior to PSMA dosing in the model. A month is assumed to take 30.5 days. In case there are not 3 acceptable measurements in the prior 2 years then no doubling time will be provided. Negative slopes will be missing in summaries.

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

In case of incomplete dates for PSA measurement, for the doubling time calculation the date may be imputed or the measurement may be ignored, based on the following rules:

- If the day part is missing but the month and year are known, then the 15th of the month will be used.
- If the day and month parts are missing, then the PSA measurement will be ignored.

In case of less than PSA values (e.g. '<0.1') the numerical value will be used after removal of the '<' character.

PSAdt will be categorized using the categories PSAdt<6, 6≤PSAdt<12, 12≤PSAdt<24, 24≤PSA (months) and not estimable (for non changing and decreasing PSA [slope <=0]). This same categorization will be used for the analysis of subgroups on PSAdt.

All PSA results (including a flag if PSA is used for the PSAdt calculation) and all PSAdt , slope, number of points used and date range used [dates and duration {months}]) will be listed by patient, center and date.

4.11 Biopsy/Surgery

If rhPSMA-7.3 (^{18}F) PET shows one or more sites of recurrence, the most accessible and feasible (as judged by the local investigator) lesion(s) will be biopsied under radiological guidance. In patients with multiple rhPSMA-7.3 (^{18}F) PET-positive regions, attempts should be made, where safe and medically feasible, to obtain histopathology on the most accessible and feasible lesion(s) in each region (prostate bed, pelvic lymph nodes, and other [bone, extra-pelvic lymph nodes, soft tissues/parenchyma]).

In cases where a patient will undergo a lymph node dissection or other surgical procedure (resection of the PET-positive lesion(s)) as part of their standard of care, a biopsy prior to the surgical procedure is not required. The histology obtained following surgery will serve as the SoT. The removed surgical samples will be carefully correlated to rhPSMA-7.3 (^{18}F) PET and the conventional imaging technique(s).

Biopsy/Surgery will only be analyzed in the context of efficacy endpoints.

A listing of Biopsy/Surgery including histopathology results will be provided by subject, region and lesion. PET positive lesions for which no biopsy is performed will not be listed.

4.12 Conventional Imaging

4.12.1 Baseline Conventional Imaging

Baseline standard of care conventional imaging may include: planar and/or single-photon emission CT bone scan (^{99m}technetiumhydroxydiphosphate [^{99m}TcHDP], ^{99m}technetium-methyldiphosphonate [^{99m}TcMDP] per institution preference), abdominal/pelvic CT or MRI, chest CT per institution preference, or PET with (^{18}F-NaF or Axumin). Baseline conventional imaging that has been performed within 90 days prior to enrollment at non-participating institutions will be accepted (when available) provided the scans are reviewed by the participating institution.

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

If not already completed within the 90 days before enrollment, baseline standard of care conventional imaging will be performed at the study site, between Visit 1 and up to 2 weeks following the rhPSMA-7.3 (^{18}F) PET scan according to site standard of care. Any conventional imaging performed up to 90 days prior to Visit 1 and up to and including Visit 2(a) will be considered baseline conventional imaging.

Baseline conventional imaging will be listed including modality, and imaging result for each scan performed.

Baseline conventional imaging result will be summarized by modality and overall using the FAS. Conventional imaging methods which are infrequently used may be combined for summary purposes, based upon the judgement of the Biostatistician. In case of replication of modality within a subject, a negative will be counted if all results are negative while a positive will be counted if any result is positive.

4.12.2 **Historical Conventional Imaging**

Historical conventional imaging acquired more than 90 days before Visit 1, if available and if performed as part of the patient's PCa staging and treatment in the prior ~24 months, can be used along with baseline conventional imaging to establish SoT where a biopsy cannot be obtained.

Patients will be asked to provide these pre-existing images to the study site, if these were done at another institution. If done at the study site, these images will be made available by the study site. Historical conventional imaging will be listed by date and modality. Imaging results of historical conventional imaging will only be utilized in the determination of SoT.

4.12.3 **Confirmatory Imaging**

In cases where baseline and historical (when available) conventional imaging are inconclusive for SOT determination, rhPSMA-7.3 (^{18}F) directed (for confirmation of lesion location only) follow-up confirmatory imaging of the site(s), will be acquired at the discretion of the local investigator(s), with reference to the Study Imaging Manual. Examples of confirmatory imaging modalities include specific body region MRI (including functional or multi-parametric MRI), CT, Axumin, ^{18}F-NaF, etc. Confirmatory imaging will be listed by date, modality and anatomical location. Imaging results of confirmatory imaging will only be utilized in the determination of SoT.

4.13 **Exposure and Treatment Compliance**

A subject listing of rhPSMA-7.3 (^{18}F) treatment including total administered activity, injection site reactions, local imaging results, incidental findings, clinical review and evaluations of independent blinded central PET readers will be provided.

A summary of total administered activity will be provided using the FAS and PP. All activity will be shown in MBq and mCi using the conversion 1mCi=37 MBq.

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

4.14 rhPSMA-7.3 (^{18}F) Image reading

Each rhPSMA-7.3 (^{18}F) image will initially be read by a site-based local reader. In addition, for the primary endpoint analysis, imaging will be read by three blinded independent PET readers (see the study Independent Review Charter for further details). The results of the blinded PET readers will be used in the primary analysis, thus requiring each (statistical) analysis to be performed three times. In addition, the majority interpretation will be displayed.

Majority will be determined on both a region and patient level. The region level majority looks at the region level decision by the blinded independent PET readers within each region, independent of anatomical location within the region. Thus, if two or three readers identify a positive lesion within a region, the majority for the region will be positive. In addition, if SoT panel confirms a positive lesion, the majority would be TP, otherwise majority would become FP. The patient level analysis will ignore region, meaning that if two or three readers find any positive lesion for a patient, the majority for the patient will be positive.

Table 5: Derivation of Overall Interpretation (2 out of 3 readers majority)

Reader 1	Reader 2	Reader 3	Majority
Positive	Positive	Positive	Positive
Positive	Positive	Negative	Positive
Negative	Negative	Positive	Negative
Negative	Negative	Negative	Negative

PET imaging results (i.e. positive/negative) will be summarized using EPSP by anatomical location by category and anatomical location within category. Categories will be prostate, pelvic lymph nodes, lymph nodes outside of pelvis, soft tissue/parenchyma and bones. All categories will be presented in the summary, but anatomical locations will only be presented where data are collected, i.e. lesion investigated in that anatomical location.

Any PET scan reads by additional independent central PET readers who do not complete the full set of reads will be listed only.

4.15 Standard of Truth

The SoT algorithm is explained in Section 3.2.

The SoT of PET positive lesions identified by local investigator will be listed by subject, region and lesion showing each of the four steps, as applicable, including final assessment (positive/negative/unknown). Lesions for which only part of the SoT steps are performed will be listed including the step(s) which is/are not performed. Lesions for which no SoT is performed will be listed including Step 1 and 2.

The central read of SoT will be listed by subject and will include SoT proven, with reason(s) for justification. In addition, a listing will be provided showing the modality of the reason, combining

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

local histology and central read consensus reasons. Finally, a listing will be made of lesion size, including detection by blinded PET reader. The central SoT read will be summarized by region.

The SoT of PET positive lesions identified by the blinded independent PET readers will be listed by subject, reader, region and lesion, showing result for either of three steps: Histological SoT (Step 1) or historical and baseline Imaging SoT (Step 2) or confirmatory Imaging SoT (Step 3 and 4). Any PET positive lesion deemed not a TP according to the SoT will be declared a FP.

The SoT at a region level will be listed by subject, blinded PET reader and region, including SoT result. Regions where no lesion(s) were identified will not be listed. PET positive regions where no SoT positive lesions are present will be FP. PET positive regions with one or more SoT positive lesion(s) will be TP. PET negative regions with one or more SoT positive regions will be FN.

The SoT at a region level will be summarized by blinded PET reader and region using the EAP. The summary will include the number of subjects with positive lesions per region, the number of TP, FP patients per region, the PPV for the regions, including 95% two-sided CIs using the clustered binary data algorithm (Section 4.16.1.3).

Patient level SoT will be listed by subject, blinded PET reader, including result. Patients where no positive lesion(s) were identified by both PET and SoT will not be listed.

Patient level SoT will be summarized by blinded PET reader using the EAP. The summary will include the CDR, including two-sided exact 95% CIs.

An additional summary will show at which step the SoT was determined by the local investigator.

Central read of SoT involving the blinded independent PET readers who did not complete the full set of rhPSMA-7.3 (^{18}F) PET reads will only be listed.

The imaging SoT will be matched with the blinded PET reader based on the lesion ID for each reader as identified by the SoT panel, and the histopathology finding by the investigator (as recorded on CRF) will be matched with the blinded PET reader finding based on the anatomical location of the lesion. Histopathology finding will only be used if within a 60 days window relative to the PET scan. Location and region of lesions as determined by the blinded PET reader will be used in all listings and tables.

4.16 Efficacy Evaluation

4.16.1 Analysis and Data Conventions

This study success criteria are based upon the diagnostic performance of rhPSMA-7.3 (^{18}F) PET exceeding pre-specified minimum thresholds for the co-primary endpoints of patient level CDR and region level PPV. The joint hypothesis, based on the assumptions as outlined in Section 4.18.1, is as follows:

$$H_0: \text{CDR} \leq 36.5\% \text{ or PPV} \leq 62.5\% \text{ versus } H_1: \text{CDR} > 36.5\% \text{ and PPV} > 62.5\%$$

For CDR, exact intervals and exact binomial tests will be used in the analysis.

As PPV is a by-region endpoint, patients may have one to three regions that may be included in the PPV assessment. Thus, variance estimated will be adjusted based on clustering of regions within a patient (Zhou, Obuchowski, and McClish, (2002), pg 104). An asymptotic normal distribution will be used to test the PPV hypotheses.

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For the study to be considered a success, the p-values for both endpoints must be statistically significant (P<0.025) for at least two out of the three blinded image evaluation readers (same readers for both CDR and PPV).

4.16.1.1 Parameters of efficacy

Considering the definition table (Table 6), based on the categorization of lesions, the patients and regions can be categorized.

Table 6: Definitions of true and false positive and true and false negative lesions

		True assessment		
		Positive	**Negative**	**Total**
PET scan assessment	**Positive**	TP	FP	TP+FP
	Negative	FN	TN	FN+TN
	Total	TP+FN	FP+TN	N (=FP+TP+TN+FN)

FN=False Negative, TN=true Negative

The data does not provide separate counts of TN and FN, however, the sum of TN and FN is known, as this is the number of PET negative scans or patients. N is therefore the total number of patients with PET scan assessment.

CDR is defined as the percentage of all patients scanned who have at least one TP lesion. Hence CDR=TP/N.

PPV is defined as the regions which are true positive out of all regions with positive region. Hence PPV=TP/(TP+FP).

Detection rate is the proportion of PET scan positive relative to total (number of patients or number of regions, depending on endpoint). Hence this is (TP+FP) out of the total population (which would be N for the EAP).

4.16.1.2 Handling of missing data

4.16.1.2.1 Primary analysis

Patients who have no positive lesions identified by the blinded independent PET readers do not have missing data. They will not be counted for PPV as they are neither TP nor FP. They will count in the denominator of CDR, since they are either FN or TN.

Positive lesions which do not get confirmed via the SoT will be designated as FP by the SoT algorithm. By extension, positive lesions which are missing both histopathology and sufficient scans to determine the SoT will be declared FP.

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4.16.1.2.2 Other

Section 4.8 contains information on date imputation to decide if medications and procedures are prior or concomitant.

Section 4.17.1 contains information on date imputation to decide if an AE is treatment emergent. It also describes imputation for missing toxicity grading or causality.

Section 4.10 contains information on date imputation for calculation of PSAdt.

4.16.1.3 Clustered binary data estimate of variance

Following Zhou et al. the following estimators will be used:

$$\widehat{PPV} = \sum_P TP_p \Big/ \sum_P Pos_p$$

$$\widehat{Var}\left(\widehat{PPV}\right) = \frac{1}{P(P-1)} \sum_P \left({Pos_p}/{\overline{Pos}} \right)^2 \left(\widehat{PPV_p} - \widehat{PPV}\right)^2$$

With:

P	: (number of) Patients
p	: individual patient
Pos_p	: Number of positive regions for patient p
TP_p	: Number of true positive regions for patient p
$\overline{Pos} = \sum_P Pos_p / P$	: Mean cluster size
$\widehat{PPV_p} = TP_p / Pos_p$	: Patient PPV

The example in Zhou et al. is coded in SAS in Appendix 6.1.

An asymptotic normal distribution for the sampling distribution of $\widehat{PPV}$ is assumed and the 95% confidence interval will be derived as:

$$\widehat{PPV} \pm Z_{1-\alpha/2} \sqrt{\widehat{Var}(\widehat{PPV})}$$

where $Z_{1-\alpha/2}$ is the upper 1-α/2 value for the standard normal distribution.

Furthermore, p-value for the primary hypothesis test will be obtained by

$$\text{p} - \text{value} = 1 - \Phi\left(\widehat{PPV} - 0.625 \Big/ \sqrt{\widehat{Var}(\widehat{PPV})} \right)$$

Where Φ() is the CDF of the standard normal distribution calculated at the critical point.

4.16.1.3.1 Additional Confidence interval

Normal approximation in constructing 95% CIs might lead to bounds exceed [0, 1] for $\widehat{PPV}$. Hence an additional CI will be derived. Logit transformation will be applied to PPV and Delta Method (Casella and Berger, 2021) will be utilized to obtain to approximate the variance of $logit(PPV)$. Accordingly, the asymptotical distribution of $logit(PPV)$ is

$$\sqrt{n}\left[log\left(\frac{\widehat{PPV}}{1-\widehat{PPV}}\right) - log\left(\frac{PPV}{1-PPV}\right)\right] \xrightarrow{d} \text{N}\left(0, \frac{1}{[PPV(1-PPV)]^2} Var\,(PPV)\right).$$

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Accordingly, an asymptotic normal distribution for the sampling distribution of $logit(\widehat{PPV})$ is assumed and the 95% confidence interval will be derived as:

$$logit(\widehat{PPV}) \pm Z_{1-\alpha/2}\sqrt{\widehat{Var}(logit(\widehat{PPV}))}$$

where $Z_{1-\alpha/2}$ is the upper 1-α/2 value for the standard normal distribution and $\sqrt{\widehat{Var}(logit(\widehat{PPV}))} \approx \frac{1}{[\widehat{PPV}(1-\widehat{PPV})]^2}\widehat{Var}(\widehat{PPV})$. Lower and upper confidence intervals values will be reported in [0,1] scale by the logit inverse transformation, as follows

$$CI_{[0,1]\,scale} = \frac{e^{CI\_logit}}{1+e^{CI\_logit}}$$

4.16.1.4 Multi-center Studies

This study will be conducted at approximately 35 sites in the United States (US) and Europe. To avoid confusion between the terms investigative sites and body sites, this document, as well as all summaries and analyses in statistical outputs, will use the word 'center' for study investigative sites. Since the primary endpoint will be determined on histopathology and centralized reading, the centers will not be part of the primary endpoint analysis.

A number of endpoints will have additional analyses by center; this will be indicated on a case by case base within each analysis. For these analyses, centers with small numbers of patients may be combined, for instance to country level. This combining will be identical for all applicable analyses.

4.16.1.5 Adjustments for Covariates

There will be no adjustment for covariates in the primary analysis.

4.16.1.6 Interim Analyses

Once 60% of the planned 190 positive cases have PSA levels recorded in the eCRF, the proportion of included patients with a PSA <1 ng/mL will be assessed. If this proportion exceeds 60% then investigators will be told to stop further enrolment of this cohort. There will be no formal TFL delivery for this interim.

4.16.2 **Primary Efficacy Variable**

The primary analysis will be performed using the EAP.

The joint hypothesis is as follows:

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H_0: CDR ≤36.5% or PPV ≤62.5% versus H_1: CDR >36.5% and PPV >62.5%

Both CDR and PPV will be displayed using a point estimate (expressed in percentage), two sided 95% CIs and a one-sided 2.5% hypothesis test for each reader.

For CDR, the two-sided 95% CIs will be exact intervals. A one-sided exact binomial test p-value will be provided for each reader for each CDR.

For PPV, the 95% CIs and p-values will be estimated using clustered binary data methodology (Section 4.16.1.3). Both CIs and binomial test p-value will be displayed for each reader.

For the study to be considered a success, the p-values for both endpoints must be statistically significant (one-sided 0.025) for at least two out of the three readers (same readers for both CDR and region level PPV). The analysis will be based on the p--value cut-offs applied to both endpoints at the interim and final analysis, if needed (Section 4.16.1.6).

In addition to the individual blinded readers, their majority CDR and PPV will be analyzed (see Section 4.14 for majority assessment).

4.16.3 **Secondary Efficacy Variables**

4.16.3.1 Patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET in the subgroup of patients who have negative baseline conventional imaging.

This will be a repeat of the primary efficacy using patients from the EAP with negative baseline conventional imaging (according to site reads). The point estimates and two-sided 95% CIs of CDR and PPV will be displayed for each of the blinded independent readers and their majority.

4.16.3.2 Patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET for recurrence in those patients with and without reference standard histopathology available.

For CDR, this will be repeats of the primary efficacy using patients from the EAP and one more condition:

1. Patients with standard histopathology for SoT assessment
2. Patients with no standard histopathology for SoT assessment

For PPV, this will be repeats of the primary efficacy using patients from the EAP and one more condition:

1. Regions with standard histopathology assessment
2. Regions with no standard histopathology assessment

The point estimates and two-sided 95% CIs of CDR and PPV will be displayed for each set of patients for each of the blinded independent readers and their majority.

4.16.3.3 Patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET stratified by PSA level.

This will be repeats of the primary efficacy using patients from the EAP. The last PSA level before the PET scan will be used to stratify the patients (see Section 4.10 for categories). The point estimates

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and two-sided 95% CI of CDR and PPV will be displayed for each set of patients for each of the blinded independent readers and their majority.

4.16.3.4 CDR of rhPSMA-7.3 (^{18}F) PET in the following regions: local recurrence, pelvic lymph nodes, other.

This analysis will use the EAP. The analysis will be performed for each region and for each of the blinded independent readers and their majority. The frequency of confirmed detection will be summarized, including proportion and exact CI of the proportion.

4.16.3.5 Percentage of patients in whom rhPSMA-7.3 (^{18}F) PET imaging results changed the intended patient management (major and other changes).

This analysis considers patients in the EAP who have documented patient management plans in the EDC for before and after the rhPSMA-7.3 (^{18}F) PET scan. Major and other changes in management plan (see section 4.7) will be summarized showing frequency, proportion (including 95% CI) overall.

4.16.3.6 Reader kappa statistics of rhPSMA7-.3 (^{18}F) scan interpretation by the blinded independent readers.

This analysis considers all patients within the EPSP.

4.16.3.6.1 Inter-reader agreement analysis

The Cohen's kappa statistic will be calculated to assess pairwise agreement between any 2 readers, including 95% exact CIs, giving 3 Kappa statistics (SAS® nomenclature: simple kappa). In addition, the Fleiss' kappa across the 3 readers, including 95% (approximate) CIs will be shown (SAS® nomenclature: overall kappa Coefficient).

This same calculation will be repeated for the regions:

Prostate/Prostate Bed

Pelvic Lymph Nodes

Other Sites

Other: Lymph nodes outside pelvis

Other: Soft Tissue/parenchyma

Other: Bones

4.16.3.6.2 Intra-reader agreement analysis

Cohen's Kappa will be used to assess intra-reader agreements in the first read and the repeat read of 10% of the randomly selected images for each of the three readers.

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4.16.4 Exploratory Efficacy Variables

4.16.4.1 The overall patient level detection rate (without SoT confirmation), including detection rate subgroup analyses of patients: a) who have negative baseline conventional imaging (according to site read), b) with reference standard histopathology available and unavailable, and detection rate stratified by PSA level and assessed by region.

This concerns several similar analyses. In each analysis the frequency of patients with a PET positive lesion will be counted, proportion of positive patients including exact CI will be provided. Each analysis will be performed for each of the blinded independent readers and their majority.

- patients in the FSP who have PET scan and who have negative (no lesions detected at all) baseline conventional imaging.
- patients in the FSP who have PET scan and have reference standard histopathology.
- patients in the FSP who have PET scan and do not have reference standard histopathology.
- For each region (local recurrence, pelvic lymph nodes, other) patients in the FSP who have PET scan using subgroups by PSA levels (Section 4.10).

4.16.4.2 Patient level PPV in which a TP patient is defined as having at least one TP region, regardless of any coexisting FP regions.

This concerns all patients in the EAP. The patient level PPV frequency and proportion, including exact CIs will be provided for each of the blinded readers and their majority.

4.16.4.3 The number of positive rhPSMA-7.3 (^{18}F) scans compared to conventional imaging in defined regions, leading to upstaging of the patient a) post-RP; b) post--RT.

This concerns patients with negative baseline scan in subgroups of the EAP with an extra subgroup condition, for a) the patient has had RP (with or without RT), for b) the patient has had RT (without RP) or c) patient has other therapies. (For definitions of RT and RP, see Section 4.8). The patients will be counted if they have any TP lesion in either of the regions (local recurrence, pelvic lymph nodes, other) for each of the blinded readers and their majority.

4.16.4.4 Patient and regional level detection rates of rhPSMA-7.3 (^{18}F) PET.

This concerns the subgroup of patients in the FSP who have a PET scan. The regions analysis will concern local recurrence, pelvic lymph nodes and other. The frequency of detection, detection rate including exact CI will be determined for each of the blinded readers and their majority.

4.16.4.5 Patient and regional level detection rates of rhPSMA-7.3 (^{18}F) PET as a function of PSA, prior Gleason score and PSAdt in a) post-RP; b) post-RT patients.

This concerns patients in subgroups of the EPSP with an extra subgroup condition, for a) the patient has had RP, for b) the patient has had RT (see Section 4.8). The regions analysis will concern local

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recurrence, pelvic lymph nodes and other. Patients will be analyzed by PSA category (Section 4.10), by total (biopsy and surgery) Gleason score (Section 4.9) and by PSAdt category (Section 4.10) for each of the blinded readers and their majority.

4.16.4.6 Reading by lesion size

Size of smallest and largest rhPSMA-7.3 (^{18}F) PET positive lesions (short axis, long axis) will be summarized using EAP.

4.17 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Set as defined in Section 4.4.

4.17.1 Adverse Events

Adverse events will be coded using the MedDRA Version 22.1 or higher.

Treatment-emergent adverse events (TEAEs) will be tabulated and are defined as those AEs that either start or worsen in severity on or after the date/time of IP administration and on or before Day 7.

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the AE started prior to the first IP administration or more than 7 days after the IP administration.

In particular this means the following rules will be applied until a classification is given:

1. An AE with a missing start date and missing end date will be a TEAE
2. An AE with a missing start date and end date after IP administration will be TEAE
3. A start date with a missing year but month present will be assumed to have a year such that the start date is after informed consent and before Day 90. If these rules conflict then the rule 'after informed consent' prevails.
4. An AE will not be a TEAE if the start date is incomplete and
    a. The end date of the AE is before the dosing date, or
    b. The end date/time of an AE is before the dosing date/time, or
    c. The day of the AE end date is missing and the month of the AE end date is before the month of dosing date
5. An AE will not be a TEAE if the AE start day of month is missing and
    a. The last day of the AE start month is before the dosing date, or
    b. The first day of the AE start month is more than 7 days after dosing (and thus the AE starts after Day 7)

All AE summaries will provide the number of subjects reporting at least one AE and the total number of events reported.

The following summaries will be provided:

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- A summary of the number and percentage of subjects reporting an adverse event, including counts of TEAEs, IP-related TEAEs, serious AE (SAEs) and IP-related SAEs.
- A summary of the number and percentage of subjects reporting a TEAE by SOC, and PT
- A summary of the number and percentage of subjects reporting a TEAE by Common Terminology Criteria for Adverse Events (CTCAE) grade, SOC and PT
- A summary of the number and percentage of subjects reporting a TEAE by causality, SOC and PT

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within an SOC and then alphabetically for SOC, and PT within SOC.

For each subject and each adverse event, the worst CTCAE Toxicity grade (Version 5) recorded will be attributed and used in the by-severity summaries. If CTCAE grade is missing, the any other non-missing grade will be considered as worst. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries. If causality is missing, the worst case will be assumed.

A by-subject listing of all adverse events (including non-treatment-emergent events) will be provided. This listing will include: center, subject identifier, age, sex, race, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, duration, CTCAE, seriousness, action taken, outcome and causality.

4.17.2 **Deaths, Serious Adverse Events, and Other Significant Adverse Events**

Deaths, SAEs, and Other Significant AEs will be listed and summarized if numbers allow.

The following summaries are planned.

- A summary of the number and percentage of TEAEs leading to deaths during the study
- A summary of the number and percentage of subjects reporting a serious TEAE, by SOC and PT
- A summary of the number and percentage of subjects with TEAEs leading to discontinuation of study treatment, by SOC and PT

The following listings will be created:

- A by-subject listing of all deaths that occurred during the study
- A by-subject listing of all SAEs
- A by-subject listing of all AEs leading to discontinuation of study treatment

Listings will follow the format described for AEs in Section 4.17.1.

4.17.3 **Clinical Laboratory Evaluation**

Not applicable.

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

4.17.4 Vital Signs

Vital signs will be listed, including change from baseline. Baseline will be the last assessment before dosing, this is planned to be Visit 2 (Day 1).

A summary of each vital sign parameter, including change from baseline by time point will be given.

Heart rate category (<40 bpm, 40-59 bpm, 60-100 bpm, 101-130 bpm, >130 bpm) will be part of the listing, summarized and a shift table will be presented.

4.17.5 Other safety

A summary of injection site reactions during or immediately after the dose will be provided.

4.17.6 Safety Monitoring (Independent Data Monitoring Committee [IDMC], Data Monitoring Committee [DMC], Data and Safety Monitoring Board [DSMB])

Not applicable.

4.18 Determination of Sample Size

4.18.1 Key Assumptions

Consistent with the data described in CSP Section 2, the detection rate of rhPSMA-7.3 (^{18}F) PET in patients with a PSA level ≥1 ng/mL is expected to be at least 75%. The anticipated PPV in this population is expected to be approximately 80%. Therefore, the expected CDR in this subpopulation is (75% × 80% =) 60%.

However, in the subpopulation with a PSA level <1 ng/mL, the detection rate is expected to be approximately 45%. The PPV is also expected to be lower (approximately 65%), since it will be more difficult to obtain proof of the lesions detected (as outlined in CSP Section 2). Therefore, the CDR in this subpopulation is estimated to be low at (45% × 65% =) 29%.

It is planned to include approximately 40% of patients with a PSA level <1 ng/mL and approximately 60% with a PSA level ≥1 ng/mL. Therefore, it is anticipated that the study will demonstrate an overall detection rate of approximately 60%, an overall PPV of at least 73.5% (taking into account multiple positive regions is anticipated in a proportion of patients), and, hence, an overall CDR of 49% (point estimates).

4.18.2 Sample Size

Approximately 316 patients will be enrolled in this study. For the PPV endpoint, based on a one-sided 0.025 exact binomial test and assuming a true PPV of 73.5%, a sample size of 190 positive cases provides >88% power for the evaluation of region level PPV (H_0: PPV ≤62.5%). Assuming that 60% of all scans have a positive finding, a total of approximately 316 evaluable patients would be

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required to obtain 190 positive rhPSMA-7.3 (^{18}F) PET cases. Note that the PPV region-based analysis is expected to provide more than 88% power based upon the number of positive regions per patient being >1, even adjusting for the correlation between the regions within a patient. Thus, 316 patients are planned to be enrolled in order to get at least 190 cases with disease detected with rhPSMA-7.3 (^{18}F) and an evaluable result.

For the patient level CDR endpoint, based on a one-sided 0.025 exact binomial test and assuming a true CDR of 49%, a sample size of 316 cases provides >99% power for the evaluation of CDR (H_0: CDR ≤36.5%).

Hence, a sample size of at least 316 patients is adequate based on the region level PPV endpoint and is expected to provide at least 90% power for the regional PPV analysis.

4.19 Changes in the Conduct of the Study or Planned Analysis

The EPSP has been added in the analysis populations for analyzing the PET scan imaging irrespective of standard of truth.

4.19.1 Changes in the Conduct of the Study or Planned Analysis Due to COVID-19

This study was conducted during the COVID-19 global pandemic (the official date of the pandemic being over has not been identified at the time of writing this SAP), which may have influenced study conduct at the investigational sites.

Missed visits and any data collection interference will be captured on a specific page of the CRF and protocol deviations due to COVID-19 will be listed separately. Any impact on the populations, endpoints and analyses will be assessed and reported on in the CSR under a specific section.

5 References

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DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

6 Appendix

6.1 SAS program to reproduce data in Zhou et al [6].

```
data one;
input TN      No_Polyps;
Cards;
1       1
2       2
2       2
1       1
2       2
2       2
1       1
1       1
1       1
1       1
2       2
0       1
2       3
2       2
1       1
1       1
1       1
2       2
1       2
0       2
1       1
2       2
2       2
2       2
0       1
;;;;
run;

proc sql;
   create table two as
      select
         TN ,
         No_Polyps,
         TN/No_Polyps as Sei_hat,
         Se_hat,
         No_Polyps/mNo as Ni_N,
         (calculated Ni_N)*(calculated Ni_N)
             * (calculated Sei_hat-Se_hat)* (calculated Sei_hat-Se_hat) as fc,
         sum(calculated fc) as sfc,
         calculated sfc/(n*(n-1)) as varSe_hat
      from
         (select
            sum(TN) as sTN,
            sum(No_Polyps) as sNo,
            mean(No_Polyps) as mNo,
            count(*) as n,
            calculated sTN/calculated SNo as Se_hat
            from one ) as o,
         one;
quit;

data final;
   set two;
   if _n_=1;
   CI_L = Se_hat - (quantile('NORMAL', .975)*varSe_hat**0.5);
   CI_U = Se_hat + (quantile('NORMAL', .975)*varSe_hat**0.5);
   p_value = 1 - CDF('NORMAL', (Se_hat-0.625)/varSe_hat**0.5);
   keep Se_hat varSe_hat CI_L CI_U  p_value;
run;
```

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6


```
data final_logit;
   set final;
   logit_Se_hat = log(Se_hat/(1-Se_hat));
   logit_varSe_hat = varSe_hat*((1/(Se_hat*(1-Se_hat)))**2);
   logit_CI_L = logit_Se_hat - (quantile('NORMAL', .975)*logit_varSe_hat**0.5);
   logit_CI_U = logit_Se_hat + (quantile('NORMAL', .975)*logit_varSe_hat**0.5);
   logit_zero_one_CI_L = (CONSTANT('E')**logit_CI_L)/((CONSTANT('E')**logit_CI_L)+1);
   logit_zero_one_CI_U = (CONSTANT('E')**logit_CI_U)/((CONSTANT('E')**logit_CI_U)+1);
run;
```

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

6.2 Study Schedule

				FOLLOW-UP PROCEDURES	
	VISIT 1 SCREENING (DAY -28)	**VISIT 2 (Day 1)***	**VISIT 3 FOLLOW-UP (up to Day 7)****	**UP TO DAY 45*****	**UP TO 90 DAYS**
Informed Consent	**X**				
Review of Inclusion/Exclusion Criteria	**X**				
Demographics	**X**				
Medical History	**X**[a]				
Height (at screening only)	**X**				
Weight	**X**	**X**			
Collect Historical Conventional Imaging[b]	**X**				
Acquire Conventional Imaging[b], Between Visit 1 and up to 2 weeks after Visit 2	**X (IF NOT YET OBTAINED)**	**X**			
Record Adverse Events	**X**	**X**	**X**	**X**	**X**
Concomitant Medication Review	**X**	**X**	**X**	**X**	**X**
Vital Signs (blood pressure, pulse, respiration rate, temperature)	**X**	**X**[c]			
Administration of IP		**X**			
Drug Accountability		**X**			
Post-IP PET Scan		**X**[d]			
Clinical Review			**X**		
Image-guided Biopsy Report[e]				**X**	
Surgery (with histology report)				**X**	
Record Salvage Therapy[f]				**X**	

DocuSign Envelope ID: 0CC20355-C4E4-44A8-B282-9FFD208622C6

				FOLLOW-UP PROCEDURES	
	VISIT 1 SCREENING (DAY -28)	**VISIT 2 (Day 1)***	**VISIT 3 FOLLOW-UP (up to Day 7)****	**UP TO DAY 45*****	**UP TO 90 DAYS**
Follow-up Confirmatory Imaging[g]				**X**	
Additional Follow-up Confirmatory Imaging [h]					**X**

CT=computed tomography; ^{18}F=fluorine-18; FP=False Positive; IP=investigational product; MRI=magnetic resonance imaging; NaF=sodium fluoride; PCa=prostate cancer; PET=positron emission tomography; PPV=positive predictive value; rhPSMA=radiohybrid prostate-specific membrane antigen; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SoT= Standard of Truth; SPECT=single-photon emission computed tomography; ^{99m}Tc-HDP=^{99m}technetium-hydroxydiphosphonate; ^{99m}Tc-MDP=^{99m}technetium-methyldiphosphonate; TP=True Positive.

* Due to the COVID-19 pandemic, Visit 1 and Visit 2 may be combined (Visit 1 and Visit 2 combined) if judged by the investigator to be necessary to decrease exposure to SARS-CoV-2 and COVID-19 for patients and/or feasibility of the study. For all patients enrolled through the Visit 1 and Visit 2 combined pathway, pre-screening via telephone contact with the patient is required prior to Day 1 to review the study eligibility criteria, obtain initial consent (remote consent is acceptable), and to promote study visit compliance and ensure patient understanding of the combined study visits and planned IP administration, as well as inquire about baseline and historic conventional imaging that may already have been performed or needs to be scheduled. Full written informed consent will be taken on Day 1 (Visit 1 and Visit 2 combined). For sites with on-site manufacturing, the visits may be combined if convenient to the Radiopharmacy and investigator even post-COVID-19 pandemic restrictions.

  Alternatively, the time from Visit 1 (initial screening) to Visit 2 (rhPSMA-7.3 (^{18}F) PET scan) may be extended to 45 days due to the COVID-19 pandemic if preferred by the site investigator.

** Visit 3 Follow-up should be performed within 7 days post-IP administration and may be performed by an appropriately qualified and credentialed clinician and can be conducted by telephone per the site investigator's discretion.

*** If feasible, the patient will undergo image-guided biopsy of a PET-positive lesion(s) suspicious for recurrence of PCa within 45 days following rhPSMA-7.3 (^{18}F) PET imaging (may be extended to Day 60 due to the COVID-19 pandemic). If biopsy is not feasible, confirmatory imaging should be performed, if indicated, as per algorithm.

a To include medical history and concomitant disease record, including a history of PCa, diagnosis date and prior PCa treatments, as well as confirmation of a history of localized adenocarcinoma of the prostate with prior curative intent treatment.

b Conventional imaging may include: planar and/or SPECT bone scan (^{99m}Tc-HDP, ^{99m}Tc-MDP per institution preference), abdominal/pelvic CT or MRI, chest CT per institution preference, or PET with ^{18}F-NaF or Axumin. Conventional imaging that has been performed at non-participating institutions will be accepted provided the scans are reviewed by the participating institution. If not already completed up to 90 days before inclusion, conventional imaging will be performed at the study site according to site standard of care (to take place following Visit 1 and up to 2 weeks after Visit 2). Historical imaging if available and if performed as part of the patient's PCa care (including approximately the past 2 years) can be used to establish SoT where a biopsy cannot be obtained. Patients will be asked to provide these pre-existing images if these were done at another institution. If done at the study site, these images will be made available by the study site.

c Vital signs to be recorded at pre-IP administration and post-IP administration.

d For full details see the Study Imaging Manual.

e If feasible, patients will undergo image-guided biopsy of a PET-positive lesion(s) suspicious for recurrence of PCa within 45 days following of rhPSMA-7.3 (^{18}F) PET imaging (may be extended to Day 60 due to the COVID-19 pandemic).

f Patients may receive salvage treatment following further consultation with their physician (outside of the scope of this study). The salvage treatment prescribed will be recorded.

g If biopsy is not feasible, rhPSMA-7.3 (^{18}F) directed (for confirmation of lesion location only) follow-up confirmatory imaging of the site(s), with one or more recommended modalities, will be acquired at the discretion of the local investigator(s).). Note: this time period may be extended Day 60 due to the COVID-19 pandemic.

h Follow-up confirmatory imaging may be performed, as necessary, up to 90 days after rhPSMA-7.3 PET.

Notes:

- Due to the COVID-19 pandemic, investigators should carefully consider the timing of confirmatory imaging procedures (when histology is not available) and are encouraged to minimize patients' exposure to COVID-19 by combining follow-up visits for multiple confirmatory imaging scans, when feasible.

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- In patients with multiple PET-positive regions, confirmation of at least one PET positive lesion in each region is required either by biopsy/surgical resection or confirmatory imaging in order to calculate the region level PPV for the efficacy analyses.
- In patients with multiple lesions in a specific region, the presence of one TP lesion determines truth for the region regardless of any concurrent FP findings in the same region. Therefore, multiple PET-positive lesions can be evaluated in a specific region in order to identify at least one TP.