CEDARS-SINAI MEDICAL CENTER

IIT2020-14-DAGNOLO-HIFU
High-Resolution, 18F-PSMA PET-MRI for Mapping Prostate Cancer in Patients Considering Focal High-Intensity Focused Ultrasound (HIFU) Therapy or Radical Prostatectomy

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

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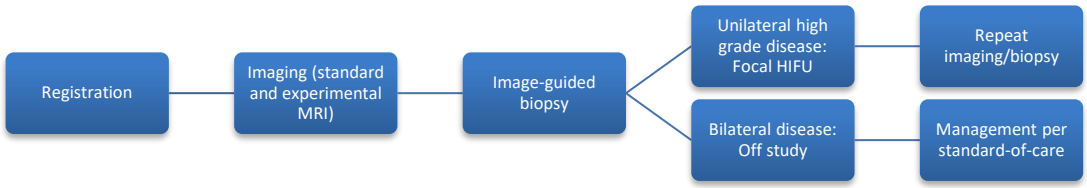
LIST OF ABBREVIATIONS

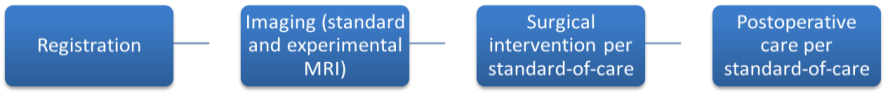
AE	Adverse Events
ADC	Apparent diffusion coefficient
AUC	Area under the curve
AS	Active Surveillance
DCE	Dynamic contrast enhanced
DWI	Diffusion-weighted imaging
EPI	Echo-planar imaging
HIFU	High-intensity focused ultrasound
hrMRI	High resolution MRI
mpMRI	Multiparametric MRI
MR/US	MRI-ultrasound
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PI-RAD	Prostate Imaging-Reporting and Data System
PSA	Prostate specific antigen
PSMA	Prostate specific membrane antigen
ROI	Region of interest
SAE	Serious Adverse Events
UTI	Urinary Tract Infection

STUDY SCHEMA

High-Resolution, 18F-PSMA PET-MRI for Mapping Prostate Cancer in Patients Considering Focal High-Intensity Focused Ultrasound (HIFU) Therapy



Radical Prostatectomy



STUDY SUMMARY

Title	High-Resolution, 18F-PSMA PET-MRI for Mapping Prostate Cancer in Patients Considering Focal High-Intensity Focused Ultrasound (HIFU) Therapy or Radical Prostatectomy
Short Title	High resolution PET-MRI before prostate cancer HIFU or radical prostatectomy
Protocol Number	Pro00000832
Phase	Two parts: Phase II and Pilot
Methodology	Single arm, paired imaging (Phase II)
Study Duration	3 years
Study Center(s)	Cedars Sinai Medical Center
Objectives	**Phase II Study (HIFU)**: Primary Endpoint: Number of additional biopsy-proven cancers that novel imaging modalities of hrMRI and/or F18-PSMA PET would detect when compared to reference standard imaging of mpMRI in patients undergoing HIFU procedure. Secondary Endpoint: Negative biopsy rate of standard 12-core biopsy 6 months following HIFU therapy. **Phase II Study (Radical Prostatectomy(RP))**: Primary Endpoint: To determine the sensitivity in detection of prostatic carcinoma of novel imaging modalities of hrMRI and /or F18-PSMA PET compared to reference standard mpMRI in patients scheduled to undergo radical prostatectomy. Secondary Endpoint: Specificity of hrMRI, F18--PSMA PET and mpMRI for detecting all tumors and metastasis at 6 months follow up.
Number of Subjects	30 Study Subjects (Phase II HIFU), 31 Study Subjects (Phase II RP)

Diagnosis and Main Inclusion Criteria	Diagnosis for Pilot trial: Any patient scheduled to undergo radical prostatectomy Diagnosis: Clinically localized, unilateral, high-grade prostate cancer OR at high risk for having unrecognized high grade Prostate Cancer Inclusion Criteria: • Biopsy consisting of ≥ 10 tissue cores sampled • PSA ≤20 ng/mL • cT1-cT2c • Either overall Gleason score ≥ 7 with Gleason grade 4 or 5 component localized to one lobe (i.e. right or left) OR overall Gleason score 6 with ≥ half of systematic biopsy cores positive and ≥ 50% of core involvement in at least one core • Patients considering focal HIFU therapy • Patients considering radical prostatectomy
Study Imaging	F18-PSMA PET-MRI in combination with multiparametric prostate MRI using high resolution DWI
Control Imaging	Standard multiparametric prostate MRI
Reference standard	MRI-targeted prostate biopsies will serve as the reference standard and all lesions seen on any MRI protocol will be biopsied. In the pilot trial, the prostatectomy pathology will serve as the reference standard.
Statistical analysis	Our hypothesis is that 20% of biopsy-proven tumors will be detected on PET-hrMRI and not on standard MRI. If we assume that no biopsy proven tumors will only be detected on standard MRI, at alpha=0.05, n=40 provides a power of at least 90% when we account for 5 cases that will not be evaluable. The RP phase II study is a parallel study arm using PSMA-PET imaging for intraprostatic cancer detection, but using radical prostatectomy pathology as the gold standard. The radical prostatectomy pilot arm will allow us to compensate for limitations and describe this data in parallel with the HIFU analysis.

1.0 STUDY ABSTRACT

The arrival of High-Intensity Focused Ultrasound (HIFU) technology along with advances in prostate imaging may make focal gland ablation feasible. While the mainstays of therapy for clinically localized prostate cancer, surgery and radiation therapy, induce significant morbidity such as urinary incontinence, erectile dysfunction, and bowel dysfunction due to bystander effects of whole-gland treatment, HIFU permits focal destruction of prostate cancers, which has the potential to minimize these morbidities and maximize quality of life. Advances in prostate MRI allow the majority of high grade cancers to be detected. Software platforms exist that enable real-time fusion of prostate MRI images with ultrasound, which allows for targeting of prostate lesions found on MRI during transrectal biopsy. The confluence of all of this technology—HIFU, multiparametric MRI (mpMRI), and MR/US-fusion targeting—creates the possibility of highly targeted focal ablation of prostate cancers. Nonrandomized clinical trials of hemigland and focal ablation with HIFU in Europe have shown promising trifecta rates—cancer control, potency, & continence—up to 1y post-treatment.

While early results of HIFU therapy for clinically localized prostate cancer are promising, the effectiveness of HIFU therapy will ultimately be limited by the accuracy of prostate cancer imaging. Because prostate cancer is often multifocal, identification of all clinically relevant prostate cancer lesions is critical to complete treatment of the disease, whether it is hemigland or true focal ablation. Modern mpMRI is unable to detect 20% of high-grade cancer and approximately 50% of low-grade cancers. To address this shortcoming, our team at Cedars-Sinai has developed high-resolution prostate MRI (hrMRI) technology that improves resolution 5-fold compared with standard multiparametric MRI. (1) High-resolution imaging has been shown to detect 60% of tumors not seen on standard MRI.(2) Pairing this technology with PET may allow highly specific targeting for focal therapy. Because the oncological effectiveness of focal therapy depends on robust targeting, PET-hrMRI could provide a significant advantage in cancer control outcomes for HIFU.

We herein propose a prospective trial to evaluate the effectiveness of F18-PSMA PET-hrMRI versus standard mpMRI at identifying prostate cancer targets for HIFU therapy. Patients with clinically localized, unilateral high grade prostate cancer (Gleason score 7-10 prostate cancer localized to one lobe on prior biopsies) OR at high risk for having unrecognized high grade prostate cancer (overall Gleason score 6 with $\geq$ half of systematic biopsy cores positive and $\geq$ 50% of core involvement in at least one core), interested in HIFU would receive both a standard mpMRI and F18-PSMA PET-hrMRI. They would then undergo a mapping biopsy using a standard sextant template plus MRI/US-fusion targeted biopsy of any suspicious lesion on mpMRI or PET-hrMRI. The primary endpoint would assess the number of biopsy-proven cancers that mpMRI would have missed compared with PET-hrMRI. Following our tumor mapping study, patients with high grade disease (i.e. Gleason grade 4 or 5) in one lobe undergo hemigland or focal HIFU of that lobe. At 6 months, patients would undergo repeat prostate biopsy to assess the negative biopsy rate in the treated region and absence of Gleason grade 4 or 5 in the untreated region as secondary endpoints.

Tumors invisible on MRI tend to be small, low-grade tumors that do not require treatment. However, it may be important to identify these tumors for future surveillance. An important limitation of this phase II study is that it will not be able to define the sensitive of imaging for these low-grade tumors. Therefore, a pilot study is included in which patients scheduled to undergo radical prostatectomy will have a preoperative PET-hrMRI. The prostatectomy pathology will be the reference standard. Since the true location of all tumors will be known, both the sensitivity and specificity of PSMA-PET MRI can be determined

2.0 BACKGROUND AND RATIONALE

2.1 Prostate Cancer: Current Standard of Care in Treatment

Prostate cancer is the most common non-cutaneous cancer and the second-leading cause of cancer mortality in American men, accounting for 25% (192,280) of new cancer diagnoses and 9% (27,360) of male cancer deaths(3). Clinically localized prostate cancer accounts for the vast majority of new cancer diagnoses, with an estimated 91% of new cases diagnosed at local or regional stages(3). Traditional treatment options for localized disease vary widely, from watchful waiting or active surveillance to aggressive treatment with surgery, radiation therapy, or brachytherapy. Active surveillance is considered the standard-of-care for low grade (e.g. Gleason score 3+3=6) prostate cancers and even some intermediate risk cancers. On active surveillance, patients with long life expectancy who develop a component of high Gleason grade cancer (i.e. Gleason grade 4 or 5) are recommended to have definitive local therapy such as prostatectomy or radiation. While aggressive therapies such as surgery and radiation do offer the opportunity for cure, they are fraught with side effects that can significantly affect quality of life, including erectile dysfunction, urinary incontinence, and bowel dysfunction(4-7). Even recent advances in robotic surgery and radiation techniques have not appeared to significantly reduce the long-term morbidities of definitive local therapy.

2.2 HIFU: Historical Background and FDA Approval

High-Intensity Focused Ultrasound (HIFU) is a noninvasive therapy that precisely delivers ablative ultrasonic energy to deep tissues through skin and mucosa, allowing for transrectal focal ablation of prostate cancers. While the mainstays of therapy for clinically localized prostate cancer induce significant morbidity such as urinary incontinence, erectile dysfunction, and bowel dysfunction due to bystander effects of whole-gland treatment, HIFU permits focal destruction of prostate cancers by ablating either half of the prostate gland or only the tumor itself; these approaches have the potential to minimize morbidities associated with whole-gland treatment and thereby maximize quality of life. HIFU treatment (primarily hemigland and whole-gland) has been used extensively over the last fifteen years in Europe, Canada, and Mexico, and there are numerous articles describing its safety and effectiveness for this application in the Urology literature.

While HIFU therapy has a long track record abroad, it has only recently been approved for prostate ablation in the US. In October 2015, the FDA gave de novo clearance to the Sonablate 450 HIFU platform (manufactured by SonaCare Medical) for the ablation of prostate tissue, making it the first to be approved for this indication in the US. In November 2015, the Ablatherm HIFU platform (manufactured by EDAP TM SA) was given 510(k) clearance for the same indication. While the approvals for these devices do not specifically mention application to prostate cancer, academic and industry leaders are hailing this technology as a major advance for focal prostate therapy, hinting that this technology can avoid the morbidities of surgery for prostate cancer. Local academic centers have already begun to use and market this technology.

2.3 HIFU: International Experience with Prostate Cancer Treatment

HIFU therapy has been a mainstay of prostate cancer care in Europe, Canada, and Mexico for the last fifteen years, and cancer control and side effect outcomes have been very

promising. A review of the randomized clinical trials, meta-analyses, and systematic reviews reporting on efficacy and safety of HIFU as primary treatment was recently reported, though this review included a mixed population with regard to tumor mix and ablation zone (whole-gland and hemigland). 5-year disease free survival rates were 61–95%. Common complications associated with HIFU were urinary retention (<1–20%), UTI (2–48%), stress urinary incontinence of any degree (<1–34%), and erectile dysfunction (20–86%). Rare complications included recto-urethral fistula (<2%), bladder neck stenosis, urethral stricture, perineal pain, urinary obstruction, epididymitis, and prostatitis. The largest institutional series of hemigland HIFU for low- (25%) and intermediate-risk (75%) prostate cancers suggested even better results, with return of erectile function for penetrative sex in 95% of men, 90% pad-free and leak-free continent, and 89% had no histological evidence of cancer at 6 months. 89% of men reached the trifecta status of pad-free, leak-free continence, erections sufficient for intercourse, and cancer control at 12 months.(8) True focal therapy is in a nascent stage of development, but early results are similar to hemigland treatment. In a prospective study of 42 men with low- and intermediate-risk cancer at University College London, 95% (95% CI 83–99%) were cancer free on biopsy at 12 months and 84% (95% CI 66–95%) reached trifecta status.(9) These results, though admittedly in highly selected populations, are clear improvements on cancer control and quality of life outcomes in modern surgical and radiation cohorts.

2.4 MRI for Prostate Cancer Imaging

Multiparametric MRI (mpMRI) combining T2-weighted, diffusion-weighted, and dynamic contrast enhanced (DCE) images is quickly becoming part of the standard of care for detection and localization of prostate cancer.(10, 11) Prostate MRI has been shown to have high sensitivity and specificity for high-grade prostate cancers, with approximately 80% false negative rate for detection of Gleason 7 or higher tumors. The Prostate Imaging-Reporting and Data System (PI-RADS) scoring system is a widely accepted rating system for estimating risk of cancer, using a 1–5 scale to provide clinicians with an estimate for likelihood of cancer; this scale uses T2-weighted imaging, diffusion weighted imaging, dynamic contrast-enhancement, and MRI spectroscopy to inform this assessment. Some variations on this scale, such as the UCLA prostate MRI scoring system, give more weight to the diffusion-weighted imaging component, since it is the component providing the most predictive utility.

Diffusion-weighted imaging (DWI) is sensitive to the diffusion of water molecules interacting with surrounding macromolecules. DWI, which provides a quantitative biological parameter called apparent diffusion coefficient (ADC) value, is a robust MRI parameter for differentiating benign and malignant prostate tissue.(12, 13) In fact, the latest version of the Prostate Imaging-Reporting and Data System (PI-RADS) scoring system relies almost exclusively on DWI to identify tumors in the peripheral zone, which is where the vast majority of prostate cancers form. Findings on T2 images are not used to identify cancer, and DCE images are only used to differentiate between some PI-RADS 3 and 4 lesions. In a pilot study of prostate cancer AS, DW-MRI was useful for detecting progression of Gleason score based on changes in ADC value.(14) Tumor size is an important clinical criterion for defining low risk prostate cancer, and tumor size based on DWI has been shown to crudely predict low risk prostate cancer.(15) However, conventional DWI using single-shot echo-planar imaging is unable to detect small tumors(16) or detect small changes in tumor size on serial imaging.

2.5 High-Resolution Prostate MRI (hrMRI)

Over the last several years, our group at Cedars-Sinai has developed technology to improve resolution of standard mpMRI, allowing for improved detection of smaller tumors. (1, 2) By using a three-dimensional (3D) high-resolution diffusion-weighted imaging sequence (HR-DWI), image quality is improved and confers a 5-fold improvement in resolution when compared to standard two-dimensional (2D) DWI (S-DWI). This novel 3D DWI technique has been developed by our team and can be applied on existing 1.5T or 3T MRI systems. S-DWI suffers from two important limitations. a) It uses single-shot echo-planar imaging (EPI) for data acquisition, which produces magnetic susceptibility induced streaking artifacts and geometric distortions so that round objects may appear oval. b) The relatively low signal-to-noise ratio and 2D image acquisition with S-DWI limit spatial resolution, which is defined by the minimum distance between two objects required to resolve them uniquely. Our hrMRI incorporating HR-DWI overcomes these limitations by using magnetization prepared, multi-shot, turbo-spin-echo acquisition, which improves signal-to-noise ratio (SNR), spatial resolution, and image quality, and eliminates geometric distortions and streaking artifacts associated with EPI.

In a prospective study assessing the performance of hrMRI in 17 prostate cancer patients on active surveillance, the technique was shown to detect tumors not seen on standard mpMRI. Standard mpMRI predicted biopsy results (AUC 0.72, Fisher's exact $p<0.001$), but high-resolution DWI sequences allowed MP-MRI to be more highly predictive of biopsy results (AUC 0.88, Fisher's exact $p<0.001$). hrMRI had a sensitivity of 95.7% and identified tumor in 22 of 23 zones proven to have cancer on biopsy. In contrast, standard mpMRI had a sensitivity of 60.9% and only identified 14 of 23 biopsy-positive zones ($p=0.004$). In all, hrMRI was shown to detect 60% of tumors not seen on standard MRI.

2.6 PSMA and PET-MRI in Prostate Cancer

Positron emission tomography (PET) imaging has been increasingly used for detection of occult distant metastases in patients with advanced prostate cancer using prostate-cancer-specific radiotracers (PSMA) or radiotracers that accumulate preferentially within prostate cancer tissue (11C choline, 11C acetate, and 18F fluciclovine). Prostate-specific membrane antigen (PSMA) is a type II membrane protein originally characterized by the murine monoclonal antibody (mAb) 7E11-C5. 3 and is expressed in all forms of prostate tissue, including carcinoma. F18-PSMA is a radiolabeled antibody that binds to PSMA antigen expressed on the surface of the prostatic cancer cells.

While PET technology is usually paired with CT imaging for 3D localization due to wide availability of CT technology, there have been efforts to pair PET technology with MRI to improve identification of lesions both within and outside of the prostate gland, given the advantages in spatial resolution of MRI over CT imaging. While mpMRI is a very sensitive imaging modality for identifying localized prostate cancers, its specificity is limited; co-localization of tumors identified on MRI with PET imaging may be able to improve specificity to account for this limitation.

Early work has suggested that co-localization of this PET radiotracer with 3-D mpMRI imaging may enhance accuracy of localization of intraprostatic cancer lesions compared with mpMRI or PET/CT alone. In a study of 21 patients who underwent 18F-fluciclovine PET/CT and mpMRI prior to radical prostatectomy, combined 18F-fluciclovine PET/CT and mpMRI imaging yielded a positive predictive value of 82% for tumor localization, which

was significantly higher than that with either modality alone.
This would suggest that pairing also F18-PSMA PET imaging with MRI directly may improve localization of cancers within the prostate for HIFU treatment planning. We hypothesize that further leveraging the sensitivity and spatial resolution of hrMRI with the specificity of PET imaging may further enhance performance in accurately identifying cancers within the prostate.

2.7 MR/US-Fusion for Targeting of Prostate Cancers

The advent of improved prostate imaging using multiparametric MRI and PET have dovetailed with advances in fusion software platforms that offer the ability to overlay static MRI images with real-time ultrasound images at the time of biopsy. This technology, called MR-US fusion, allows clinicians to target potential regions of interest in the prostate seen on mpMRI during an transrectal ultrasound-guided biopsy. Targeted MR-US fusion biopsies have been shown to significantly improve sensitivity and overall accuracy of biopsy over standard sextant biopsy by 24% and 14%, respectively. Most academic centers now offer MR-US fusion biopsies for patients with persistent rising PSA after negative standard biopsy and for surveillance biopsies while on active surveillance. MR-US fusion techniques are also being applied to focal ablation of prostate cancers with HIFU; both the Sonablate and Ablatheram HIFU platforms have announced partnerships with MR-US fusion companies to provide targeting during tumor ablation with HIFU. However, despite these improvements, the accuracy of targeted biopsy and targeted focal therapy is necessarily limited by accuracy of the MRI imaging for detection and localization of lesions.

2.8 Combining MR/US-Fusion, hrMRI, and PET-MRI with HIFU for Focal Treatment of Prostate Cancer

Because the oncological effectiveness of HIFU depends on robust mapping and targeting of lesions within the prostate, improved detection of lesions using hrMRI and/or PET-MRI could provide a significant advantage in HIFU cancer control outcomes. Patients who are eligible for hemigland and focal HIFU absolutely depend on imaging for treatment planning; for example, in a patient with an index lesion of the right side of the prostate only, if imaging fails to detect a small focus of prostate cancer present on the left, hemigland HIFU (only treating the right side of the prostate) will not be effective at eradicating the entire bulk of his disease. It is even more important to accurately identify all prostate cancers when mapping for true focal therapy, since only identified lesions are ablated. We have previously shown that hrMRI detects up to 60% of tumors within the prostate not seen on mpMRI, and PET-MRI techniques may be able to improve the accuracy of this detection. Even if lesions that are ignored by mpMRI but detected on PET-hrMRI are indolent, long-term growth of these lesions may certainly affect cancer control outcomes over time and require costly and morbid retreatment. We believe that improved imaging at the outset of focal therapy would provide more comprehensive eradication of cancer burden from the start, resulting in improved long-term outcomes.

2.9 PET-hrMRI prior to prostatectomy

An important limitation of studying a new imaging modality in patients undergoing HIFU is that tumors are identified by biopsy, which is susceptible to sampling error. In other words, tumors invisible on MRI and missed on systematic prostate biopsy are not considered in

defining the limitation of our novel imaging. These tumors are expected to be small, low grade tumors that do not require treatment. However, future research will need to consider appropriate surveillance strategies for these MRI-invisible tumors. To define sensitive of PET-hrMRI, we would need to know where all the tumors are. Therefore, a pilot study is included in which patients scheduled to undergo radical prostatectomy will have a preoperative PET-hrMRI. The prostatectomy pathology will be the reference standard. Since the true location of all tumors will be known, both the sensitivity and specificity of PSMA-PET MRI can be determined.

3.0 STUDY DESIGN:

3.1 Overview

This prospective trial will evaluate the effectiveness of F18-PSMA PET-hrMRI versus standard mpMRI at identifying prostate cancer targets for HIFU therapy. Patients with clinically localized, Gleason score 7-10 prostate cancer localized to one lobe on prior biopsies or overall Gleason score 6 with ≥ half of systematic biopsy cores positive and ≥ 50% of core involvement in at least one core, interested in HIFU would receive both a standard mpMRI and F18-PSMA PET-hrMRI. They would then undergo a mapping biopsy using a standard sextant template plus MR/US-fusion targeted biopsy of any lesions with PI-RADS scores ≥3 on hrMRI or 18F-PSMA PET positivity. The primary endpoint of the Phase II study would assess the number of biopsy-proven cancers that mpMRI would have missed compared with hrMRI and/or F18-PSMA PET. Following our tumor mapping study, patients with high grade disease (i.e. Gleason grade 4 or 5) in one lobe undergo hemigland or focal HIFU of that lobe. At 6 months, patients would undergo repeat mpMRI and prostate biopsy (MR/US-fusion biopsy plus standard sextant biopsy) to assess the negative biopsy rate in the treated region and absence of Gleason grade 4 or 5 in the untreated region which will be the secondary endpoint of the Phase II study.

As the gold standard for evaluation of sensitivity and specificity of any imaging test is the pathologic analysis of the whole prostatic gland obtained at prostatectomy (as the biopsy is subject to error sampling), a concurrent pilot study will enroll patients scheduled to undergo prostatectomy with the primary endpoint to define sensitivity of PET-hrMRI versus mpMRI compared against the prostatectomy pathology and with the secondary endpoint define specificity of hrMRI, F18-PSMA PET and mpMRI for detecting all tumors and metastasis at 6 months follow up.

3.2 Study Population

The study population for recruitment will be patients within the academic urology practice at Cedars-Sinai Medical Center. After initial visit, any patient with clinically localized prostate adenocarcinoma with Gleason score 7-10 prostate cancer localized to one lobe on prior biopsy desiring therapy with HIFU may be considered a potential study participant. Subjects with newly diagnosed disease or on active surveillance may be considered.

3.2.1 Inclusion Criteria

1. Biopsy consisting of ≥ 10 tissue cores sampled
2. PSA ≤20 ng/mL (for HIFU arm only)
3. cT1-cT2c

4. Either overall Gleason score ≥ 7 with Gleason grade 4 or 5 component localized to one lobe (i.e. right or left) OR overall Gleason score 6 with ≥ half of systematic biopsy cores positive and ≥ 50% of core involvement in at least one core (for HIFU arm only)
5. Patient considering focal HIFU therapy or robotic radical prostatectomy

3.2.2 Exclusion criteria:

1. Previous local therapy for prostate cancer
2. Inability to receive PET tracer
3. Inability to receive MRI
4. Estimated glomerular filtration rate (GFR) <15 mL/min/1.73 m^2
5. Any other condition which, in the investigator's option, may make the patient a poor candidate for participation in a clinical trial.

3.3 Study endpoints

Primary Endpoint (HIFU): Number of additional biopsy-proven cancers that novel imaging modalities of hrMRI and/or F18-PSMA PET would detect when compared to reference standard imaging of mpMRI in patients undergoing HIFU procedure.

Secondary Endpoint (HIFU): Negative biopsy rate on standard 12-core biopsy 6 months following HIFU therapy.

Primary Endpoint (Prostatectomy): To determine the sensitivity in detection of prostatic carcinoma of novel imaging modalities of hrMRI and/or F18-PSMA PET compared to reference standard mpMRI in patients scheduled to undergo radical prostatectomy.

Secondary Endpoint (Prostatectomy): Specificity of hrMRI, F18-PSMA PET and mpMRI for detecting all tumors and metastasis at 6 months follow up.

Exploratory Endpoint: RNAseq transcriptome analysis of lesions that are positive on mapping biopsy. Sensitivity and specificity of PET-hrMRI for detecting all tumors detected on prostatectomy pathology.

3.4 Study Procedures

3.4.1 Screening/Baseline Procedures

Subjects will be identified by study investigators within the academic urology practice at Cedars-Sinai Medical Center during routine clinical practice. All study assessments for eligibility are performed as part of standard of care. Once a patient has been diagnosed, expressed interest in HIFU, and recommended study participation, they will be presented with the Informed Consent Form, including a description of the study purpose, risks, benefits and possible alternatives. The prospective participant will be given sufficient time to consider participation in the research. Patients will be asked to sign the study consent form after receiving a complete explanation of the study.

This study will enroll patients with clinically localized, Gleason score 7-10 prostate cancer

localized to one lobe on prior biopsies or overall Gleason score 6 with ≥ half of systematic biopsy cores positive and ≥ 50% of core involvement in at least one core, interested in HIFU as primary treatment. Patients with low Gleason grade cancer (e.g. Gleason grade 3) on the contralateral lobe are allowed since the standard-of-care for such low grade disease is observation. Patients with very low risk disease and low-volume, low-risk disease are excluded since their preferred management is active surveillance. Patients will present with newly diagnosed disease or after a period of active surveillance. If there is suggestion of extracapsular disease or seminal vesicle involvement on MRI, these patients will be excluded. Metastatic workup with cross sectional imaging and/or bone scan will not be mandatory, since they are not indicated for low- and intermediate-risk prostate cancers according to AUA and NCCN guidelines.

The pilot study will allow enrollment of patients scheduled to undergo radical prostatectomy performed either at Cedars-Sinai Medical Center (CSMC) or an outside hospital (OSH). If the radical prostatectomy is performed at an OSH, authorization from subjects will first be obtained. Then the final pathology report of the radical prostatectomy from OSH will be obtained, reviewed and considered at CSMC for final data analysis. Additionally, the outside pathology slides may need to be reviewed here at CSMC for final data analysis as well, however this decision will be made later. They will get a preoperative PET-hrMRI. All surgical interventions and postoperative care are per standard-of-care. Scan results may identify patients who do not qualify for surgery.

The investigator may decide to change arms for a subject (i.e. HIFU to RP or RP to HIFU) based on MRI finding or replace the subject after imaging review.

Screening procedures include:

3.4.1.1 Informed Consent

Informed consent must be obtained prior to any protocol assessment or procedure which is not performed as part of local routine care. Subjects must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA). Signed and dated ICF and HIPAA for enrolled participants who are not subsequently screened or undergo study intervention will be maintained at the study site.

3.4.1.2 Medical history

Medical history (comorbidities) includes clinically significant diseases that are currently active or that were active, including past surgical history, medications, social history, family history including history of prostate cancer, dates of previous prostate biopsies, prostate biopsy pathology results, PSA results, dates and results of previous prostate imaging

3.4.1.3 Reporting on Concomitant medication

Any current concomitant medications and treatments will be recorded

3.4.1.4 Demographics

Age, ethnicity/race

3.4.1.5 Review subject eligibility criteria

All necessary procedures and evaluations must be performed to document that the subject meets all of the inclusion and none of the exclusion criteria.

3.4.1.6 Physical exam including vital signs, height, and weight

Physician directed physical exam. This may be collected within 180 days of screening. Vital Signs will include heart rate (pulse), respiratory rate, blood pressure, and body temperature.

3.4.1.7 Adverse event assessment

Adverse events will be assessed at imaging, post imaging (biopsy), HIFU/Prostatectomy, and HIFU follow up. See section 5.1 and 5.2 for Adverse Event and reporting. Only grade 3 and above imaging-related AEs will be captured and all SAEs following the receipt of 18F-DCFPyL agent.

3.4.2 Study Calendar for Focal High-Intensity Focused Ultrasound (HIFU) Therapy

Procedure	**Screening**	**Imaging**	**Post-imaging[2]**	**Standard of Care (SOC) Treatment**	**Post SOC Treatment 6 months (+/- 1.5 months) following HIFU**
Informed Consent/Registration	X				
Review Eligibility	X				
Demographics	X				
Medical History	X				
Prior and Current Medication Review	X				
Vital Signs[5]		X	X		
Physical Exam (including symptoms assessment, height, weight) [5]	X				
Standard MRI with Gadolinium		X (at least one day prior to targeted prostate biopsy)			X (at least one day prior to targeted prostate biopsy)
Optional: Tissue collection[4]			X		X
Optional: Blood collection[6]	X[7]	X[7]	X[7]	X[7,8]	X[8]

18-PSMA PET-hrMRI		X (at least one day prior to targeted prostate biopsy)			
Adverse Event Review		X	X	X	X
Hemigland or Focal High Intensity Focused Ultrasound (HIFU)[1]				X (performed within 4 months after mapping and/or targeted prostate biopsy)	
Standard Sextant Mapping Biopsy			X		X
MR/US-fusion targeted biopsy			X[3]		X

1. Focal HIFU performed on study for patients with confirmed unilateral high grade prostate cancer.
2. End of study for bilateral Gleason ≥7 disease
3. Of any lesions with PI-RADS scores ≥3 on hr MRI or 18F-PSMA PET positivity
4. Tissue collection includes left over tissue from standard of care collection only.
5. Need to be obtained within 180 days of screening. Vital signs will be assessed before and after administration of 18F-DCFPyL.
6. Blood collection will be approximately 17 mL (approximately 1 tablespoon) of whole blood. As of August 2023, optional blood draw has been removed from ICF (MODCR00000250).
7. Pre-treatment blood will be drawn once before HIFU or on the day of surgery with standard of care blood draw.
8. Post-treatment blood will be drawn once after HIFU with standard of care blood draw.

Study Calendar for Radical Prostatectomy

Procedure	**Screening**	**Imaging**	**Standard of Care (SOC) Treatment**	**Post SOC Treatment 6 months (+/- 1.5 months) following Prostatectomy**
Informed Consent/Registration	X			
Review Eligibility	X			
Demographics	X			
Medical History	X			
Prior and Current Medication Review	X			
Vital Signs[2]		X		
Physical Exam (including symptoms assessment, height, weight)[2]	X			

Standard MRI with Gadolinium		X (preoperative PET-hrMRI prior to prostatectomy)		
Optional: Tissue collection[1]			X	
Optional: Blood collection[3]	X[4]	X [4]	X[5]	
18-PSMA PET-hrMRI		X (at least one day prior to prostatectomy)		
PSA Lab Result				X
Adverse Event Review		X	X	X
Prostatectomy			X	

1. Tissue collection includes left over tissue from standard of care collection only.
2. Need to be obtained within 180 days of screening. Vital signs will be assessed before and after administration of 18F-DCFPyL.
3. Blood collection will be approximately 17 mL (approximately 1 tablespoon) of whole blood. As of August 2023, optional blood draw has been removed from ICF (MODCR00000250).
4. Pre-treatment blood will be drawn once before prostatectomy or on the day of surgery with standard of care blood draw.
5. Post-treatment blood will be drawn once after prostatectomy with standard of care blood draw.

3.4.3 Study Intervention

3.4.3.1 Study Intervention(s) Administration

Study Interventions Description

18F-DCFPyL Injection is a radioactive diagnostic PET imaging agent indicated for (1) use in staging of men with high risk prostate cancer and (2) the detection of recurrent or metastatic prostate cancer.

Dosing and Administration

The recommended dose of 18F-DCFPyL Injection is 9 mCi (333 MBq), administered intravenously as a bolus injection followed by a flush of normal saline. The drug product contains radioactive material and will only be handled by personnel trained and certified in the use of radioactive isotopes with proper shielding and monitoring.

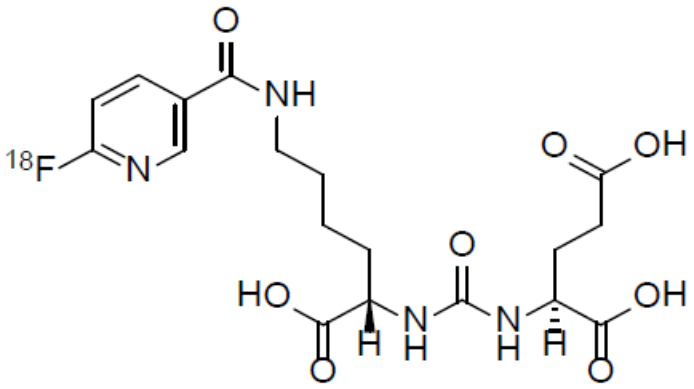
3.4.3.2 Preparation/ Handling/ Storage/ Accountability

Acquisition and Accountability

Progenics Pharmaceuticals will be providing the injection to the investigator.

Formulation, Appearance, Packaging, and Labeling

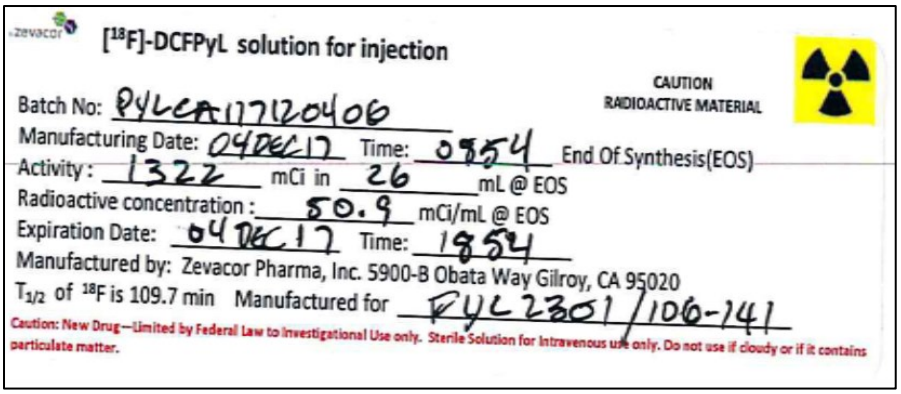
18F-DCFPyL Injection is a Fluorine-18 labeled small molecule that targets the extracellular domain of PSMA. 18F-DCFPyL is a radioactive diagnostic agent used with PET imaging. Chemically, 18F-DCFPyL is 2-(3-{1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}ureido)-pentanedioic acid. The structural formula is:



18F-DCFPyL Injection is a sterile, clear particle-free solution for intravenous use. It is supplied at a specific activity of at least 1000 mCi/μmol at the Time of Administration, corresponding to a total administered chemical mass of DCFPyL of ≤ 4 μg, and a radioactivity concentration of 1 to 80 mCi/mL at the Time of Calibration (TOC), or, end of synthesis (EOS). The pH is between 4.5 and 7.5. The product is to be stored at room temperature; beyond-use date is 10 hours from EOS.

Based on information provided by the cross-referenced IND 129,952, there are a total of three labels for the drug product, 18F-DCFPyL: a label on the finished drug product vial, a prescription label for the lead pig, and a label for the unit-dose syringe. The finished drug product within the vial is dispensed into unit-dose(s) at the radiopharmacy and shipped in the lead pig to the clinical site.

•The batch label of the finished drug product vial: An example label of the 18F-DCFPyL finished drug product vial from Sofie (formerly Zevacor)-Gilroy facility is provided. It complies with 21 CFR 312.6.

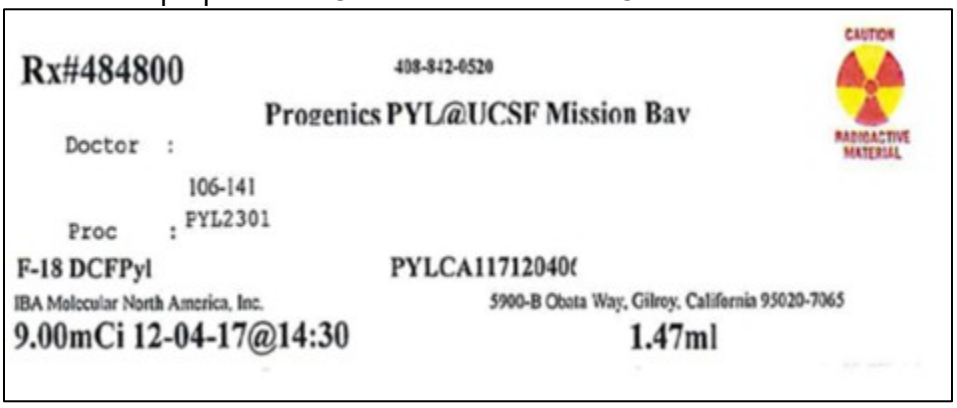


•The prescription label on the lead pig: This label is for the lead pig shipped from the radiopharmacy to the clinical site. The labeling provides detailed information of the drug product for the clinical sites. It is in compliance with 21 CFR 312.6 requirements.

Example prescription label on the lead pig as dispensed by the Gilroy-radiopharmacy; similar label will be prepared for Cedars-Sinai Medical Center:

•The unit-dose syringe label: This label is for the unit-dose syringe as dispensed by the radiopharmacy. The labeling provides the minimum necessary and useful information (due to the space limitation and high levels of radioactivity) of the drug product for the clinical sites during drug administration. It is in compliance with the 21 CFR 312.6 requirements.

Example label on the unit-dose syringe as dispensed by the Gilroy-radiopharmacy; similar label will be prepared for Cedars-Sinai Medical Center:



Product Storage and Stability
Based on routine pharmacy practice and State Board of Pharmacy regulation, the storage condition is not specified on the labeling if the drug is to be stored at room temperature, which is the case for 18F-DCFPyL. Beyond-use date is 10 hours from EOS.

Preparation
The study drug will be prepared and shipped by the radiopharmacy. They will label the injections with detailed information of the drug product for the clinical sites. It is in compliance with 21 CFR 312.6 requirements.

3.4.3.3 Measures to Minimize Bias: Randomization and Blinding

The study will not have randomized or blinding components. All participants will be provided with the intervention drug if they meet the inclusion criteria listed in section 3.2.1.

3.4.3.4 Study Intervention Compliance

Physicians will recruit patients that meet the inclusion criteria for the study. Throughout the process, patients will be monitored by the physician and the study team assisting with the trial. They will keep track of the administration of 18F-PSMA by entering it on RedCap, a software used to capture data for research studies. The study staff will follow up with the patient if needed.

3.4.3.5 Concomitant Therapy and Rescue Medicine

Not applicable to this study

Pre-HIFU Imaging Protocol for Tumor Mapping
Eligible participants will then undergo mapping MRI in advance of HIFU therapy using both standard mpMRI and PET-hrMRI. All imaging will be completed in one sitting. hrMRI increases the length of the MRI by approximately 5 minutes. PET-MRI sequences increased the length of mpMRI by 30 minutes. Scanning will be done on the Siemens Biograph mMR scanner at the Research Imaging Core facility in the Davis Building.

Subjects undergoing a PET-hrMRI will be screened using the standard clinical protocol to determine whether it is safe to administer contrast to the subject.

PET scans involve injection of a radioisotope. Subjects undergoing a contrast-enhanced MR-PET will be screened using the standard clinical protocol to determine whether it is safe to administer contrast to the subject. An IV line will be inserted, and the participant will receive 9 mCi ±20% F18-PSMA injection diluted up to 10mL injected via the IV, as an IV bolus injection followed by 10mL flush with normal saline solution. The participant will then be positioned supine in the scanner and will be scanned in the area of the prostate. The time from end of injection of F18-PSMA injection to the start of imaging should be 60 minutes. For the PET acquisition, participants will be imaged for approximately 30 minutes.

All MRI images will be read according to PI-RADS (version 2) by a dedicated GU radiologist who has experience reading over 500 prostate MRIs. All PET scans will be read by nuclear medicine investigators on the study (DA, LT). All lesions with PI-RADS greater than or equal to 3 and all PET positive areas will be considered suspicious for cancer. A region of interest (ROI) application will be used. The circumference of a

suspicious lesion will be drawn on each individual MRI slice. The lesion volume and average ADC will be calculated from the ROI's. The tumor volumes and ADCs will be provided by the radiologist. To prevent the hrMRI from influencing the review of the mpMRI, all mpMRI's will be reviewed first. The radiologist will always be blinded to previous pathology.

Mapping Biopsy Protocols
After the pre-HIFU imaging protocol for tumor mapping, all patients will undergo a transrectal ultrasound-guided targeted mapping biopsy. The biopsy will include a standard sextant template plus MR/US-fusion targeted biopsy of any lesions with PI-RADS scores ≥3 on hrMRI or F18-PSMA PET positivity. These areas will be targeted using the UroNav targeting software platform. We use the UroNav platform for performing MR-PET-US fusion biopsies. It is an FDA approved, commercially available platform. Uronav received 510(k) clearance from the FDA and it is a commercially available platform, link to document:
https://www.accessdata.fda.gov/cdrh_docs/pdf15/K153073.pdf. As an exploratory analysis, remnant formalin-fixed paraffin embedded tumor tissue will be requested for RNAseq transcriptome analysis of lesions that are positive on mapping biopsy.

Eligibility for HIFU
If subjects are found to have unilateral high grade disease (i.e. Gleason grade 4 or 5), they will be considered as a candidate for hemigland or focal HIFU therapy. Clinician judgment may be exercised in determining eligibility for HIFU, since established criteria based on volume and extent of disease do not exist. If patients have high grade disease in both lobes, they will not be eligible for HIFU therapy on this trial. Their data will be used to assess the primary endpoint but they will not be considered for secondary endpoints.

HIFU Therapy and Follow Up Schedule
Patients who are eligible for HIFU will receive hemigland or focal HIFU per standard-of-care. All subjects will receive repeat mpMRI and MR/US-guided biopsy of all positive sites + systematic 12-core prostate biopsy at 6 months (or as clinically indicated). As an exploratory analysis, remnant formalin-fixed paraffin embedded tumor tissue will be requested for RNAseq transcriptome analysis of lesions that are positive on biopsy.

3.5 Removal of Subjects from study

Patients can be taken off the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

3.5.1 Patient voluntarily withdraws (follow-up permitted);

3.5.2 Patient withdraws consent (discontinue all study procedures and follow-up)

3.5.3 Patient is unable to comply with protocol requirements;

3.5.4 Treating physician determines continuation on the study would not be in the patient's best interest;

3.5.5 Lost to follow-up. If a research subject cannot be located in order to obtaining data to inform the primary or secondary endpoint, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented.

4.0 Study Risks

This study investigates a novel software-based MRI imaging protocol that improves image resolution, and it investigates the use of F18-PSMA for prostate PET-MRI.

F18-PSMA is currently not approved by FDA. MR/ultrasound fusion biopsies and HIFU for prostate ablation are approved procedures that are being routine performed as standard-of-care. All invasive procedures will therefore be performed following standard informed consent.

Magnetic Resonance Imaging (MRI)
MRI imaging is among the least invasive of all imaging modalities. The U.S. Food and Drug Administration has labeled MR systems of up to 4.0 Tesla as having "non-significant risk" and currently there is no evidence that MR imaging causes any long-term or irreversible effects in human beings. However, there are certain risks, which are detailed below.

MRI imaging utilizes magnetic fields and radiofrequency fields, both of which can be harmful in certain situations. Magnetic fields can cause ferromagnetic implants or ferromagnetic foreign bodies, such as intracranial aneurysm clips, shrapnel, and intraocular metal chips to become dislodged and tear the surrounding soft tissue. Therefore, MRI imaging is contraindicated in persons with ferromagnetic implants or ferromagnetic foreign bodies. It is also contraindicated in persons with electrically, magnetically or mechanically activated implants because the magnetic field can cause these to function erratically. In addition, persons wearing metallic objects may be at danger for them becoming dangerous projectiles, due to them inadvertently becoming introduced into the magnetic field. All subjects will be prescreened carefully and all scanners are used in accordance with guidelines set by the Bureau of Radiological Health.

F18-PSMA
The recommended dose is 333 MBq (9 mCi) administered as an intravenous bolus injection. The (radiation absorbed) effective dose resulting from this dose of F18-PSMA is 8 mSv. The clinical trial database for F18-PSMA includes data from 208 subjects. The mean administered activity was 333 MBq. Adverse reactions were reported in ≤1% of subjects during clinical studies with F18-PSMA. The most common adverse reactions were injection site pain, injection site erythema and dysgeusia.

Hypersensitivity to Medications - Occasionally, people have allergic reactions when taking any medication. Subjects may receive medications such as contrast. Hypersensitivity reactions may include symptoms such as shortness of breath, wheezing, flushing, nasal congestion and skin rash. In most cases, initial symptoms occur within minutes of drug administration and quickly reverse themselves or resolve with prompt medical treatment.

In general, allergic reactions to medicines are more likely to occur in people who have allergies to other drugs, foods, or things in the environment. Subjects will be asked about any pre-existing allergies before administering any medications during the study.

Incidental Findings

Only noted clinically significant incidental findings will be communicated to the subject, per CSMC IRB and Legal Department approved policy, as a result of agreeing to undergo a research MRI scan. No reports or images will be provided to subjects and their medical records. However, MRI mapping results will be provided to the treating physicians who will use this information for MR/ultrasound guided prostate biopsy.

5.0 ADVERSE EVENTS (AE)

5.1 Definitions

5.1.1 Adverse Event: An adverse event is any untoward medical occurrence in a patient receiving study intervention and which does not necessarily have a causal relationship with this intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

5.1.2 Serious Adverse Events (SAE): A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

- Results in death. If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- Is life-threatening.
  (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.

Evaluable for toxicity

Any patient who receives at least one dose of investigational product is evaluable for toxicity and will be included in the safety analysis.

Severity of Adverse Events

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

Reporting Requirements for Adverse Events

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE – CURRENT VERSION 5.0).

Step 2: Grade the adverse event using the CTCAE – CURRENT VERSION 5.0.

Step 3: Determine whether the adverse event is related to the protocol therapy

Attribution categories are as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert
- the current Investigator's Brochure

5.1.3 Unanticipated Problem (UP)

Unanticipated problems include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known to an individual or group of individuals (including research subjects, research staff, or others not directly involved in the research).

5.2 Reporting Requirements

5.2.1 Reporting to Principal Investigator

The Principal Investigator must be notified by study staff or co-investigators within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days (refer to Section 7.1) of the last administration of the study drug.

Phone Number for Expedited Reporting:
Alessandro D'Agnolo, MD
310-423-4682
Alternate Phone Number for Expedited Reporting:
ALTERNATE NAME AND PHONE
Timothy Daskivich, MD
310-423-4700

5.2.1.1 Participating Site Reporting Responsibilities

Any serious adverse event or unanticipated problem at all participating sites, which occur in research subjects on protocols for which SOCCI is the DSMC of record requires reporting to the DSMC regardless of whether IRB reporting is required. All SAEs/UPIRSOs occurring during the protocol-specified monitoring period should be submitted to the SOCCI DSMC, copying the CCTO Coordinating Center Study Lead, as detailed in section 7.4.2.3. In addition, for participating centers other than SOCCI, local IRB guidance should be followed for local reporting of serious adverse events.

If the event occurs on a multi-site clinical trial coordinated by the SOCCI, the Study Lead at the Coordinating Center will ensure that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. Copies of all serious adverse event reports or unanticipated problems reports will be kept on file in the Cedars-Sinai CCTO.

Reporting of SAEs/UPIRSOs must be accompanied by a cover letter which: identifies the event, is signed by the local principal investigator or treating physician from the participating site, includes the applicable study number and title, and contains the following:

- Site assessment of the event attribution to investigational product or study procedure
- Site assessment of event expectedness (expected vs. unexpected)
- Assessment of whether or not the research places subjects at a greater risk of harm than was previously known or recognized
- Assessment of the event's effect on the risk to benefit ratio
- Statement as to whether the informed consent statement should reflect changes in the potential risks involved
- Statement as to whether the event has been reported previously, and if so, whether the frequency is considered unusually high

Send to: SOCCI Cancer Clinical Trials Office
ATTN: SPIN/ Protocol # STUDY00000832
Fax: (310) 423-1998
E-mail: GroupSOCCICCTODSMCAdmin@cshs.org
CC: GroupCCTOSPIN@cshs.org

5.2.1.2 Reporting to DSMC:

Serious Adverse Events deemed to be related to the protocol and on-study deaths, including death of a research subject unless the death is expected (e.g. due to disease progression) to be reported to the DSMC within 24 hours of awareness. Hardcopies or electronic versions of the MedWatch Form 3500A (Mandatory Reporting) or SAE Form, along with any other supporting documentation available, should be submitted to the DSMC Coordinator. The DSMC Coordinator will forward the information to the DSMC Chair, and/or medical monitor. The DSMC Chair will review all SAEs/UPIRSOs upon receipt from the DSMC Coordinator and determination of whether the following actions are required: 1) takes action immediately, 2) convenes a special DSMC session (physical or electronic), or 3) defers the action until a regularly scheduled DSMC meeting. Reports are to be emailed to the DSMC team at GroupSOCCICCTODSMCAdmin@cshs.org.

5.2.1.3 Reporting to Drug Manufacturer

In accordance with Applicable Laws, Study Staff will advise the sponsor of any adverse reactions or side effects occurring during and after the conduct of the Study that become known to it. Institution agrees and shall cause Principal Investigator to comply with all applicable safety reporting regulations as set forth in the Code of Federal Regulations. Any correspondence to the FDA regarding adverse events or other safety issues associated with the Study Drug will be simultaneously copied via facsimile or e-mail to Progenics. Within 24 hours of becoming aware of a serious adverse event, Institution will communicate the occurrence of such event to Progenics and, if another drug or product is being used in the Study, to the manufacturer of the associated drug or product. Please note that the reporting period begins when a subject receives the Study Drug. Adverse event reports should reference the Progenics Clinical Grant Number, which will be supplied to the Principal Investigator by Progenics. The MedWatch 3500A form or such other form as may be required by the FDA from time to time should be utilized to report serious adverse events to the FDA. For Progenics products, report the adverse event information to the following: DocuSign Envelope ID: 3191B4AA-7E39-4BB7-9A69-037F85430112 DocuSign Envelope ID: C3AF2C8C-BFA9-423E-95B8-26A66809B56A4 Pharmacovigilance Agent Phone: 1-800-343-7851 or 1-978-667-9531 Fax: 1-978-436-7296 Email: lantheussafety@lantheus.com

5.2.2 Reporting to the Institutional Review Board (IRB)

The IRB must be notified within 10 business days of “any unanticipated problems involving risk to subjects or others.”

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

5.2.3 Reporting to the FDA

The sponsor-investigator of the IND, or designee at the Coordinating Center, must submit all reported SAEs from all participating sites to the FDA on the FDA Form 3500A (MedWatch) according to the following reporting criteria:

<u>7-Day Reports:</u>
The investigator-sponsor of the IND must notify the FDA as soon as possible but no later than **7 calendar** days after the investigator-sponsor’s initial receipt of the

information and all participating sites in a written IND safety report of any adverse reaction:

- **fatal or life-threatening adverse reaction** that is ***both***
- **suspected to be associated with use of the drug *and***
- **unexpected**

15-Day IND Reports:
The investigator-sponsor of the IND must notify the FDA as soon as possible but no later than **7 calendar** days after the investigator-sponsor's initial receipt of the information and all participating sites in a written IND safety report of any adverse reaction:

- **suspected to be associated with use of the drug** that is ***both***
- **serious *and***
- **unexpected**

Copies of Expedited Safety Reports will be kept in the Trial Master File in the SOCCI CCTO.

6.0 STATISTICAL ANALYSIS

6.1 HIFU Phase II Study

Our preliminary data suggests that up to 60% of tumors invisible to standard mpMRI are detected on hrMRI in an active surveillance population. It is unclear how many additional lesions will be identified on PSMA PET-MRI. Since all areas of concern will be biopsied and only biopsy-proven tumors will be treated with HIFU, the morbidity of the surgical intervention is minimized and its potential to achieve cure is maximized.

Power Assessment: The main hypothesis to be tested is whether the sensitivity of PSMA PET-hrMRI is greater than mpMRI alone in 20% considering the prostate divided in 6 sections for each patient. The power is evaluated using 1000 simulations based on the McNemar`s type test proposed by Yang et al. (17,2010). Data is generated based on four correlations: r1: between lesions evaluated by PSMA PET-hrMRI for the same patient, r2: between lesions evaluated by mpMRI for the same patient, r3: between evaluations PSMA PET-hrMRI and mpMRI for the same lesion and r4: between evaluations PSMA PET-hrMRI and mpMRI for the different lesions at the same patient. Based on preliminary data, we estimated mpMRI sensitivity of 42%, (r1, r2, r3, r4) = (-0.249, -0.119, 0.714, -0.172) using Spearman correlation, average number of lesions of 2.5 per patient and prevalence of patients with at least one positive biopsy section equal to 82%. The results are presented in Table 1.

Table 1. Power for McNemar test proposed by Yang et al. (2010) to detect a difference of 20% between sensitivities of the combination (PET-hrMRI or mpMRI) and mpMRI

Total Sample Size	# Patients with at least one positive biopsy section	Power

20	16	70.2
25	21	81.5
30	25	88.9
35	29	93.1
40	33	95.5

The minimum sample size to reach at least 85% of power is 30 patients with complete imaging data. Patients with incomplete imaging data will be replaced.

Statistical Analysis: Sensitivities will be compared using McNemar`s type test proposed by Yang et al. (17,2010). for cluster matched binary data. In addition, the 95% confidence interval for difference between sensitivities will be calculated as proposed by Yang et al. (18,2012).

Secondary Endpoints: Negative biopsy rate within treatment zones on standard 12-core biopsy 6 months following HIFU therapy; rate of high grade cancer in the untreated lobe.

Exploratory Endpoint: Formalin-fixed paraffin embedded biopsy tissue will be requested from a subset of patients for RNAseq transcriptome analysis. The number of cases analyzed will depend on availability of future funding. The subset of cases requested will depend on the exploratory object of the pilot study and may include discovery of signatures to predict presence of high grade cancer, unilateral disease or treatment success.

6.2 Radical Prostatectomy Phase II Study

Our previously conducted pilot study investigating the impact of fluciclovine PET imaging on improving sensitivity of prostate cancer detection (identical to this study but using fluciclovine tracer instead of PSMA) was criticized due to lack of a gold standard based on radical prostatectomy (outcome was based on biopsy only). Since the HIFU arm in this PSMA PET study has a biopsy-only gold standard, we elected to include a parallel study arm using PSMA-PET imaging for intraprostatic cancer detection but using radical prostatectomy pathology as the gold standard. While there are historical references for sensitivity of PSMA-PET for intraprostatic cancer detection, they are not ideal to be used as a reference for our study since: they are few in number and may not provide generalizable estimates; the analysis to date has only been done on a per-patient (rather than a per-lesion) basis; and there is variation in reading of mpMRI by center/radiologist. The described parallel radical prostatectomy pilot arm will allow us to compensate for these limitations and describe this data in parallel with our HIFU analysis.

Power Assessment: The main hypothesis to be tested is whether the sensitivity of PSMA PET-hrMRI is 20% greater than mpMRI alone on a per lesion basis. It is expected 6 lesions in average per patient. Therefore, the power considerations are the same as presented for the HIFU cohort as displayed on Table 1.

Table 1. Power for McNemar test proposed by Yang et al. (2010) to detect a difference of 20% between sensitivities of the combination (PET-hrMRI or mpMRI) and mpMRI

Total Sample Size	# Patients with at least one positive biopsy section	Power
20	16	70.2
25	21	81.5
30	25	88.9
35	29	93.1
40	33	95.5

Statistical Analysis: Sensitivities will be compared using McNemar`s type test proposed by Yang et al. (17,2010). for cluster matched binary data. In addition, the 95% confidence interval for difference between sensitivities will be calculated as proposed by Yang et al. (18,2012).

Secondary Endpoints: Specificity of imaging for detecting all tumors on prostatectomy

Exploratory Endpoint: Formalin-fixed paraffin embedded biopsy tissue will be requested from a subset of patients for RNAseq transcriptome analysis. The number of cases analyzed will depend on availability of future funding. The subset of cases requested will depend on the exploratory object of the pilot study and may include discovery of signatures to predict presence of high grade cancer, unilateral disease or treatment success.

6.3 Exploratory Objectives

Residual tissue and blood may be stored for future correlative studies that will be performed when funding is available. Examples of studies that may be performed include DNA or RNA sequencing from tumor or blood. As of August 2023, optional blood draw has been removed from ICF (MODCR00000250).

7.0 STUDY MANAGEMENT

Conflict of Interest

Any reportable conflict of interest will be disclosed to the local IRB and will be outlined in the Informed Consent Form.

Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The protocol and consent form will be reviewed and approved by the IRB of each participating center prior to study initiation, unless participating sites are utilizing a reliance agreement with the Coordinating Center's IRB of record.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRBs written approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated and prior to the shipment of study supplies to participating

sites, if applicable. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

Required Documentation (for multi-site studies)
Before the study can be initiated at any site, the following documentation must be provided to the Study Lead at the Coordinating Center.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal-wide Assurance letter
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if {institution} holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A financial conflict of interest statement from each investigator has been obtained.
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

Registration Procedures

All subjects that sign informed consent will be assigned a subject number sequentially by their date of consent. Those subjects that do not pass the screening phase will be listed as screen failures on the master list of consented subjects. Eligible subjects, as determined by screening procedures and verified by a treating investigator, will be registered on study at Cedars Sinai Medical Center by the Study Coordinator.

Issues that would cause intervention delays after registration should be discussed with the Principal Investigator (PI). If a patient does not receive protocol intervention following

registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Assignment of Subject ID: The study teams will track all subjects who sign consent using OnCore. Subjects found to be ineligible will be recorded as screen failures. Subjects found to be eligible will be registered using a six-digit numeric ID that follows the standard SOCCI format (832-001, 832-002, etc.). Participating sites for multi-center studies will also need to track all subjects consented. Upon registration, the participating site will enter patient study ID and limited patient information into OnCore, updating status to enrolled, as per CCTO guidance. If a participating site does not or cannot gain access to OnCore, an exception will be granted with approval of the Executive Director of the CCTO.

Note: For multi-center studies, assign a lead-in identifier for each site and define in the protocol. For example, the first site will be designated a lead-in number of 001, while the second site will be designated a lead-in number of 002. For a study which includes two sites, the first patient consented and enrolled at the first site will be subject 01-001. As a general rule CSMC will always have the lead-in identifier 01. The third subject enrolled at the second site might be 02-003. It is the responsibility of each site to track subjects enrolled at their respective sites and assigned consecutive subject numbers.

A) Eligibility Verification

Prior to registration, all subjects must undergo an eligibility verification by the study-specific research staff. Minimal risk studies are exempt from SOCCI Quality Management Core (QMC) central eligibility checklist review and eligibility verification. QMC central eligibility checklist review and eligibility verification for all subjects enrolled is performed only if requested by the PI at any time during the life of the study.

B) Registration

After eligibility is verified, each site will assign the subject a study number and site staff will then register the patient in OnCore®.

Registration is completed as follows:

- Assignment of a patient study number
- Assignment to the patient a dose/treatment arm as determined through communication with Biostatistics and the principal investigator, if applicable
- Enter the patient in OnCore
- Notify the investigational pharmacy and treating physicians that a subject has gone on study and anticipated treatment start date

Oversight by the principal investigator is required throughout the entire registration process.

Data Management and Quality Control and Reporting

REDCap is the Cedars-Sinai Cancer institutional choice for the electronic data capture of case report forms for SOCCI Investigator Initiated Trials. REDCap, a HIPAA-compliant database, will be used for electronic case report forms in accordance with institutional requirements, as appropriate for the project. The Study Staff will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

In order to facilitate remote source to case report form verification, the CCTO study team will require other institutions participating in this trial as sub-sites to enter data into the selected EDC system and upload selected de-identified source materials when instructed, or as applicable.

Frequency of trial monitoring will be conducted based on risk level of the study and this review includes but is not limited to accuracy of case report forms, protocol compliance, timeliness and accuracy of CTMS entries and AE/SAE management and reporting. The investigator and study team at all participating sites will ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (i.e., EMR and pharmacy access), and has adequate space to conduct the monitoring visit. Such monitoring visits may include on-site and/or remote monitoring. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

Data and Safety Monitoring

PI should assess the protocol for risk and assign an appropriate level of monitoring in concurrence with the CCTO. The risk level is then reviewed for final determination by the Protocol Review and Monitoring Committee (PRMC). PRMC will notify the PI of the final risk determination and of any changes to the protocol as needed. Please refer to the SOCCI Data and Safety Monitoring Committee Charter for more information.

Data Monitoring and Quality Assurance

Adherence to the protocol, Good Clinical Practices (GCP), and institutional policy will be monitored by the PI during the course of the study through routine Disease Research Group (DRG) meetings (or equivalent). In addition, the SOCCI Cancer Clinical Trials Office (CCTO) Quality Management Core (QMC) will conduct focused internal monitoring visits and audits for data quality and protocol adherence. QMC reports will be forwarded to the SOCCI Data and Safety Monitoring Committee (DSMC). Refer to the DSMC Charter for more details. For any protocol, QMC has the authority to request more frequent reviews or focused safety monitoring if it is deemed appropriate for any reason.

7.1.1 Safety Monitoring

Oversight of the progress and safety of the study will be provided by the PI. The PI will maintain continuous safety monitoring for the duration of the study by reviewing subject/study data. Adverse events and unanticipated problems are not expected, but if

they occur, they will be documented and reported according to CS-IRB policies and procedures. If the PI becomes aware of any new safety information that may place subjects at increased risk than what was previously known, the IRB will be promptly notified and if warranted, enrollment may be held until the PI determines whether a modification to the study is necessary and/or the informed consent documents are updated accordingly. It is the responsibility of the principal investigator to adhere to the Data Safety Monitoring Plan throughout the life of the study.

In addition, this protocol will utilize the SOCCI Data and Safety Monitoring Committee will provide another layer of data and safety oversight. DSMC membership and responsibilities are governed by the committee charter. The annual DSMC findings and recommendations will be reported in writing to the Principal Investigator as a summary letter which will be forwarded by the Principal Investigator or designee to the CS-IRB. The DSMC may increase or decrease the frequency of study review, at their discretion. Refer to the DSMC Charter for details of the DSMC review.

Multicenter Monitoring Plan

This trial will comply with the current requirements of the SOCCI Data and Safety Monitoring Committee. The SOCCI CCTO will be the Coordinating Center for this multicenter phase trial.

In accordance with the Data and Safety Monitoring Committee, investigators will conduct continuous review of data and patient safety. In addition, conference calls facilitated by the Study Lead at the Coordinating Center with investigators and staff at all participating sites will be scheduled at least monthly (and more often as needed) to discuss study progress. If there are no patients on treatment or in follow-up, email communication may be used in lieu of a teleconference, or in the circumstance where a scheduling conflict does not permit phone attendance. Meeting summaries will be included and document review of data and patient safety; meeting minutes will be submitted and reviewed by the DSMC.

All multicenter investigator-initiated trials conducted at the SOCCI are subject to data monitoring by the CCTO Quality Monitoring Committee (QMC). QMC has the responsibility for study monitoring for protocol compliance, data accuracy, performance of audits and monitoring of accrual (details found in the SOCCI Data Safety Monitoring Plan). All open trials are reviewed at a minimum once a year by the QMC (or more often depending on risk). This annual review includes the following: evaluation of the current accrual relative to the planned total accrual; examination of all reported violations; review of past monitoring visits and correspondence with the PI; review of previous correspondence between the PI and the QMC/DSMC. External sites will be notified of upcoming monitoring visits and will be expected to provide de-identified source documents for remote monitoring of patients, and/or access to the site EMR. Queries will be issued in the EDC and a detailed monitoring report will be provided to the participating site. The SOCCI CCTO will also forward any monitoring and/or auditing reports to the DSMC.

7.2 Replacement of subjects

Any subject who signs consent but does not undergo study intervention (i.e. high-res imaging) will be replaced.

7.3 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, monitoring/auditing logs/letters, records of study drug receipt, dispensation, destruction and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file in accordance with all applicable federal guidelines and local guidelines.

Investigators must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB, and Regulatory Agency (e.g., FDA) inspectors upon request.

Following closure of the study, each participating site will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

7.4 Adherence to Protocol

7.4.1 It is the responsibility of the Investigator-sponsor to ensure that patient recruitment and enrollment, treatment, follow-up for toxicities and response, and documentation and reporting at SOCCI are all performed as specified in the protocol. For multi-site studies, the site Principal Investigator at each participating site will assume the responsibilities for the day-to-day monitoring of the trial, including but not limited to review of eligibility of new subjects, proper documentation informed consent, administration of treatment per protocol, thorough documentation and capturing of research notes in the subject's charts, and timely completion of required case report forms. Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, or a protocol exception request approved by the SOCCI Medical Director and IRB of record, the study shall be conducted exactly as described in the approved protocol.

7.4.2 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, the IRB must be notified as soon as possible, but no more than 10 days from the investigator's awareness of the event.

7.4.3 Protocol Exceptions and Eligibility Waivers

A protocol exception is an anticipated or planned deviation from the IRB-approved research protocol, as described in the CSMC IRB Policy, Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement. For multi-site studies, the policy of the IRB of record must be followed. A protocol exception most often involves a single subject and is not a permanent revision to the research protocol. Protocol exceptions that extend beyond a single subject should result in a protocol amendment to avoid serial violations.

Planned exceptions to the protocol that are more than logistical in nature and/or impact an eligibility criterion, affect timing of study drug administration, or the investigator assesses the event may impact subject safety and/or study integrity, may not be implemented without prior IRB approval. The PI or her/his designee is responsible for submitting a protocol exception request and its supporting documents to the CSMC IRB if it meets the CS-IRB UPIRSO policy guidelines of a reportable exception/waiver. Study team should also refer to the IRB Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement guidelines to determine which deviations and exception requests require IRB reporting. For multi-site studies, the policy of the IRB of record must be followed. Once IRB approved, the deviation or exception can be implemented.

Special considerations for Eligibility Waivers (EW)

In general, subjects who do not meet the eligibility requirements should not be enrolled. In the rare event that it is appropriate for subject inclusion, the rationale/justification and subject case history should be submitted to the IRB for approval. Such requests for minimal risk studies do not require prior review by the CCTO Medical Director.

7.4.4 Other Protocol Deviations

Logistical deviations from the protocol (e.g., minor changes to the study schedule for an individual subject) do not require prior IRB approval unless the deviation has the potential to affect the subject's safety or study integrity. Such planned deviations that do meet this definition and do not affect the subject's safety or study integrity should be noted in the subject's research record or deviation log as described in the SOCCI CCTO's Standard Operating Procedure 12: Deviation and Noncompliance Reporting. For multi-site studies, follow local policy.

Unintentional deviations from the protocol that might affect subject safety or study integrity should be reported to the IRB within 10 days from when the investigator becomes aware that such a deviation has occurred, as outlined in the SOCCI CCTO's Standard Operating Procedure 12: Deviation and Noncompliance Reporting (or local policy, for multi-site studies). In this case, a Protocol Deviation report must be submitted in CS-IRB (or the IRB of Record), per CSMC IRB policy, Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement. For multi-site studies, the policy of the IRB of record must be followed. All submissions should include a description of the plan to avoid similar deviations or exceptions in the future.

7.4.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation. Repeat exceptions or deviations to the protocol may suggest a protocol amendment is needed.

7.5 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms and/or into a HIPAA-compliant study database. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data

Publications
The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the sponsor-investigator and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

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9.0 Summary of Changes

Protocol Version 1.0, dated 15 July 2020, amends Protocol Version 1.1, dated 22 March 2021.

Amendment 1: See changes below:

Section Study Schema added for clarification of study procedures for HIFU and prostatectomy patients. Both HIFU and prostatectomy patients will undergo the same screening procedures, research scan and the rest is standard of care. The only difference is that the repeat mpMRI only applies to the HIFU patients.

Section 3.4.2 Study calendar
Revised to include separate calendar for prostatectomy patients.

Section 5.0 Adverse Events
Revised to include minimal risk study language.

Section 5.2 Reporting Requirements
Revised to include minimal risk study language.

Section 7.0 Study Management
Revised to minimal risk study language.

Protocol Version 1.1, dated 22 March 2021, amends Protocol Version 2.0, dated 20 May 2021.

Amendment 2: See changes below:

Section 3.2.2 Exclusion criteria
Exclusion criteria #5, eGFR revised from less than 45 to less than 15 to follow current SOC Imaging guidelines.

Section 3.4.1.6 Physical exam including vital signs, height, and weight
Revised to define what are included for vital signs, which are heart rate, respiratory rate, blood pressure, and body temperature.

Section 3.4.1.7 Adverse event assessment
Revised to clarify only grade 3 and above imaging-related AEs will be captured and all SAEs following the receipt of 18F-DCFPyL agent.

Section 3.4.2 Study Calendar
Screening data expanded from 90 days to 180 days.

7.0 Study Management
Subject ID number clarified from three to six digits (ex. 832-001) to match sources.

For the Prostatectomy flowchart, study participation is complete after the SOC prostatectomy; there are no additional study related procedure after the SOC prostatectomy. Flowchart revised accordingly for clarification and to match MCA reviewed flowchart.

Sub-investigator list on protocol's first page updated to remove Grant Dagliyan and Beatrice Knudsen.

Protocol Version 2.0, dated 20 May 2021, amends Protocol Version 3.0, dated 14 September 2021.

Amendment 3: See changes below:

Section 3.2.2 Exclusion criteria
Exclusion criteria #4 revised to state that the exclusion applies to the HIFU arm only. The following reflects the modification "Suggestion of extracapsular extension or seminal vesicle invasion on imaging, if imaging was completed per SOC prior to or during screening for HIFU arm only"

Protocol Version 3.0, dated 14 September 2021, amends Protocol Version 4.0, dated 23 September, 2021.

Amendment 4: See changes below:

3.2.1 Inclusion Criteria
Inclusion criteria #2 revised to state that the inclusion applies to the HIFU arm only. The following reflects the modification "PSA $\leq$20 ng/mL (for HIFU arm only)".

Inclusion criteria #4 revised to state that the inclusion applies to the HIFU arm only. The following reflects the modification "Either overall Gleason score $\geq$ 7 with Gleason grade 4 or 5 component localized to one lobe (i.e. right or left) OR overall Gleason score 6 with $\geq$ half of systematic biopsy cores positive and $\geq$ 50% of core involvement in at least one core (for HIFU arm only)"

Inclusion #5 revised to add robotic radical prostatectomy. The following reflects the modification "Patient considering focal HIFU therapy or robotic radical prostatectomy".

3.2.2 Exclusion Criteria
Exclusion criteria #4 was removed.

Protocol Version 4.0, dated 23 September 2021, amends Protocol Version 5.0, dated 07 February 2022.

Amendment 5: See changes below:

Sub-investigators(s) Table
Removed Dr. Amit Gupta and added Dr. Susan Win and Dr. Michael Ahdoot.

Study Summary Table
The number of subjects in the Study Summary table was revised from 40 Study Subjects (Phase II), 20 Study Subjects (Pilot) to 40 Study Subjects (Phase II), 40 Study Subjects (Phase II).

Modified the objectives to reflect clarifications in primary and secondary endpoints for both cohorts.

Modified statistical analysis to reflect clarifications in primary and second endpoints for both cohorts.

3.1 Overview
Per PRMC recommendations, provided clarifications to the primary and secondary endpoints for both cohorts.
3.3. Study Endpoints
Per PRMC recommendations, provided clarifications to the primary and secondary endpoints for both cohorts.

3.4 Study Procedures
The following text were added " Scan results may identify patients who do not qualify for surgery" and "The investigator may decide to change arms for a subject (i.e. HIFU to RP or RP to HIFU) based on MRI finding or replace the subject after imaging review".

3.4.2 Study Calendar
For tissue collection, in addition to left-over tissue, the study allows for collection of 2 tubes of blood for research. We added "..and 2 yellow top (8.5mL) tubes of whole blood".

6.1 HIFU Phase II Study
Added HIFU Phase II Study as header at the beginning of the statistical analysis section.

6.2 Radical Prostatectomy Phase II Study
Added Radical Prostatectomy Phase II Study description per PRMC's recommendation for two separate primary and secondary endpoints for both cohorts.

6.3 Exploratory Objectives
This section was added to explain that tissue and blood will be used for future correlative studies.

Protocol Version 5.0, dated 07 February 2022, amends Protocol Version 6.0, dated 24 October 2022.

Amendment 6: See changes below:

3.4.1

This section is changed to allow enrollment of patients scheduled to undergo radical prostatectomy performed either at Cedars-Sinai Medical Center (CSMC) or an outside hospital (OSH). If the radical prostatectomy is performed at an OSH, authorization from subjects will first be obtained. Then the final pathology report of the radical prostatectomy from OSH will be obtained, reviewed and considered at CSMC for final data analysis.

Additionally, the outside pathology slides may need to be reviewed here at CSMC for final data analysis as well, however this decision will be made later. The principal investigator has confirmed that completing the radical prostatectomy at an OSH does not compromise the study and does not impact subject safety or study integrity.

6.1

This section is changed to allow the number of patients enrolled in the HIFU arm to decrease from 40 to 30, and the number of patients enrolled in the Radical Prostatectomy arm to decrease to 31. The reduction in sample size allows for 85% power for both arms, which the investigators consider adequate for the scope of the study.

Protocol Version 6.0, dated 24 October 2022. amends Protocol Version 7.0, dated 16 August 2023.

Amendment 7: See changes below

3.4.2 Study Calendar has noted that optional blood collection has been removed from ICF for patients consented after August 2023 (MODCR00000250)

6.3 Exploratory Objectives has been updated to note optional blood collection was removed from ICF for patients consented after August 2023 (MODCR00000250)

Protocol Version 7.0, dated 16 August 2023. amends Protocol Version 8.0, dated 08 November 2023.

Amendment 8: See changes below

3.4.2 Study calendar added 6-month follow up procedures in the Study Calendar for Radical Prostatectomy section