

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212643Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA Multi-Disciplinary Review and Evaluation

Application Type	NME & 505 (b)(2)
Application Number	NDA 212643
Priority or Standard	Standard
Submit Date	September 6, 2019
Received Date	September 6, 2019
PDUFA Goal Date	December 6, 2020
Division/Office	Division of Imaging and Radiation Medicine/Office of Specialty Medicine (DIRM/OSM)
Review Completion Date	November 23, 2020
Established/Proper Name	Gallium Ga 68 PSMA-11 Injection
Trade Name	N/A
Pharmacologic Class	Radioactive diagnostic agent
Code name	IC2000
Applicant	University of California, San Francisco
Dosage form	Injection
Applicant Proposed Dosing Regimen	111 MBq to 259 MBq (3 mCi to 7 mCi) as a bolus intravenous injection
Applicant Proposed Indication/Population	(b) (4)
Applicant Proposed SNOMED CT Indication Disease Term	254900004 Carcinoma of prostate (disorder)
Regulatory Action	Approval
Indications/Populations	Ga 68 PSMA-11 Injection is a radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer: • with suspected metastasis who are candidates for initial definitive therapy. • with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.
SNOMED CT Indication Disease Term	254900004 Carcinoma of prostate (disorder)
Recommended Dosing Regimen	111 MBq to 259 MBq (3 mCi to 7 mCi) as a bolus intravenous injection

Table of Contents

Table of Tables	5
Table of Figures.....	9
Reviewers of Multi-Disciplinary Review and Evaluation	10
Glossary.....	13
1 Executive Summary.....	14
1.1. Product Introduction	14
1.2. Conclusions on the Substantial Evidence of Effectiveness.....	14
1.3. Benefit-Risk Assessment.....	16
1.4. Patient Experience Data.....	21
2 Therapeutic Context	22
2.1. Analysis of Condition	22
2.2. Analysis of Current Treatment Options.....	24
3 Regulatory Background.....	25
3.1. U.S. Regulatory Actions and Marketing History	25
3.2. Summary of Presubmission/Submission Regulatory Activity.....	26
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	27
4.1. Office of Scientific Investigations.....	27
4.2. Product Quality	27
4.3. Clinical Microbiology.....	27
4.4. Devices and Companion Diagnostic Issues.....	28
5 Nonclinical Pharmacology/Toxicology.....	28
5.1. Executive Summary.....	28
5.2. Referenced NDAs, BLAs, DMFs	28
5.3. Pharmacology	28
5.4. ADME/PK.....	33
5.5. Toxicology	35
5.5.1. General Toxicology	35
5.5.2. Genetic Toxicology.....	36
5.5.3. Carcinogenicity	36
5.5.4. Reproductive and Developmental Toxicology.....	36
5.5.5. Other Toxicology Studies.....	36
6 Clinical Pharmacology.....	37
6.1. Executive Summary.....	37
6.2. Summary of Clinical Pharmacology Assessment	38

6.2.1.	Pharmacology and Clinical Pharmacokinetics	38
6.2.2.	General Dosing and Therapeutic Individualization	38
6.3.	Comprehensive Clinical Pharmacology Review	39
6.3.1.	General Pharmacology and Pharmacokinetic Characteristics.....	39
6.3.2.	Clinical Pharmacology Questions.....	46
7	Sources of Clinical Data and Review Strategy.....	48
7.1.	Table of Clinical Studies	48
7.2.	Review Strategy	49
8	Statistical and Clinical and Evaluation	50
8.1.	Review of Relevant Individual Trials Used to Support Efficacy	50
8.1.1.	PSMA-PreRP.....	50
8.1.2.	Study Results – PSMA-PreRP	55
8.1.3.	PSMA-BCR.....	72
8.1.4.	Study Results – PSMA-BCR	80
8.1.5.	PSMA-PreRP-Meta and van Kalmthout, et al. 2019	94
8.1.6.	PSMA-BCR-Meta	96
8.1.7.	Integrated Assessment of Effectiveness.....	97
8.2.	Review of Safety.....	101
8.2.1.	Safety Review Approach.....	101
8.2.2.	Review of the Safety Database.....	102
8.2.3.	Adequacy of Applicant’s Clinical Safety Assessments.....	103
8.2.4.	Safety Results.....	104
8.2.5.	Analysis of Submission-Specific Safety Issues	106
8.2.6.	Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability	106
8.2.7.	Safety Analyses by Demographic Subgroups.....	107
8.2.8.	Additional Safety Explorations	107
8.2.9.	Safety in the Postmarket Setting.....	108
8.2.10.	Integrated Assessment of Safety.....	108
8.2.11.	Specific Safety Studies/Clinical Trials.....	108
8.3.	Statistical Evaluation.....	109
8.3.1.	PSMA-PreRP Study.....	109
8.3.2.	PSMA-BCR Study.....	110
8.4.	Conclusions and Recommendations.....	121
9	Advisory Committee Meeting and Other External Consultations	121
10	Pediatrics.....	121

11 Labeling Recommendations..... 121
 11.1.Prescription Drug Labeling..... 121
12 Risk Evaluation and Mitigation Strategies 123
13 Postmarketing Requirements and Commitment..... 123
14 Office Director (or Designated Signatory Authority) Comments..... 123
15 Appendices..... 124
 15.1.References 124
 15.2.Financial Disclosure..... 128

Table of Tables

Table 1. Imaging Prostate Cancer	24
Table 2. PSMA Binding Data.....	29
Table 3. Equilibrium Dissociation Constant of ⁶⁸ Ga-PSMA-11 for Multiple Cell Lines	30
Table 4. Radiation-Absorbed Doses for Various Organs and Effective Dose for ⁶⁸ Ga-PSMA-11.....	44
Table 5. Listing of Clinical Trials	48
Table 6. PSMA-PreRP Schedule of Events.....	52
Table 7. Patients Scanned in the PSMA-PreRP Study Under Each UCLA Protocol Version	54
Table 8. Patients Scanned in the PSMA-PreRP Study Under Each UCSF Protocol Version	55
Table 9. Management of Patients Who Did Not Proceed to Radical Prostatectomy After ⁶⁸ Ga PSMA-11 PET in the PSMA-PreRP Study.....	56
Table 10. Demographic Characteristics of Patients in the PSMA-PreRP Full Analysis Set	59
Table 11. Comparison of Demographic Characteristics Among Several PSMA-PreRP Patient Sets	60
Table 12. ⁶⁸ Ga-PSMA-11 PET Positivity Rates in Patients Who Did (FAS) or Did Not Proceed to Surgery.....	62
Table 13. Patient-Level Comparison of ⁶⁸ Ga-PSMA-11 PET Majority Read Versus Histopathology for Detection of Pelvic Lymph Node Metastases.....	63
Table 14. Patient-Level Performance of ⁶⁸ Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases	64
Table 15. Patient-Level Performance of ⁶⁸ Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases, Stratified by Patient Age	64
Table 16. Patient-Level Performance of ⁶⁸ Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases, Stratified by Risk Factors.....	64
Table 17. Patient-Level Performance of ⁶⁸ Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases, Stratified by Study Site.....	65
Table 18. Patient-Level Performance of ⁶⁸ Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases, Stratified by PET Scan Date.....	66
Table 19. Per Reader Comparison of ⁶⁸ Ga-PSMA-11 PET Versus Pathology for Detection of Pelvic Lymph Node Metastases in the PSMA-PreRP Study	67
Table 20. Measures of Inter-Reader Agreement for ⁶⁸ Ga-PSMA-11 PET in the 123 Patients Used for Primary Endpoint Analysis	67

Table 21. Patients Included in the Applicant’s Post Hoc Analysis	68
Table 22. Result of Post-Hoc Analysis for Patient-Level Performance of ⁶⁸ Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases.....	70
Table 23. Patient-Level, Node Group-Level, and Region-Level Performance of ⁶⁸ Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases.....	70
Table 24. Patient-Level Performance of ⁶⁸ Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases, Stratified by Availability of Conventional Imaging at Enrollment	71
Table 25. Patient-Level Comparison of ⁶⁸ Ga-PSMA-11 PET to Conventional Imaging Results for Pelvic Nodal Metastases Using a Histopathology Reference Standard (N=67)	72
Table 26. List of Regions and Subregions to Be Evaluated by ⁶⁸ Ga-PSMA-11 PET	73
Table 27. Summary of Criteria Used to Classify ⁶⁸ Ga-PSMA-11 PET-Positive Findings for the Composite Reference Standard of PSMA-BCR.....	74
Table 28. PSA-BCR Schedule of Events	76
Table 29. Patients Scanned in the PSMA-BCR Study Under Each UCLA Protocol Version	78
Table 30. Patients Scanned in the PSMA-BCR Study Under Each UCSF Protocol Version	79
Table 31. Demographic Characteristics of Patients in the PSMA-BCR Study	82
Table 32. Patient-Level Comparison of ⁶⁸ Ga-PSMA-11 PET Majority Read Versus Histopathology Reference for Detection of Recurrent Prostate Cancer	85
Table 33. Region-Level Comparison of ⁶⁸ Ga-PSMA-11 PET Majority Read Versus Histopathology Reference for Detection of Recurrent Prostate Cancer*	85
Table 34. Distribution of Regions Evaluated in the Primary Analysis of PPV for ⁶⁸ Ga-PSMA-11 PET Versus Histopathology Reference	86
Table 35. Patient-Level Performance of ⁶⁸ Ga-PSMA-11 PET Versus Histopathology for Detection of Recurrent Prostate Cancer, Stratified by Patient Age	86
Table 36. Patient-Level PPV of ⁶⁸ Ga-PSMA-11 PET Versus Histopathology Reference for Detection of Recurrent Prostate Cancer, Stratified by Study Site	86
Table 37. Patient-Level PPV of ⁶⁸ Ga-PSMA-11 PET Versus Histopathology Reference for Detection of Recurrent Prostate Cancer, Stratified by PET Scan Date	87
Table 38. Patient-Level PPV of ⁶⁸ Ga-PSMA-11 PET Versus Histopathology Reference for Detection of Recurrent Prostate Cancer, Stratified by Possible Confounding Variables.....	87
Table 39. PPV of ⁶⁸ Ga-PSMA-11 PET Versus Composite Reference for Detection of Recurrent Prostate Cancer.....	88

Table 40. Distribution of Regions Evaluated in the Secondary Analysis of PPV for ⁶⁸ Ga-PSMA-11 PET Versus Composite Reference	89
Table 41. Utilization of Criteria to Characterize Lesions Under the Composite Reference Standard	89
Table 42. ⁶⁸ Ga-PSMA-11 PET Positivity Rate Stratified by PSA Level	90
Table 43. Per Reader Patient-Level Comparison of ⁶⁸ Ga-PSMA-11 PET Versus Composite Reference Standard for Detection of Recurrent Prostate Cancer	90
Table 44. Measures of Inter-Reader Agreement for ⁶⁸ Ga-PSMA-11 PET in the Inter-Reader Set.....	91
Table 45. Results of the Survey of Intended Management in PSMA-BCR, Including Patients With and Without Reference Standard Data	91
Table 46. Correct Detection Rate for ⁶⁸ Ga-PSMA-11 PET by Histopathology and Composite Reference Standards	93
Table 47. PPV for ⁶⁸ Ga-PSMA-11 PET by Histopathology and Composite Reference Standards in the Subset of Patients With a Single Subregion Assessed for the Reference Standard	93
Table 48. PPV for ⁶⁸ Ga-PSMA-11 PET by Composite Reference Standard, Stratified by Baseline Conventional Imaging Result.....	94
Table 49. Overview of the Five Studies in PSMA-PreRP-Meta Reporting a Total of 266 Patients	95
Table 50. Comparison of ⁶⁸ Ga-PSMA-11 Performance for Detection of Pelvic Lymph Nodes Between the PSMA-PreRP-Meta, (van Kalmthout et al. 2019), and PSMA-PreRP Studies	95
Table 51. Summary of Literature-Based Studies Included for Meta-Analysis PSMA-BCR-Meta	96
Table 52. Demographic Characteristics of the Safety Analysis Population	102
Table 53. Treatment-Emergent Adverse Events in the Safety Population.....	105
Table 54. Adverse Event Rates by Patient Age	107
Table 55. Adverse Event Rates by Administered Dose of ⁶⁸ Ga-PSMA-11.....	107
Table 56. Tipping Point Analysis – PSMA-PreRP Study*	109
Table 57. Patient-Level Tipping Point Analysis – PSMA-BCR Study	111
Table 58. Region-Level Tipping Point Analysis – PSMA-BCR	112
Table 59. Reference Standard Distribution in Patients With Respect to PSA Level	113
Table 60. Analysis by PSA Level Using PPV in Composite Reference Standard Patients	114
Table 61. Analysis by PSA Level Using PPV in Histopathology Patients	114
Table 62. Reference Standard Distribution in Patients With Respect to Region	115
Table 63. Analysis by Region Using PPV in Composite Reference Standard Patients	115

Table 64. Analysis by Region Using PPV in Histopathology Patients..... 116

Table 65. Region-Level PPV for Subcentimeter Lesions by PSA Level 117

Table 66. Region-Level Analysis With Imputation Derived From Table 65 117

Table 67. Patient-Level PPV for Subcentimeter Lesions by PSA Level..... 117

Table 68. Patient-Level Sensitivity Analysis With Imputation Derived From Table 67 .. 118

Table 69. Region-Level PPV Using Histopathology for Subcentimeter Lesions by PSA
Level 118

Table 70. Region-Level Sensitivity Analysis With Imputation Derived From Table 69... 119

Table 71. Patient-Level PPV Using Histopathology for Subcentimeter Lesions by PSA
Level 119

Table 72. Patient-Level Sensitivity Analysis With Imputation Derived From Table 71 .. 120

Table of Figures

Figure 1. ⁶⁸ Ga-PSMA-11 PET Uptake at 1 Hour Post-Injection in NOD/SCID Mouse Xenograft Model	31
Figure 2. ⁶⁸ Ga-PSMA-11 PET Uptake in Nude Mice Bearing LNCaP, CWR22Rv1, and PC-3 Xenografts.....	32
Figure 3. Biodistribution of ⁶⁸ Ga-PSMA-11 in Nude Mice Bearing LNCaP, CWR22Rv1, and PC-3 Xenografts.....	34
Figure 4. ⁶⁸ GaPSMA-11 Cell Binding, Internalization, and Binding Affinity	40
Figure 5. Whole-Body Images of a Patient Injected With ⁶⁸ Ga-PSMA-11 at Seven Time Points (0 Minutes to 4 Hours 25 Minutes Post-Injection)	41
Figure 6. Biodistribution of ⁶⁸ Ga-PSMA-11	42
Figure 7. Boxplots of Pathological Versus Non-Pathological Uptake in the Prostate, Lymph Nodes, and Bone	42
Figure 8. Sequential PET/CT of a Patient Following the Injection of 170 MBq ⁶⁸ Ga-PSMA-11.....	45
Figure 9. Patient Disposition in the PSMA-PreRP Study	56
Figure 10. Patient Disposition in the PSMA-BCR Study	80
Figure 11. Patient Disposition in the PSMA-BCR Study	111

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Diane Hanner, MPH, MSW
Nonclinical Reviewer	Sunny Awe, PhD
Nonclinical Team Leader	Adebayo A. Laniyonu, PhD
Office of Clinical Pharmacology Reviewer(s)	Christy S John, PhD
Office of Clinical Pharmacology Team Leader(s)	Nam Atiqur Rahman, PhD
Clinical Reviewer	Shane Masters, MD, PhD
Clinical Team Leader	August Hofling, MD, PhD
Statistical Reviewer	Kelly Yang, PhD
Statistical Reviewer	Sungwon Lee, PhD
Statistical Team Leader	Sue Jane Wang, PhD
Cross-Disciplinary Team Leader	August Hofling, MD, PhD
Division Director (DIRM)	Liberio Marzella, MD, PhD
Office Director (or designated signatory authority)	Alex Gorovets, MD

DIRM = Division of Imaging and Radiation Medicine

Additional Reviewers of Application

OPQ	John Amartey, PhD Krishnakali Ghosh, PhD Eldon Leutzinger, PhD Danae Christodoulou, PhD
Microbiology	Maritere Carattini, PhD John Metcalfe, PhD
OPDP	David Foss, Pharm D Jim Dvorsky, Pharm D
OSI	John Lee, MD Phillip Kronstein, MD
DPMH	Jeannie Best, MSN, RN, PNP Tamara Johnson, MD, MS Lynn Yao, MD
OSE/DMEPA	Devin Kane, Pharm D Hina Mehta, Pharm D
Other	Mitchell Anscher, MD (DO1) Daniel Suzman, MD (DO1) Kish Chakrabarti, PhD (DIRM) Anthony Fotenos, MD, PhD (DIRM)

OPQ = Office of Pharmaceutical Quality

OPDP = Office of Prescription Drug Promotion

OSI = Office of Scientific Investigations

DPMH=Division of Pediatric and Maternal Health

OSE = Office of Surveillance and Epidemiology

DMEPA = Division of Medication Error Prevention and Analysis

DO1 = Division of Oncology 1

DIRM = Division of Imaging and Radiation Medicine

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Sunny Awe, PhD	OSM/DIRM	Sections: 5	Select one: ☒ Authored ☐ Approved
	Signature: See end of document			
Nonclinical Supervisor	Adebayo Lanijonu, PhD	OSM/DIRM	Sections: 5	Select one: ☐ Authored ☒ Approved
	Signature: See end of document			
Clinical Pharmacology Reviewer	Christy S. John, PhD	OCP/DCP5	Sections: 6	Select one: ☒ Authored ☐ Approved
	Signature: See end of document			
Clinical Pharmacology Team Leader	Nam Atiqur Rahman, PhD	OCP/DCP5	Section: 6	Select one: ☐ Authored ☒ Approved
	Signature: See end of document			
Clinical Reviewer	Shane Masters, MD, PhD	OSM/DIRM	Sections: 1, 2, 3, 7, 8.1, 8.2, 8.4, 11	Select one: ☒ Authored ☐ Approved
	Signature: See end of document			
Clinical Team Leader, Cross-Disciplinary Team Leader	August Hofling, MD, PhD	OSM/DIRM	Sections: All	Select one: ☒ Authored ☒ Approved
	Signature: See end of document			

NDA Multi-Disciplinary Review and Evaluation: NDA 212643, Gallium Ga 68 PSMA-11 Injection

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Kelly Yang, PhD	OB/DB1	Sections: 8.3.1	Select one: ☒ Authored ☐ Approved
	Signature: See end of document			
Statistical Reviewer	Sungwon Lee, PhD	OB/DB1	Sections: 8.3.2	Select one: ☒ Authored ☐ Approved
	Signature: See end of document			
Statistical Secondary Reviewer	Jyoti Zalkikar, PhD	OB/DB1	Sections: 8.3	Select one: ☒ Authored ☐ Approved
	Signature: See end of document			
Deputy Division Director (Statistical)	Sue Jane Wang, PhD	OB/DB1	Sections: 8.3	Select one: ☐ Authored ☒ Approved
	Signature: See end of document			
Division Director	Louis Marzella, MD, PhD	OSM/DIRM	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature: See end of document			
Deputy Director	Alex Gorovets, MD	OSM	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature: See end of document			

Glossary

ADT	androgen deprivation therapy
AE	adverse event
AR	adverse reaction
ASTRO	American Society for Radiation Oncology
BCR	biochemical recurrence
BLA	biologics license application
CFR	Code of Federal Regulations
CSR	clinical study report
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	good clinical practice
IND	investigational new drug
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NPV	negative predictive value
OSI	Office of Scientific Investigation
PET	positron emission tomography
PIP	PSMA positive PC-3 cell line
PPV	positive predictive value
PRO	patient reported outcome
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen

1 Executive Summary

1.1. Product Introduction

Gallium Ga 68 PSMA-11 Injection (referred to as ^{68}Ga -PSMA-11 in this review) is a peptide-based, positron-emitting radiopharmaceutical that binds to prostate-specific membrane antigen (PSMA), a protein that is overexpressed in most prostate cancers. ^{68}Ga -PSMA-11 is a new molecular entity. The proposed indications are for positron emission tomography (PET) of PSMA-positive lesions in men with prostate cancer in two defined clinical settings. The first setting is when metastasis is suspected in patients who are candidates for initial definitive therapy. The second setting is when cancer recurrence is suspected based on elevated serum prostate-specific antigen (PSA) level. ^{68}Ga -PSMA-11 is intended to be administered intravenously at a dose of 3 to 7 mCi.

New drug application (NDA) 212642 and NDA 212643 for ^{68}Ga -PSMA-11 were submitted simultaneously under the 505(b)(2) pathway. As further described in Section 3.2, the two NDAs share all data except for separate manufacturing information. As such, the review of non-clinical, clinical pharmacology, clinical, and statistics information is identical for each NDA. A unique product quality review has been separately written for each NDA.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence was submitted that demonstrates the ability of ^{68}Ga -PSMA-11 to image prostate cancer in two populations: 1) men with suspected metastasis who are candidates for initial definitive therapy, and 2) men with suspected recurrence based on elevated serum PSA. Main support for efficacy was derived from two adequate and well-controlled trials which were conducted prospectively by the Applicant and were supported by reviews of published literature.

The first adequate and well-controlled trial evaluated the imaging of prostate cancer-bearing pelvic lymph nodes in intermediate- to high-risk patients preparing for radical prostatectomy. Using histopathology as the reference standard in patient-level analysis, ^{68}Ga -PSMA-11 PET had a sensitivity of 47% (95% confidence interval 29-65%), specificity of 90% (84-96%), and positive predictive value (PPV) of 61% (41-81%).

The second adequate and well-controlled trial evaluated the imaging of metastatic disease in patients with biochemical recurrence of prostate cancer. ^{68}Ga -PSMA-11 had a patient-level PPV of 83% (75-91%) using a histopathology reference standard.

The performance of ^{68}Ga -PSMA-11 PET in these two trials demonstrates the clinical usefulness of this imaging test in the studied patient populations. Reviews of the published literature submitted by the Applicant for each of the populations of intended use support the

generalizability of the results beyond the two sites of the trials conducted by the Applicant. In summary, the Applicant has provided substantial evidence of effectiveness of ⁶⁸Ga-PSMA-11 PET.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In American men, prostate cancer is the most common malignancy and the second-most common cause of cancer death. While many imaging techniques have been applied to prostate cancer, none have optimal performance. The need for improved prostate cancer imaging is reflected in the recurrence rate of up to 30% after definitive therapy of what was thought to be localized disease. Similarly, many patients with biochemical recurrence fail to have their disease localized by imaging. Diagnostic challenges persist despite recent imaging advances, such as multiparametric MRI and PET drugs approved for prostate cancer, such as ¹⁸F-fluciclovine.

⁶⁸Ga-PSMA-11 injection is a positron emitting radiopharmaceutical proposed by the Applicant [REDACTED] (b) (4). [REDACTED] The data submitted in this application from two adequate and well-controlled trials prospectively conducted by the Applicant support approval for imaging evaluation of suspected prostate cancer metastasis in two patient populations, men who are candidates for initial definitive therapy and men with biochemical evidence (serum PSA level) of prostate cancer recurrence (hereafter referred to as biochemical recurrence).

In patients with intermediate- to high-risk prostate cancer who are candidates for prostatectomy, the data submitted show low sensitivity but high specificity of ⁶⁸Ga-PSMA-11 PET for detection of pelvic lymph node metastases. Of note, there is reason to suspect that the diagnostic performance was underestimated due to trial design and conduct. The data also suggest that ⁶⁸Ga-PSMA-11 PET performs better in patients with higher grade prostate cancer in this setting. Regardless, it is anticipated that many patients with pelvic lymph node metastases will not be detected by ⁶⁸Ga-PSMA-11 PET. However, given similar limitations in available imaging techniques, such false negative results are expected to have no impact on the treatment plan of definitive therapy in affected patients. The potential value of ⁶⁸Ga-PSMA-11 PET lies in the demonstration that PPV exceeds the expected prevalence of lymph node metastasis in the population of intended use. While a positive PET scan may still need to be confirmed by other means, the results would allow a patient with metastasis to avoid the morbidity of surgery for more appropriate treatment. A positive PET scan might also help target therapy as part of the emerging paradigm of treatment of patients with limited metastases, also referred to as oligometastatic disease.

In patients with biochemical recurrence, the submitted data clearly show favorable performance of ⁶⁸Ga-PSMA-11 PET. Although traditional

evaluation of sensitivity and specificity were precluded by the disease condition and trial design, the PPV results demonstrate that PET positive lesions are highly likely to be prostate cancer. Additionally, ⁶⁸Ga-PSMA-11 PET displays good detection of lesions at lower, more clinically meaningful PSA levels. Such imaging qualities have the potential to positively impact patient care in this clinical setting where detection and localization of disease are critical.

The diagnostic performance of ⁶⁸Ga-PSMA-11 in patients with biochemical recurrence supports the performance in patients who are candidates for definitive therapy of primary tumor, and vice versa. Also, while the two adequate and well-controlled trials prospectively conducted by the Applicant were restricted to two academic sites in the same geographical region, data from the published literature support the generalizability of the trial results.

For the safety evaluation, 960 patients with prostate cancer received ⁶⁸Ga-PSMA-11 in the studies performed by the Applicant. No deaths, serious adverse reactions, or discontinuations due to adverse reaction (AR) were reported from this drug that is administered in microgram doses. Treatment emergent adverse events were uncommon and mild in intensity. Radiation effective dose from ⁶⁸Ga-PSMA-11 is typical of PET oncology imaging and estimated to impart minimal risk. Risk of misdiagnosis related to false negative and false positive results is applicable to imaging tests in general.

In summary, the benefit of ⁶⁸Ga-PSMA-11 PET in the indicated patient populations with prostate cancer outweighs the acceptably low risks. Therefore, approval of this application is warranted.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Prostate cancer is the most common cancer in American men and the second most common cause of cancer related death in this population. - The course of prostate cancer varies widely. While many men will have slow growing cancer that needs no treatment, others will have aggressive disease that leads to pain, debilitation, and death.	- Prostate cancer is a serious condition that causes substantial morbidity and mortality. - Imaging of disease can have important impact on patient management.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The pelvic lymph nodes are typical sites of initial metastasis of prostate cancer. • Proper management of prostate cancer involves assessment of the risk of aggressive disease as well as evaluation of the location and extent of disease.	
<u>Current Treatment Options</u>	• Many imaging techniques have been applied to prostate cancer, including ultrasound, CT, MRI, bone imaging using ^{99m}Tc-medronate or ¹⁸F-fluoride, ¹¹¹In-capromab pentetide SPECT, and PET using ¹¹C-choline or ¹⁸F-fluciclovine. The technique used varies depending on what information is needed. • For patients with newly diagnosed prostate cancer who are at intermediate or higher risk, treatment choice is influenced by whether cancer has spread to regional lymph nodes and more distant sites. Current standard-of-care relies on imaging with ^{99m}Tc-medronate bone scan along with CT or MRI of the abdomen and pelvis to detect such metastases. The diagnostic performance of these techniques is moderate. Recurrent prostate cancer after prostatectomy has been estimated to occur in up to 30% of men who had no evidence of metastatic disease on initial conventional imaging. While therapeutic methods may be a factor, this recurrence rate suggests that disease outside the prostate gland is missed by conventional imaging techniques in a number of cases. • Prostate cancer recurrence is usually first recognized due to an increase in serum PSA level. Bone scan and CT or MRI are used to locate recurrent disease, because this information might guide	• Despite the availability of many different techniques for imaging prostate cancer, there is an unmet need for better diagnostic performance. • Standard-of-care imaging in most scenarios is based largely on anatomic modalities such as CT and MRI, which are best at finding large lesions. • Functional bone imaging tends to be either insensitive at lower, clinically relevant PSA levels in the case of ^{99m}Tc-medronate or limited by low specificity in the case of ¹⁸F-fluoride. • With the marketing discontinuation of ¹¹¹In-capromab pentetide, no imaging drugs are currently approved specifically for imaging of prostate cancer prior to definitive therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	optimal therapy. ¹¹C-choline and ¹⁸F-fluciclovine PET might also be used as they are both specifically approved for prostate cancer imaging in the setting of biochemical recurrence. There is a need for higher detections rate when the PSA level is low.	¹¹C-choline and ¹⁸F-fluciclovine are PET drugs approved specifically for imaging of prostate cancer in patients with biochemical recurrence. Lesion detection rates with these agents are limited at the low PSA levels of early recurrence.
Benefit	- Two adequate and well-controlled prospective trials were conducted by the Applicant and submitted in this NDA. - Trial PSMA-PreRP (pre-radical prostatectomy) enrolled 325 men with intermediate- to high-risk prostate cancer before therapy with radical prostatectomy to determine how effective ⁶⁸Ga-PSMA-11 is at identifying prostate cancer in the pelvic lymph nodes. In the 123 patients who could be evaluated, the sensitivity was low, but the specificity was high. Positive predictive value (PPV) exceeded the estimated prevalence of lymph node metastasis in this patient population. Design and conduct of the trial suggest that diagnostic performance was underestimated. Subgroup analysis suggests that the test may perform better in patients with higher grade cancer. - Trial PSMA-BCR (biochemical recurrence) enrolled 635 men with biochemically recurrent prostate cancer to determine the effectiveness of ⁶⁸Ga-PSMA-11 for identifying sites of recurrent disease. In the 86 men who had tissue sampling of a PET positive lesion, the lesion usually was prostate cancer. Results were also favorable in 210 men who had PET positive lesions compared to composite reference standard data derived from a combination of	- There is substantial evidence of effectiveness for ⁶⁸Ga-PSMA-11. - Although pre-specified statistical goals of the PSMA-PreRP trial were not met, the observed diagnostic performance supports clinical utility in this patient population. While the low sensitivity means that pelvic nodal disease will be missed in certain patients, a similar limitation applies to current standard-of-care imaging and it is not expected to negatively impact traditional patient management. A positive scan may sometimes need to be confirmed by other means, but could ultimately impact treatment strategy. Because ⁶⁸Ga-PSMA-11 PET does not rely on size for identification of abnormal lymph nodes, it can be considered a complementary test to CT and MR.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	histopathology, imaging, and PSA levels. The PET scan was read as positive in approximately three fourths of imaged patients. Even in those patients with PSA level of 1 ng/mL or less, the PET was read as positive approximately half of the time. While there was likely bias in selection of patients for evaluation in this study, subgroup analysis suggests it had only minor impact on performance results. It also appears that ⁶⁸Ga-PSMA-11 does not perform as well in the prostate fossa as elsewhere in the body.	For imaging of disease in patients with biochemical recurrence, ⁶⁸Ga-PSMA-11 PET met clinically relevant performance goals. The detection rate of ⁶⁸Ga-PSMA-11 PET is affected by PSA level. However, its performance may represent a meaningful advance for patients with prostate cancer.
Risk and Risk Management	- The studied safety population consisted of 960 men with prostate cancer. - No deaths, serious adverse events, or study withdrawals related to adverse events occurred. - Adverse events were rare, and all reported events were mild. - The radiation effective dose is estimated to be 4.4 mSv.	No safety concerns are identified. The radiation effective dose is typical of oncologic PET imaging.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify):	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☒	Patient experience data were not submitted as part of this application.	

2 Therapeutic Context

2.1. Analysis of Condition

The American Cancer Society estimated that in 2019, prostate cancer would be the most commonly diagnosed cancer in American men, with 174,650 new cases predicted (Siegel et al. 2019). While prostate cancer-specific mortality has decreased over recent history, by 51% from 1993 to 2016, prostate cancer was predicted to be the second most common cause of cancer induced fatality in men for 2019, with 31,620 deaths predicted. Also, in recent years there has been a trend toward diagnosis of prostate cancer at higher stages, which is presumably due to changes in prostate cancer screening practices. These statistics demonstrate the need for continued advances in prostate cancer diagnosis and therapy.

The large majority of prostate cancers are carcinomas of two broad types, glandular and neuroendocrine (Humphrey 2017). The most common prostate cancer overall is a glandular type, acinar adenocarcinoma, although another glandular type, intraductal carcinoma, may often coexist with it and suggests a more aggressive course (Humphrey 2017). While less common, the neuroendocrine carcinomas of the prostate are important to recognize as they are treated differently. One of these, small cell carcinoma, is notable for its propensity to arise after treatment of acinar adenocarcinoma, accounting for about of one of three patients with small cell carcinoma of the prostate.

The natural history of prostate cancer is variable, ranging from indolent tumors that remain confined to the prostate for decades to highly aggressive tumors that rapidly metastasize and lead to death. Accordingly, it is necessary to predict the aggressiveness of the cancer at diagnosis to determine management and prevent undertreatment or overtreatment. Typically, a panel of risk factors is evaluated, but because there are many contributory factors, several methods have been devised. One of the earliest was the D'Amico risk classification, which includes the tumor stage by the American Joint Committee on Cancer TNM criteria (T: primary tumor features, N: involvement of regional lymph nodes, and M: the presence or absence of distant metastases), tumor grade by Gleason score, and serum level of prostate-specific antigen (PSA) and divides patients into low-, intermediate-, and high-risk categories (D'Amico et al. 1998). The widely used National Comprehensive Cancer Network (NCCN) classification (Mohler et al. 2019) includes additional information from the prostate biopsy, such as the number of positive cores and PSA density, to generate six risk categories. Most risk stratification schemes do not explicitly incorporate imaging, with the goal of minimizing unnecessary testing procedures and associated expense. Instead, imaging of patients with newly diagnosed prostate cancer is performed once a risk threshold has been passed.

As with most other malignancies, prostate cancer can metastasize throughout the body and very often follows typical pathways of progression. Prostate cancer is most likely to spread initially to the pelvic lymph nodes, including the obturator, internal iliac, and external iliac

chains. These sites are designated regional metastases. Once beyond the pelvic lymph nodes, the abdominal retroperitoneal lymph nodes and bones are the most common locations of metastasis. More advanced patterns of tumor progression can involve extrapelvic, non-nodal soft tissue sites like liver and lung.

For prostate cancer localized to the prostate gland, if the risk of progression is considered high enough, curative intent therapy using radical prostatectomy or radiation therapy has good success rates (Mohler et al. 2019). After definitive therapy, the patient's PSA level should fall and become undetectable in the case of prostatectomy or reach a nadir in the case of radiotherapy. Monitoring for recurrence largely focuses on a combination of clinical signs and symptoms as well as serum PSA level. A rising PSA level after definitive therapy indicates a very high likelihood that prostate cancer is present and is termed biochemical recurrence (Roach et al. 2006; Cookson et al. 2007). Current treatment in this situation is typically non-curative in intent, but optimal management still depends on knowledge of disease location and extent. In addition, localized therapies such as radiotherapy or percutaneous ablative techniques are being tested on oligometastatic prostate cancer in initial and recurrent settings, and precise localization of disease could further facilitate such therapies.

⁶⁸Ga-PSMA-11 allows PET imaging of prostate cancer through binding to the prostate-specific membrane antigen (PSMA). This molecule, also known as glutamate carboxypeptidase II or folate hydrolase I, is a transmembrane protein with an extracellular enzymatic domain. PSMA is expressed in normal prostate epithelial cells where its function is unknown (Silver et al. 1997; Bostwick et al. 1998). PSMA is also expressed in other normal tissues, particularly the glia of the central nervous system where it is involved in glutaminergic neurotransmission, the renal proximal tubules, in breast epithelium, and in the gut where it may be involved with folate uptake.

In the majority of prostate adenocarcinomas, PSMA is overexpressed compared to benign prostate epithelium. For example PSMA was overexpressed in 33 of 35 tumor specimens in one case series (Silver et al. 1997). PSMA also appears to be more highly expressed in higher grade tumors (Bravaccini et al. 2018). However, neuroendocrine prostate cancer, particularly when it arises after treatment of prostate adenocarcinoma, may have low or absent PSMA expression. PSMA expression is also less common in bone metastases than in the primary prostate tumor (Silver et al. 1997).

The term prostate-specific membrane antigen is somewhat misleading as there are many literature reports of PSMA overexpression in certain non-prostate malignancies and non-malignant conditions. For many malignancies, this effect may be mediated by expression of PSMA in the neovasculature rather than in malignant cells (Chang et al. 1999). This phenomenon has been reported in several cancers, including non-small cell lung cancer, melanoma, colon cancer, clear cell renal cell carcinoma, and thyroid carcinoma. In certain case series, PSMA expression results in visualization of non-prostate cancers on ⁶⁸Ga-PSMA-11 PET (Salas Fragomeni et al. 2018). Similarly, benign tumors such as thyroid adenoma and

hemangioma (soft tissue and bone) may be visualized by ⁶⁸Ga-PSMA-11 PET. Normal osteoblasts express PSMA, and this observation may explain the increased uptake of ⁶⁸Ga-PSMA-11 in a variety of benign bone diseases such as Paget disease, fibrous dysplasia, osteoarthritis, and fracture (Hofman et al. 2018).

2.2. Analysis of Current Treatment Options

The use and effectiveness of imaging in patients with prostate cancer varies with the task to be accomplished. Imaging options are summarized in [Table 1](#). Only ¹¹¹In-capromab pentetide, ¹¹C-choline, and ¹⁸F-fluciclovine are approved specifically for prostate cancer imaging. Note that imaging is not recommended for prostate cancer screening.

Table 1. Imaging Prostate Cancer

Technique	Use in Practice	Efficacy	Comments
Ultrasound	Diagnosis (guide biopsy) Restaging	Detection of prostate bed recurrence after RP: Sensitivity 76% Specificity 67%	Limited to prostate and prostate bed
CT	Initial staging Restaging	Identifying pelvic lymph nodes prior to initial definitive therapy: Sensitivity 57% Specificity 68%	Poor performance for lesions contained within the prostate
MRI	Diagnosis (guide biopsy) Initial staging Restaging Active surveillance	Identifying pelvic lymph nodes prior to initial definitive therapy: Sensitivity 59% Specificity 79% (using DWI)	Current best choice for imaging prostate gland
^{99m} Tc-medronate	Initial staging Restaging Therapy monitoring	Detection of spinal metastases: Sensitivity 51% Specificity 82%	Limited to bone imaging Usually negative if PSA <10 ng/mL
¹⁸ F-fluoride	Initial staging Restaging	Detection of spinal metastases: Sensitivity 93% Specificity 54%	Limited to bone imaging NCCN recommends second line use behind ^{99m} Tc-medronate due to lower specificity

Technique	Use in Practice	Efficacy	Comments
¹¹¹ In-capromab pentetide	Initial staging Restaging	Identifying pelvic lymph nodes prior to initial definitive therapy: Sensitivity 63% Specificity 67% Identifying disease after BCR: PPV 50%	Discontinued by BLA holder Approved for SPECT imaging of prostate cancer prior to definitive therapy and in the BCR setting Trial supporting BCR claim only sampled lesions in the pelvis
¹¹ C-choline	Restaging	Identifying disease after BCR: PPV 82%	Approved for PET imaging of prostate cancer only in the BCR setting Labeling indicates performance may be more reliable if PSA >2 ng/mL
¹⁸ F-fluciclovine	Restaging	Identifying disease after BCR: PPV 76% Detection rate 60% (for PSA ≤1.78 ng/mL) Detection rate 96% (for PSA >1.78 ng/mL)	Approved for PET imaging of prostate cancer only in the BCR setting

Sources: (Leventis et al. 2001; Heck et al. 2014; Poulsen et al. 2014; Mohler et al. 2019), labels for ¹¹¹In-capromab pentetide, ¹¹C-choline, and ¹⁸F-fluciclovine.

Abbreviations: BCR = biochemical recurrence, BLA = biologics license application, CT = computed tomography, DWI = diffusion weighted imaging, MRI = magnetic resonance imaging, NCCN = National Comprehensive Cancer Network, PET = positron emission tomography, PPV = positive predictive value, PSA = prostate-specific antigen, RP = radical prostatectomy, SPECT = single photon emission computed tomography

The diagnostic yield of these tests depends on the likelihood that unknown disease is present in the imaged area. Therefore, imaging is usually restricted to patients with higher risk disease. This dependence also explains some of the variability in the published test performance results; values in the table are from selected studies, or where available from the approved labeling. However, it can be summarized that currently available imaging techniques have less than optimal sensitivity and specificity for detection of prostate cancer, particularly in clinically meaningful situations where tumor lesions are small in volume.

3 Regulatory Background

3.1.U.S. Regulatory Actions and Marketing History

⁶⁸Ga-PSMA-11 is a new molecular entity.

3.2. Summary of Presubmission/Submission Regulatory Activity

Two new drug applications for ⁶⁸Ga-PSMA-11 injection were received by the Food and Drug Administration (FDA) on September 6, 2019, NDA 212642 from the University of California, Los Angeles (UCLA), and NDA 212643 from the University of California, San Francisco (UCSF). The two Applicants collaborated to conduct the two prospective trials to support both NDAs. They do not wish to file a single NDA due to separate manufacturing processes, and neither wishes to file an ANDA after approval of an NDA submitted by the other. FDA concurrence with the dual NDA approach was sent to the Applicants by email on December 17, 2017, with the conditions that the second NDA be filed before the action date of the first and that the first NDA Applicant waives all exclusivity and patent rights. These conditions have been met; both applications contain waivers of exclusivity and state that there are no relevant patents. Modules 4 and 5 of the applications are identical except for the protocol versions used for the clinical trials.

Investigational New Drug (IND) 130649 from UCLA was received May 3, 2016, and IND 127621 from UCSF was received on August 24, 2015. For most of the regulatory milestones related to the NDAs, the Applicants acted in concert and each provided a letter of cross-reference to the other's IND.

On March 15, 2016, there was a teleconference with faculty from UCSF, (b) (4) with a representative from (b) (4) to discuss a clinical development program for ⁶⁸Ga-PSMA-11 based on multicenter trials of the agent for imaging patients with prostate cancer both prior to definitive therapy and at the time of suspected disease recurrence.

On August 10, 2016, there was a teleconference with faculty from UCSF, UCLA, (b) (4) to discuss the design of the protocols that would later be known as PSMA-PreRP and PSMA-BCR. At this meeting, the Applicant and FDA agreed that the PSMA-PreRP primary endpoint should be assessed at the patient-level using a pathology reference standard.

There was a subsequent transition in phase 3 development such that UCSF and UCLA jointly led two dual-center trials. On August 29, 2018, faculty from UCSF and UCLA participated in a pre-NDA meeting that primarily focused on the content and format of the planned application.

During review of NDA 212642 and NDA 212643, additional requested CMC information received on August 28, 2020, was determined to constitute a major amendment to each application. Therefore, the standard review timeline was extended by an additional three months to allow full review of the submissions.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

Because the PSMA-PreRP and PSMA-BCR studies provided the primary efficacy results for the regulatory decision regarding ^{68}Ga -PSMA-11, Office of Scientific Investigation (OSI) audit of the two studies was requested. The inspections were conducted at UCLA and UCSF study sites in February 2020 and March 2020. No significant GCP deficiencies were observed for either study and OSI determined that the data from the inspected sites appeared reliable as reported in the NDA.

4.2. Product Quality

Reference is made to the separate complete product quality review (Integrated Quality Assessment, DARRTS 11/12/20).

The drug product, Ga 68 PSMA-11 Injection, contains the active ingredient ^{68}Ga -labeled Glu-NH-CO-NH-Lys(Ahx)-HBED-CC (PSMA-11) and the excipients ethanol and 0.9% sodium chloride injection (USP). The drug product is a sterile, clear, pyrogen free, colorless aqueous solution presented in a multiple-dose vial. The synthesis process is conducted

(b) (4)

under cGMP.

The product met all the drug product quality and microbiological quality regulatory specifications. The stability data provided supports the proposed 4-hour expiration.

The Agency's preapproval inspection of the Applicant's manufacturing facility (UCSF Biomedical Cyclotron Radiopharmaceutical Facility) identified deficiencies in analytical methodology and in-process controls. The Agency notified the Applicant on August 24, 2020 that there were insufficient data in the NDA to assess product quality. The Agency requested that the Applicant provide the data not previously submitted in the original application and subsequent amendments by August 28, 2020. The Applicant agreed.

Upon review of the major amendment received on August 28, 2020, no product quality deficiencies remained. Additional manufacturing facilities have been assessed by a 706/704(a) process and previous inspectional findings.

4.3. Clinical Microbiology

This section is not applicable to this NDA.

4.4. Devices and Companion Diagnostic Issues

This section is not applicable to this NDA.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This NDA should be approved from a nonclinical perspective.

Prostate-specific membrane antigen (PSMA) is a target of interest for development of low molecular weight radiopharmaceuticals (Kratochwil et al. 2016; Lenzo et al. 2018; von Eyben et al. 2018). The submission supports the marketing authorization of ⁶⁸Ga-PSMA-11 for PET imaging of prostate cancer. The Applicant did not conduct any nonclinical studies to support the application. However, the Applicant is relying on published reports of the safety and efficacy of ⁶⁸Ga-PSMA-11 in addition to available clinical experience to support the NDA application.

Based on agreement reached with the Agency, the Applicant provided peer-reviewed scientific literature on the nonclinical pharmacology of ⁶⁸Ga-PSMA-11 to support the safety and efficacy of the product. The Applicant cross-referenced an extended single dose acute toxicity study of PSMA-11. Pharmacology data (see Section 5.3) demonstrate PSMA-specific surface binding and internalization in human prostate cancer cell lines and ⁶⁸Ga-PSMA-11 uptake in tumor animal models on micro-PET. No safety pharmacology data are required for a microdose product. Moreover, no safety concerns have been reported during the extensive clinical experience with ⁶⁸Ga-PSMA-11. The pharmacokinetics data indicate rapid clearance of ⁶⁸Ga-PSMA-11 from the circulation. The use of ⁶⁸Ga-PSMA-11 as a microdose does not necessitate a genotoxicity study, and no reproductive and developmental toxicity studies are required for the intended male population. Therefore, no other nonclinical studies are necessary to support the safety of ⁶⁸Ga-PSMA-11 for the indication in the intended populations.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

No pharmacology study was conducted to support the efficacy or safety of ⁶⁸Ga-PSMA-11. Following an agreement with the Agency at the pre-NDA meeting held on August 29, 2018, the Applicant provided the nonclinical pharmacology data below from peer-reviewed scientific literature to support the NDA submission.

In Vitro Pharmacology:

The Applicant cited binding data (Table 2) for PSMA obtained from a cell-based binding assay performed on LNCaP cells with ⁶⁷Ga-PSMA-11 (referred to as ⁶⁸Ga-7) as the radioligand (Eder et al. 2012). Data from a comparative cell uptake and internalization experiment with LNCaP cells (PSMA-positive) and PC-3 cells (PSMA-negative) demonstrated specific cell surface accumulation and internalization in LNCaP cells, and no uptake in PC-3 cells or in LNCaP cells blocked with 100 μM 2-(phosphonomethyl)-pentanedioic acid (PMPA), a potent PSMA inhibitor (Eder et al. 2012).

Table 2. PSMA Binding Data

Ga-peptide complexes	m/z ^a	m/z calculated as [M+H] ⁺	Analytical HPLC retention ^b	Affinity related IC ₅₀ [nM] determined in enzyme-based assay ^c	Affinity related K _i [nM] determined in cell-based assay
[Ga]7 [*]	947.4257	947.4250	3.1 min	7.5 ± 2.2	12.0 ± 2.8
[Ga]8	819.4104	819.4100	2.4 min	19.4 ± 7.1	37.6 ± 14.3
[Ga]12	1284.6368	1284.6364	3.7 min	8.7 ± 3.9	11.1 ± 1.8

Source: Eder et al. (2012).

^a High-resolution mass spectrometry data of the free ligands ([M+H]⁺).

^b Compounds were labeled with ⁶⁸Ga; runs were performed using a linear A-B gradient (0% B to 100% B in 6 minutes) at a flow rate of 4 mL/min. Solvent A was 0.1% aqueous TFA and solvent B was methanol.

^c Compounds were compiled with ^{nat}Ga.

* [Ga]7 is an alias of ⁶⁸Ga-PSMA-11

Abbreviations: Ga = gallium, HPLC = high-performance liquid chromatography, IC₅₀ = medial inhibitory concentration, K_i = inhibitory constant, M+H = quasi-molecular ion, m/z = mass to charge ratio, ^{nat}Ga = natural gallium, PSMA = prostate-specific membrane antigen, TFA = trifluoroacetic acid

Eder et al. (2012) also compared ⁶⁸Ga-PSMA-11 to different chelator derivatives, ⁶⁸Ga-8 and ⁶⁸Ga-12, which utilize a DOTA chelator compared to *N,N'*-bis (2-hydroxybenzyl) ethylenediamine-*N,N'*-diacetic acid (HBED)-CC in ⁶⁸Ga-PSMA-11. In a cell uptake study involving incubation of these compounds at 2.5nM, 25 nM, and 250 nM concentrations with either LNCaP or PC-3 cells, ⁶⁸Ga-PSMA-11 showed higher uptake in LNCaP cells and lower nonspecific uptake in PC-3 cells compared to the other two compounds, ⁶⁸Ga-8 and ⁶⁸Ga-12.

In Eder et al. (2014), ⁶⁸Ga-PSMA-11 was further evaluated in cell-based binding and internalization assays. The study demonstrated that the PSMA-specific cell surface binding and internalization of a mixture of diastereomers at room temperature were comparable to the thermodynamically most stable diastereomer at 95°C .

The Applicant also cited a study (Ray Banerjee et al. 2016) in which cell uptake and internalization of ⁶⁸Ga-PSMA-11 in isogenic human prostate cancer PSMA-positive PC-3 PIP and PSMA-negative PC-3 flu cells was investigated along with other similar compounds (⁶⁸Ga-1 and ⁶⁸Ga-2). ⁶⁸Ga-PSMA-11 demonstrated favorable uptake and internalization in PSMA-positive cells and low nonspecific uptake in PSMA-negative cells.

The Applicant cited studies of the equilibrium dissociation constant (K_d) of ^{68}Ga -PSMA-11 for multiple cell lines (LNCaP, CWR22Rv1, PC-3, and VCaP cells in vitro), demonstrating the specificity of ^{68}Ga -PSMA-11 for human prostate cancer cell lines (Wang et al. 2018) as shown in [Table 3](#). The data indicate that the number of ^{68}Ga -PSMA-11 binding sites is proportionally related to the K_d of the tracer for the multiple cell lines.

Table 3. Equilibrium Dissociation Constant of ^{68}Ga -PSMA-11 for Multiple Cell Lines

	LNCaP	CWR22Rv1	PC-3	VCaP
Kd (nM)	4.3 ± 0.8	16.4 ± 1.3	225.3 ± 20.8	125.6 ± 13.1

Source: (Wang et al. 2018).

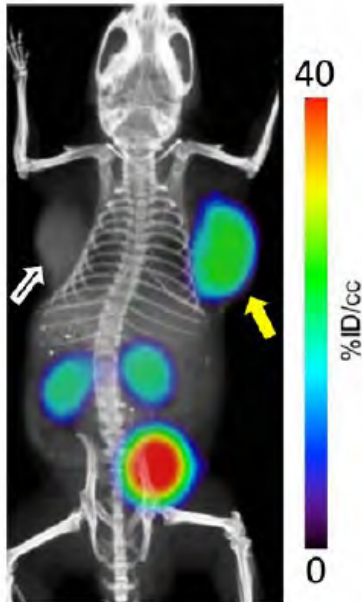
Abbreviations: ^{68}Ga = gallium-68, CWR22Rv1 = androgen-independent human prostate cancer cell line, K_d = equilibrium dissociation constant, LNCaP = androgen sensitive human prostate adenocarcinoma cell line, PC-3 = human prostate cancer cell line that does not express PSMA, PSMA = prostate-specific membrane antigen, VCaP = cell line of human prostate cancer with high androgen receptor and prostate-specific antigen expression

In Vivo Pharmacology/ Proof of Concept Studies in Mice:

In a study of ^{68}Ga -PSMA-11 (1-2 MBq/mouse) published by (Eder et al. 2012), the radioactive tracer was injected into mice bearing LNCaP tumor xenografts. The mice were then placed in an Inveon small animal PET scanner for 50 minutes for a dynamic micro-PET scan. ^{68}Ga -PSMA-11 (^{68}Ga -7) adequately imaged the tumor.

The Applicant cited a whole-body PET/CT study of ^{68}Ga -PSMA-11 (Ray Banerjee et al. 2016) performed in intact male NOD/SCID mice bearing PSMA-positive PC-3 PIP and PSMA-negative PC-3 flu xenografts in opposite, upper flanks. As shown in [Figure 1](#) below, uptake in PSMA-positive tumor (yellow solid arrow) was demonstrated at 1 hour post-injection while very low uptake was demonstrated in PSMA-negative tumor (white open arrow).

Figure 1. ^{68}Ga -PSMA-11 PET Uptake at 1 Hour Post-Injection in NOD/SCID Mouse Xenograft Model

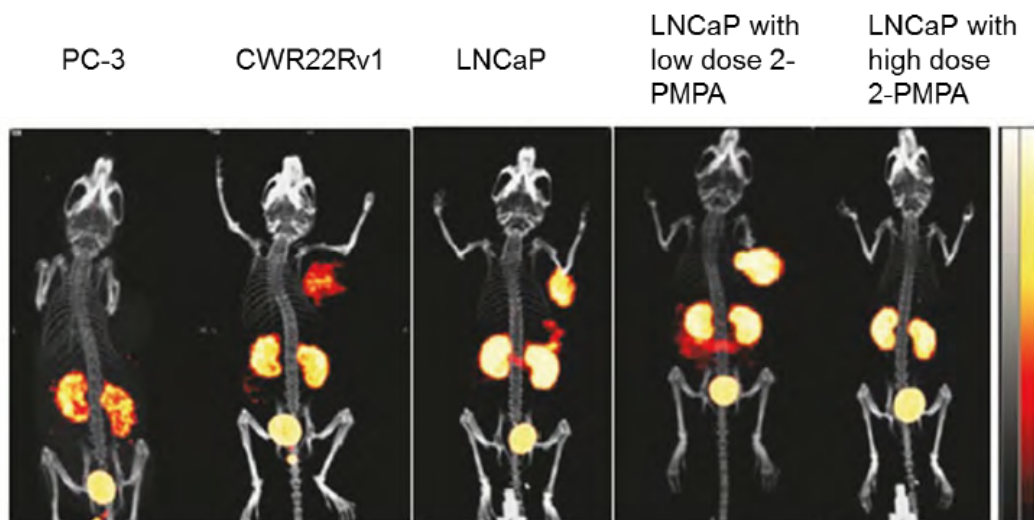


Source: Ray Banerjee et al. (2016).

Abbreviations: ^{68}Ga = gallium-68, ID = injected dose, NOD/SCID = non-obese diabetic/ severe combined immunodeficiency, PET = positron emission tomography

Additional proof of concept data collected with ^{68}Ga -PSMA-11 in mice bearing PC-3, CWR22Rv1, and LNCaP xenografts were cited (Wang et al. 2018). The highest uptake occurred in LNCaP xenograft and the lowest uptake occurred in PC-3 xenograft. The uptake in LNCaP xenograft could be blocked by pre-injection of 2-PMPA. [Figure 2](#) shows representative micro-PET/CT images of nude mice bearing PC-3, CWR22Rv1, LNCaP, and LNCaP xenografts with low dose (2.5 μg) or high dose (250 μg) pre-injection of 2-PMPA (from left to right).

Figure 2. ^{68}Ga -PSMA-11 PET Uptake in Nude Mice Bearing LNCaP, CWR22Rv1, and PC-3 Xenografts



Source: (Wang et al. 2018).

Abbreviations: ^{68}Ga = gallium-68, CWR22Rv1 = androgen-independent human prostate cancer cell line, LNCaP = androgen sensitive human prostate adenocarcinoma cell line, PC-3 = human prostate cancer cell line that does not express PSMA, PET = positron emission tomography, 2-PMPA = 2-(Phosphonomethyl)-pentanedioic acid, PSMA = prostate-specific membrane antigen

Wang et al. (2018) also demonstrated that tumor uptake of ^{68}Ga -PSMA-11 ($\%ID/\text{cm}^3$) on micro-PET correlated with PSMA expression determined by flow cytometry.

Safety Pharmacology:

According to the Applicant, no safety pharmacology data on ^{68}Ga -PSMA-11 were identified in the scientific literature. The Applicant cited a cardiovascular safety study of *N,N'*-bis (2-hydroxybenzyl) ethylenediamine-*N,N'*-diacetic acid monosodium salt (NaHBED) conducted in normotensive rats (Bergeron et al. 2002). In this study, 300 mmol/kg of NaHBED in 0.5-mL distilled water was administered via a jugular vein catheter (n=5 for both saline control and NaHBED). NaHBED produced no effects on either blood pressure or heart rate when given as a bolus injection or 20-minute infusion. The no observed effect level (NOEL) for the cardiovascular safety of NaHBED was 300 mmol/kg (121.3 mg/kg) with an estimated human equivalent dose (HED) of 19.6 mg/kg or 1.2 g in a 60 kg adult.

Drug Interactions:

The Applicant reported that no concerning pharmacodynamic drug interactions were identified in the scientific literature.

5.4. ADME/PK

The Applicant conducted no nonclinical pharmacokinetics studies of ^{68}Ga -PSMA-11. The Applicant and the Agency agreed on August 29, 2018, that the required nonclinical pharmacokinetic data for the NDA submission could be provided by the scientific literature.

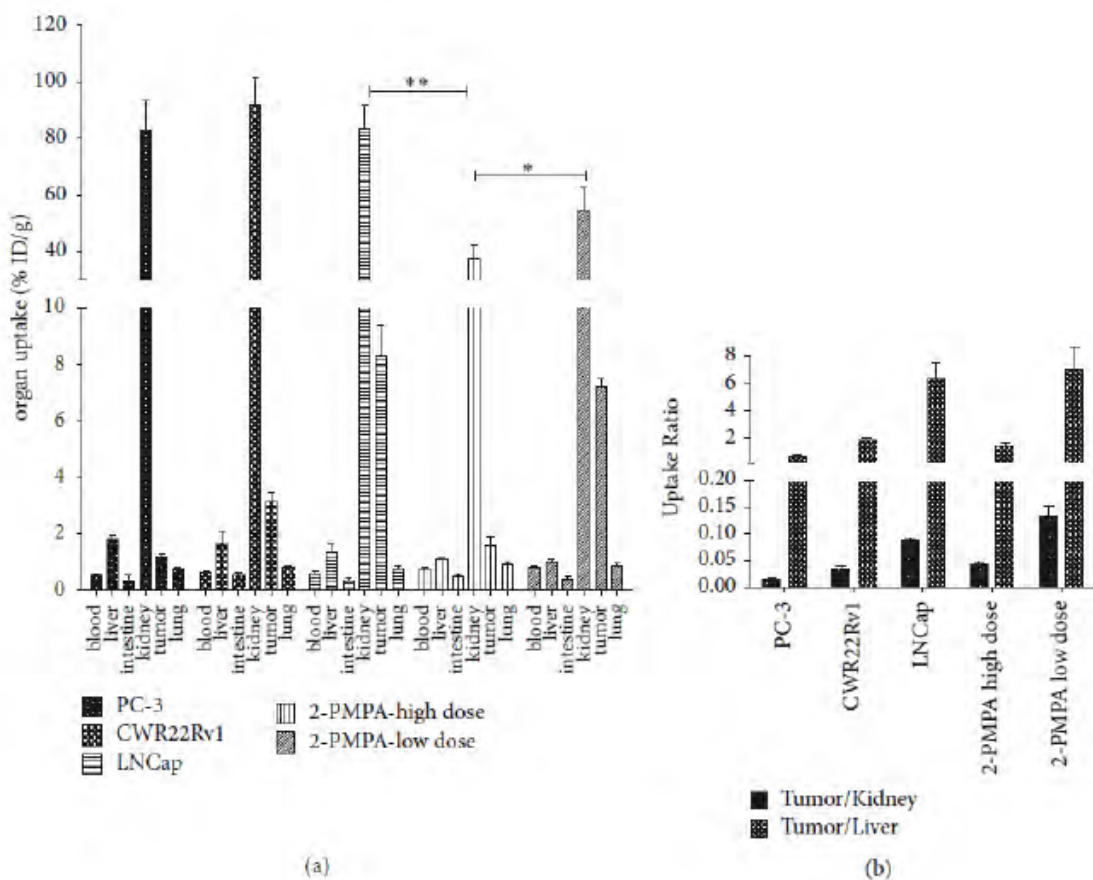
Distribution:

The Applicant cited a tissue distribution study that compared ^{68}Ga -PSMA-11 (^{68}Ga -7) with two other potential candidates with different chelators (^{68}Ga -8 and ^{68}Ga -12; (Eder et al. 2012)). In the study, mice bearing either LNCaP or PC-3 xenografts were injected with 1-2 MBq of ^{68}Ga -PSMA-11 via the tail vein and then were sacrificed at 1-hour after injection. Selected organs were collected for biodistribution analysis. The data demonstrated that ^{68}Ga -PSMA-11 was rapidly cleared from the circulation and PSMA-negative tissue. The liver activity was $0.87\% \pm 0.05\%$ ID/g as early as 1-hour after injection. The high kidney, spleen, and lung uptake of $139.4\% \pm 21.4\%$ ID/g, $17.90\% \pm 2.87\%$ ID/g, and $2.49\% \pm 0.27\%$ ID/g was nearly completely blocked to $4.02\% \pm 1.14\%$ ID/g, $1.54\% \pm 0.33\%$ ID/g, and $0.64\% \pm 0.32\%$ ID/g, respectively, after the co-injection of 2 mg/kg 2-PMPA. The tumor uptake amounted to $7.70\% \pm 1.45\%$ ID/g on LNCaP xenografts and $1.30\% \pm 0.12\%$ ID/g on PC-3 xenografts.

The Applicant also cited the published article by Ray Banerjee et al. (2016) on the distribution of ^{68}Ga -PSMA-11 in selected organs of mice bearing PSMA-positive PC-3 PIP and PSMA-negative PC-3 flu xenografts (n=4) following injection of a single intravenous dose of 740 kBq ^{68}Ga -PSMA-11. The mice were sacrificed at 1-, 2-, and 3-hours post-injection and biodistribution analysis of selected organs isolated from the mice demonstrated that PSMA-positive PC-3 PIP tumor was visible as early as 15 minutes post-injection. Renal uptake of the radiotracer, specific uptake from the expression of PSMA in mouse proximal renal tubules, and significant bladder activity indicated rapid renal clearance.

The Applicant also cited a ^{68}Ga -PSMA-11 biodistribution study conducted by Wang et al. (2018) involving a single intravenous injection of 1.0 MBq ^{68}Ga -PSMA-11 in mice bearing subcutaneous prostate cancer (LNCaP, CWR22Rv1, and PC-3) xenografts. The mice were sacrificed 1 hour after tail vein injection for biodistribution analysis (n=5 for each). As shown in Panel A of [Figure 3](#), uptake of ^{68}Ga -PSMA-11 (% ID/g) in LNCaP tumor ($7.28\% \pm 0.82\%$) was higher than that of CWR22Rv1 ($3.12\% \pm 0.35\%$) and PC-3 ($1.21\% \pm 0.07\%$) and was blocked by co-injection of 2.5 μg (low dose) or 250 μg (high dose) of 2-PMPA, indicating PSMA binding specificity. The graph of tumor-to-kidney and tumor-to-liver uptake ratio in mice bearing the different types of prostate cancer xenografts with or without 2-PMPA is shown in Panel B of [Figure 3](#).

Figure 3. Biodistribution of ⁶⁸Ga-PSMA-11 in Nude Mice Bearing LNCaP, CWR22Rv1, and PC-3 Xenografts



Source: (Wang et al. 2018).

Abbreviations: ⁶⁸Ga = gallium-68, CWR22Rv1 = androgen-independent human prostate cancer cell line, ID = injected dose, LNCaP = androgen sensitive human prostate adenocarcinoma cell line, PC-3 = human prostate cancer cell line that does not express PSMA, 2-PMPA = 2-(Phosphonomethyl)-pentanedioic acid, PSMA = prostate-specific membrane antigen

In another biodistribution study (Schafer et al. 2012), mice injected with ⁶⁸Ga-PSMA-11 via the tail vein at a dose of 12 MBq were sacrificed 1-hour after injection and organs of interest were dissected, blotted dry, and weighed and tissue radioactivity was measured using a gamma counter to calculate % ID/g. The highest percentage of injected ⁶⁸Ga-PSMA-11 radioactivity was obtained in the kidney (139.44 ± 21.40) and in the spleen (17.90 ± 2.87). The micro-PET images demonstrated rapid elimination of radioactivity from liver, heart, and muscle.

Metabolism:

The Applicant did not provide any nonclinical metabolism data for ⁶⁸Ga-PSMA-11. The Applicant stated that generally following internalization of a ligand-bound receptor, the ligand dissociates from the receptor and undergoes proteolytic degradation into amino acids. The Applicant cited a study on long-term stability of radiogallium labelled PSMA-11 in human serum using the longer-lived radionuclide ⁶⁷Ga (Eder et al. 2014). There was no evidence of non-complexed ⁶⁷Ga after 48-hour incubation in human serum at 37°C. ⁶⁷Ga-PSMA-11 remained unchanged after 1

week in phosphate buffered saline (PBS) at room temperature. The stability of the tracer was further investigated by incubating ^{68}Ga -PSMA-11 in the presence of an excess of apo-transferrin for 2 hours at 37°C. No radiogallium was trans-chelated to apo-transferrin.

Excretion:

A study conducted by Ray Banerjee et al. (2016) involving renal uptake of ^{68}Ga -PSMA-11 in non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice bearing PSMA-positive and PSMA-negative PC-3 xenografts suggested rapid renal clearance of ^{68}Ga -PSMA-11.

Pharmacokinetic Drug Interactions:

Available data demonstrated the potential of PSMA blockers (i.e., 2-PMPA) to inhibit the binding and intracellular accumulation of ^{68}Ga -PSMA-11 (Eder et al. 2012; Ray Banerjee et al. 2016; Wang et al. 2018). However, no clinical concern is currently present given the lack of approved drugs containing PSMA blockers at this time.

5.5. Toxicology

5.5.1. General Toxicology

Single-Dose Toxicity Study:

The Applicant provided right of reference to the extended single-dose toxicity study in Wistar rats conducted at (b) (4). The rats were intravenously administered 0 or 86 $\mu\text{g}/\text{kg}$ PSMA-11 and evaluated for clinical signs, with the main study animals euthanized and necropsied on Day 2 while the recovery group was euthanized and necropsied on Day 15. There were no adverse effects observed in rats administered 86 $\mu\text{g}/\text{kg}$ PSMA-11. The maximum proposed clinical mass dose is 5 μg (0.08 $\mu\text{g}/\text{kg}$ assuming a 60 kg body weight; over 1000-fold safety factor). The safety margin obtained from this study suggests that ^{68}Ga -PSMA-11 is safe at the clinical mass dose of 5 μg in the intended population.

Repeated-Dose Toxicity Study:

The Applicant did not provide any data on repeated dose toxicity of PSMA-11. However, the Applicant cited a published study (Bergeron et al. 2002) on the safety evaluation of NaHBED. In the study, a single dose of NaHBED (75 $\mu\text{mol}/\text{kg}$) was intravenously administered as a 20-minute infusion once daily for 14 days to iron overloaded Beagle dogs. Necropsy conducted following euthanasia of the animals 24 and 48 hours after the last dose demonstrated no systemic toxicity at the employed dose. A NOEL of 75 $\mu\text{mol}/\text{kg}$ (0.303 mg/kg) NaHBED was obtained in this dog study. The safety margin could not be estimated because the no observed adverse effect level could not be determined in this study.

General toxicology; additional studies:

Not conducted and not needed.

5.5.2. Genetic Toxicology

Not required for microdose and single use product.

5.5.3. Carcinogenicity

Not required for a single use product.

5.5.4. Reproductive and Developmental Toxicology

Not conducted. The Applicant requested and was granted a waiver from conducting the studies.

5.5.5. Other Toxicology Studies

Not conducted and not needed.

Nonclinical Pharmacology/Toxicology Summary:

The Applicant did not conduct any nonclinical studies to support this submission. In line with an agreement reached with the Agency during the pre-NDA meeting held on August 29, 2018, the Applicant provided scientific literature on the nonclinical pharmacology of ⁶⁸Ga-PSMA-11 to support the safety and activity of the product.

The available in vitro data demonstrate that PSMA-11 exhibits satisfactory levels of specific surface binding and internalization in human prostate cancer cell lines with affinity constant values in the nanomolar range. Proof of concept data from mice show that ⁶⁸Ga-PSMA-11 uptake in tumor on micro-PET correlates with PSMA expression determined by flow cytometry. In line with FDA guidance on microdose products, the Applicant did not need to provide any safety pharmacology data on ⁶⁸Ga-PSMA-11. The available favorable clinical experience with the tracer provided additional justification.

The pharmacokinetic data suggest that ⁶⁸Ga-PSMA-11 is cleared from the circulation within 1-hour post-injection with highest uptake found in kidney and spleen. The Applicant has the right of reference to [REDACTED] ^{(b) (4)} data on the single dose acute and extended toxicity study on PSMA-11 and provided the data to support the safety of the tracer. An adequate safety margin of 1000-fold the clinical dose was established by the toxicity study suggesting no safety concerns.

The available nonclinical data on ⁶⁸Ga-PSMA-11 support the safety and activity of the product. The Applicant did not provide any genotoxicity data on ⁶⁸Ga-PSMA-11. Genotoxicity data is however not required for such microdose and single-dose products. The Applicant requested and received a waiver for conducting reproductive and developmental toxicity studies.

Therefore, based on the available nonclinical data on ^{68}Ga -PSMA-11 and the safe clinical experience with the tracer, there are no safety concerns with the product for the proposed indication.

Nonclinical Pharmacology/Toxicology Recommendation:

Based on the available nonclinical data and clinical experience with ^{68}Ga -PSMA-11, it is recommended that ^{68}Ga -PSMA-11 be approved from a nonclinical perspective.

6 Clinical Pharmacology

6.1. Executive Summary

This NDA is approvable from a clinical pharmacology perspective.

No clinical pharmacology studies were performed by the Applicant. Scientific literature was used to support the clinical pharmacology section of this NDA.

In adult patients, the recommended amount of radioactivity to be administered for PET imaging is 3 to 7 mCi (111 to (b) (4) MBq) administered as a bolus intravenous injection. The individual dose contains a mass dose of 5 μg .

No dose finding study was done by the Applicant. The Applicant used reports from the scientific literature to select the dose.

Intravenously injected ^{68}Ga -PSMA-11 is cleared from the blood and accumulates preferentially in the kidneys, liver, spleen, and salivary glands. The blood activity showed bi-exponential behavior with 6.5-minute and 4.4-hour half-life components. The highest absorbed radiation dose was found in kidney, then urinary bladder and spleen, followed by liver.

PET images are acquired starting at 50 minutes and up to 100 minutes after administration of ^{68}Ga -PSMA-11. Scanning should include a whole-body acquisition from the skull through the pelvis, with the acquisition beginning at the pelvis.

The urinary excretion of ^{68}Ga -PSMA-11 can be associated with imaging artifact that can obscure lesions in the pelvic area. Given the high frequency of pelvic disease in these patients, it is important to consider this artifact. The administration of a diuretic that is active during the uptake of the radiotracer might decrease the artifact by decreasing the activity in the urinary bladder and ureters. The value of diuresis was not systematically evaluated. Most patients (87-93%) received 20 mg of furosemide at the time of radiotracer injection in the Applicant's clinical

studies to reduce bladder radioactivity. The potential use of a diuretic is cited in Section 2.2 of the package insert.

Patients with prostate cancer can be divided into two major categories, hormone-sensitive and castrate-resistant. Certain patients with prostate cancer receive androgen deprivation therapy (ADT) or other treatments targeting the androgen pathway. The literature suggests that concomitant ADT and other treatments targeting the androgen pathway might affect the uptake of ⁶⁸Ga-PSMA-11 in the setting of either hormone-sensitive or castrate-resistant tumor. However, further studies are needed to confirm these findings.

6.2. Summary of Clinical Pharmacology Assessment

See Section [6.3](#).

6.2.1. Pharmacology and Clinical Pharmacokinetics

See Section [6.3](#).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

In adult patients, the recommended amount of radioactivity to be administered for PET imaging is 3 to 7 mCi (111 to ^{(b) (4)} MBq) administered as a bolus intravenous injection. The individual dose contains a mass dose of 5 µg.

No dose finding study was done by the Applicant. The Applicant used reports from the literature to select the dose.

The Applicant conducted two prospective studies (PSMA-BCR and PSMA-PreRP) to support this application. The injected dose averaged from 5.1±1.1 mCi to 5.4±1.1 mCi in these two trials. The recommended dose was selected based on the extensive use of ⁶⁸Ga-PSMA-11 in multiple published studies with doses ranging from 3 to 7 mCi. A dose of 3 to 7 mCi is acceptable based on its efficacy and low radiation absorbed dose to the patient. The absorbed radiation dose associated with an injected radioactivity of 5 mCi results in an effective whole-body dose of approximately 3.1 mSv.

Therapeutic Individualization

None.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

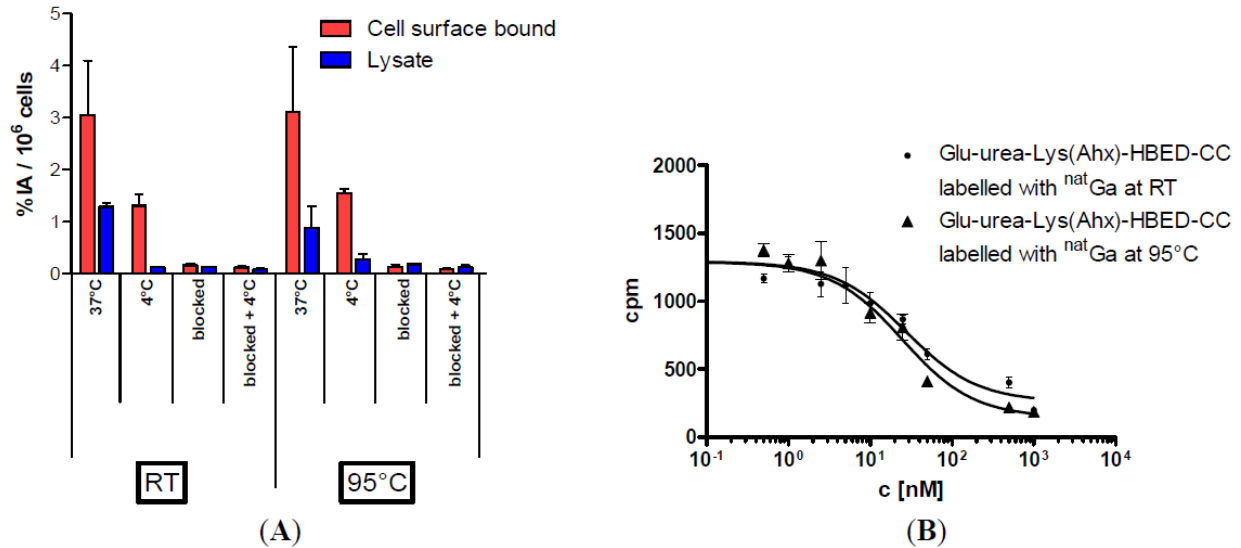
Cell binding to PSMA and internalization of ^{68}Ga -PSMA-11

Competitive cell binding assays and internalization experiments were reported by Eder et al. (2014) in LNCaP cells (human prostate cancer cell line). To determine specific cell uptake and internalization, 10^5 cells per well were seeded in poly-L-lysine coated 24-well cell culture plates 24 hours before incubation. After washing, the cells were incubated with 25 nM of the radiolabeled compounds (either radiolabeled at room temperature (RT) or 95 °C) for 45 minutes at 37 °C and at 4°C, respectively. Specific cellular uptake was determined by competitive blocking with the PSMA inhibitor, 2-(phosphonomethyl)pentanedioic acid (500 μM final concentration, 2-PMPA). Cellular uptake was terminated by washing four times with 1 mL of ice-cold PBS. Cells were subsequently incubated twice with 0.5 mL glycine-HCl in PBS (50 mM, pH = 2.8) for 5 minutes to remove the surface-bound fraction. The cells were washed with 1 mL of ice-cold PBS and lysed using 0.5 mL 0.3 N NaOH. The radioactivity of the probes was measured in a gamma counter. The cell uptake was calculated as percent of the initially added radioactivity bound to 10^6 cells [%IA/ 10^6 cells].

The results of internalization showed that for both preparations (RT and 95 °C), there was radioactivity bound to cell surface membranes and internalized within the cells (Panel A of [Figure 4](#)). As expected, there was more internalization at 37 °C incubation (approximately 20-35%) as compared to 4 °C incubation. More importantly, there was complete blockage of radioactivity when the cells were incubated in the presence of 500 μM of 2-PMPA (a competitive blocking agent for PSMA).

Panel B of [Figure 4](#) shows determination of binding affinity of nonradioactive Ga-PSMA-11 (natGa-PSMA-11) to LNCaP cells as a function of the labelling temperature. The cells were incubated with the radioligand (^{68}Ga -PSMA-11) in the presence of different concentrations of nonradioactive Ga-PSMA-11 (0–5000 nM, 100 μL /well). The 50% inhibitory concentration (IC50) was found to be 27 ± 1.3 nM.

Figure 4. ⁶⁸GaPSMA-11 Cell Binding, Internalization, and Binding Affinity



Source: (Eder et al. 2014).

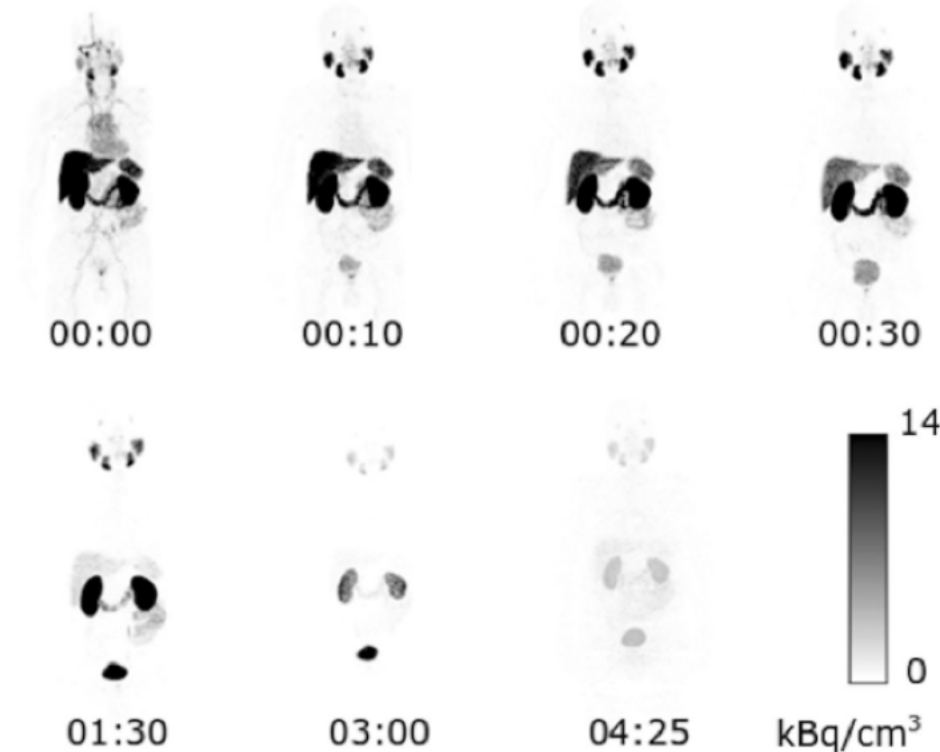
Abbreviations: cpm = counts per minute, IA = initially applied radioactivity, natGa = natural gallium, 2-PMPA = 2-(Phosphonomethyl)-pentanedioic acid, RT = room temperature

Biodistribution of ⁶⁸Ga-PSMA-11 uptake in tumor and normal tissues

Biodistribution of ⁶⁸Ga-PSMA-11 was evaluated in a study in six patients with low-risk prostate cancer to determine the effective dose and organ doses. Urine was collected up to 4 hours post-injection, and venous blood samples were drawn at 45, 85, 175, and 245 minutes post-injection. Major organs and the total body were delineated, and accumulated activities and absorbed organ doses were calculated (Sandgren et al. 2019).

Intravenously injected ⁶⁸Ga-PSMA-11 cleared from the blood and accumulated preferentially in the kidneys (7%), liver (15%), spleen (2%), and salivary glands (0.5%). The blood activity showed a bi-exponential behavior, containing a fast component with a 6.5-minute half-life, and an additional slow 4.4-hour half-life component reflecting biological clearance from blood. The biodistribution (pharmacokinetics) of ⁶⁸Ga-PSMA-11 for a patient at seven time points (0 minutes to 4 hours and 25 minutes) is shown in [Figure 5](#).

Figure 5. Whole-Body Images of a Patient Injected With ^{68}Ga -PSMA-11 at Seven Time Points (0 Minutes to 4 Hours 25 Minutes Post-Injection)



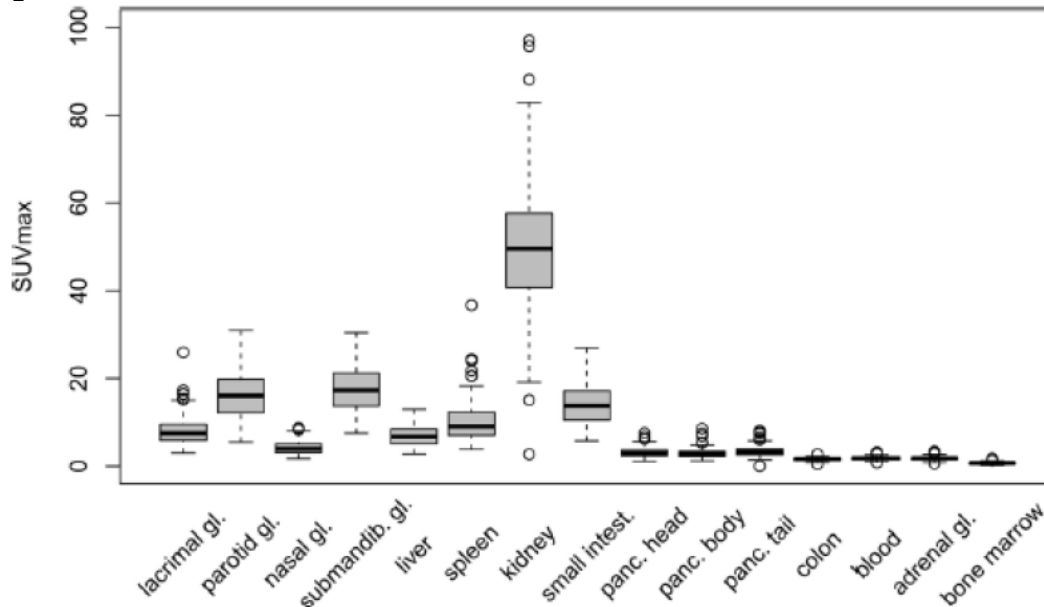
Source: (Sandgren et al. 2019).
Abbreviations: ^{68}Ga = gallium-68, PSMA = prostate-specific membrane antigen

The effective dose was calculated to be 0.022 mSv/MBq. The kidneys received approximately 40 mGy absorbed dose after an injection with 160 MBq of ^{68}Ga -PSMA-11 while the lacrimal glands received an absorbed dose of 0.12 mGy per administered MBq. The absorbed dose to the kidneys (0.24 mGy/MBq) is in line with the estimation by Afshar-Oromieh et al. (2016). The dosimetry details and radiation absorbed doses by Afshar-Oromieh are described after biodistribution studies below.

Published data determined the physiological and pathophysiological biodistribution of ^{68}Ga -PSMA-11 in patients with prostate cancer to establish the range of uptake in relevant organs and tumors as well as metastases (Prasad et al. 2016). There were 101 patients analyzed to assess the tracer biodistribution. ^{68}Ga -PSMA-11 uptake was quantified using maximum standardized uptake values (SUVmax) in normal organs as well as in primary tumors and/or metastases.

In the biodistribution results, the highest uptake organ was kidney, followed by the submandibular glands, parotid glands and duodenum. Other organs that demonstrated high uptake (SUVmax >3) were the lacrimal glands and the spleen ([Figure 6](#)).

Figure 6. Biodistribution of ⁶⁸Ga-PSMA-11

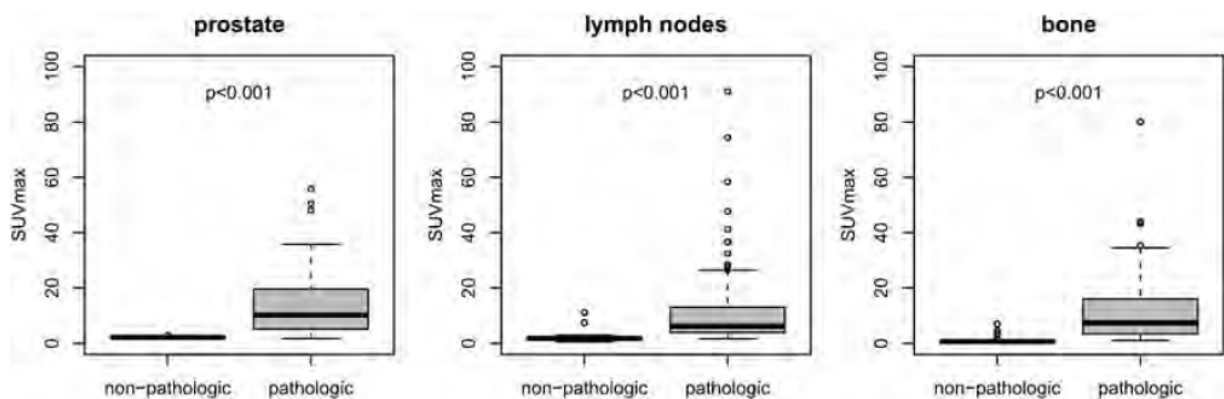


Source: (Prasad et al. 2016).

Abbreviations: ⁶⁸Ga = gallium-68, PSMA = prostate-specific membrane antigen, SUV_{max} = maximum standardized uptake value

As reported, all patients tolerated ⁶⁸Ga-PSMA-11 injection well, and no adverse events were noted. The median SUVmax in normal prostate glands was 2.2, with a cut-off SUVmax of 3.2 for differentiating prostate tumors from normal prostate tissue ([Figure 7](#)).

Figure 7. Boxplots of Pathological Versus Non-Pathological Uptake in the Prostate, Lymph Nodes, and Bone



Source: (Prasad et al. 2016).

Abbreviations: SUV_{max} = maximum standardized uptake value

Afshar-Oromieh et al. (2016), studied radiation dosimetry of ⁶⁸Ga-PSMA-11 and evaluated optimal imaging timing in four patients with recurrent prostate cancer. Whole-body PET with low-dose CT scan was conducted at 5 minutes, and 1, 2, 3, 4 and 5 hours after injection of 152 to 198 MBq of ⁶⁸Ga-PSMA-11. The fused PET/CT images were used to define the organs

showing moderate and high uptake of ^{68}Ga -PSMA-11. The corresponding volume of interest (VOI) borders were drawn on each PET image and were verified visually for adequate placement. The VOIs were defined such that the whole activity of the organ was taken into account, and care was taken to minimize interference of adjacent activity distribution in other organs. VOIs were drawn for lacrimal and salivary glands (all of them summed), liver, spleen, both kidneys (summed), proximal small intestines, colon (those parts which took up the tracer, mostly the descending parts), and urinary bladder. Integration of the time-activity curves for organs and tumor sites was used to estimate the time-integrated activity coefficient ($\text{Bq}\cdot\text{h}/\text{Bq}$) of the tracer in the organs. A bi-exponential fit was used for the integration of the time-activity curves.

Organs of moderate to high uptake were used as source organs; their total activity was determined at all measured time points. Time-activity curves were created for each source organ as well as for the remainder. In addition, tracer uptake was measured in 16 sites of metastases. The highest tracer uptake was observed in the kidneys, liver, upper large intestine, and the urinary bladder. Mean organ doses were: kidneys 0.262 ± 0.098 mGy/MBq, liver 0.031 ± 0.004 mGy/MBq, upper large intestine 0.054 ± 0.041 mGy/MBq, urinary bladder 0.13 ± 0.059 mGy/MBq ([Table 4](#)).

Table 4. Radiation-Absorbed Doses for Various Organs and Effective Dose for ⁶⁸Ga-PSMA-11

Patient →	1	2	3	4	Mean (± SD)
	Absorbed Organ Dose (mGy/MBq)				
Adrenals	0.0134	0.0138	0.0139	0.0155	0.0142 (±0.0009)
Brain	0.0098	0.0084	0.0085	0.0091	0.0090 (±0.0007)
Breasts	0.0092	0.0084	0.0085	0.0092	0.0088 (±0.0004)
Gallbladder	0.0141	0.0148	0.0136	0.0150	0.0144 (±0.0006)
Lower colon	0.0128	0.0122	0.0121	0.0119	0.0123 (±0.0004)
Small intestine	0.0159	0.0195	0.0148	0.0149	0.0163 (±0.0022)
Stomach	0.0121	0.0119	0.0114	0.0125	0.0120 (±0.0005)
Upper colon	0.0284	0.1160	0.0391	0.0325	0.0540 (±0.0416)
Heart	0.0117	0.0103	0.0104	0.0113	0.0109 (±0.0007)
Kidneys	0.1190	0.2790	0.3060	0.3420	0.2620 (±0.0984)
Liver	0.0322	0.0287	0.0265	0.0361	0.0309 (±0.0042)
Lungs	0.0109	0.0096	0.0097	0.0105	0.0102 (±0.0006)
Muscle	0.0110	0.0101	0.0101	0.0106	0.0105 (±0.0004)
Pancreas	0.0133	0.0136	0.0133	0.0149	0.0138 (±0.0008)
Red marrow	0.0094	0.0090	0.0089	0.0094	0.0092 (±0.0003)
Osteogenic cells	0.0153	0.0135	0.0136	0.0145	0.0142 (±0.0008)
Skin	0.0095	0.0084	0.0085	0.0090	0.0085 (±0.0005)
Spleen	0.0255	0.0561	0.0284	0.0682	0.0446 (±0.0209)
Testes	0.0112	0.0099	0.0102	0.0102	0.0104 (±0.0006)
Thymus	0.0108	0.0093	0.0094	0.0101	0.0099 (±0.0007)
Thyroid	0.0106	0.0091	0.0093	0.0099	0.0097 (±0.0007)
Urinary bladder	0.1220	0.1480	0.1660	0.0874	0.1300 (±0.0341)
Total body	0.0123	0.0123	0.0121	0.0130	0.0124 (±0.0004)
Effective dose (mSv/MBq)	0.0183	0.0254	0.0263	0.0242	0.0236 (±0.0036)

Source: (Afshar-Oromieh et al. 2016).

Abbreviations: ⁶⁸Ga = gallium-68, PSMA = prostate-specific membrane antigen, SD = standard deviation

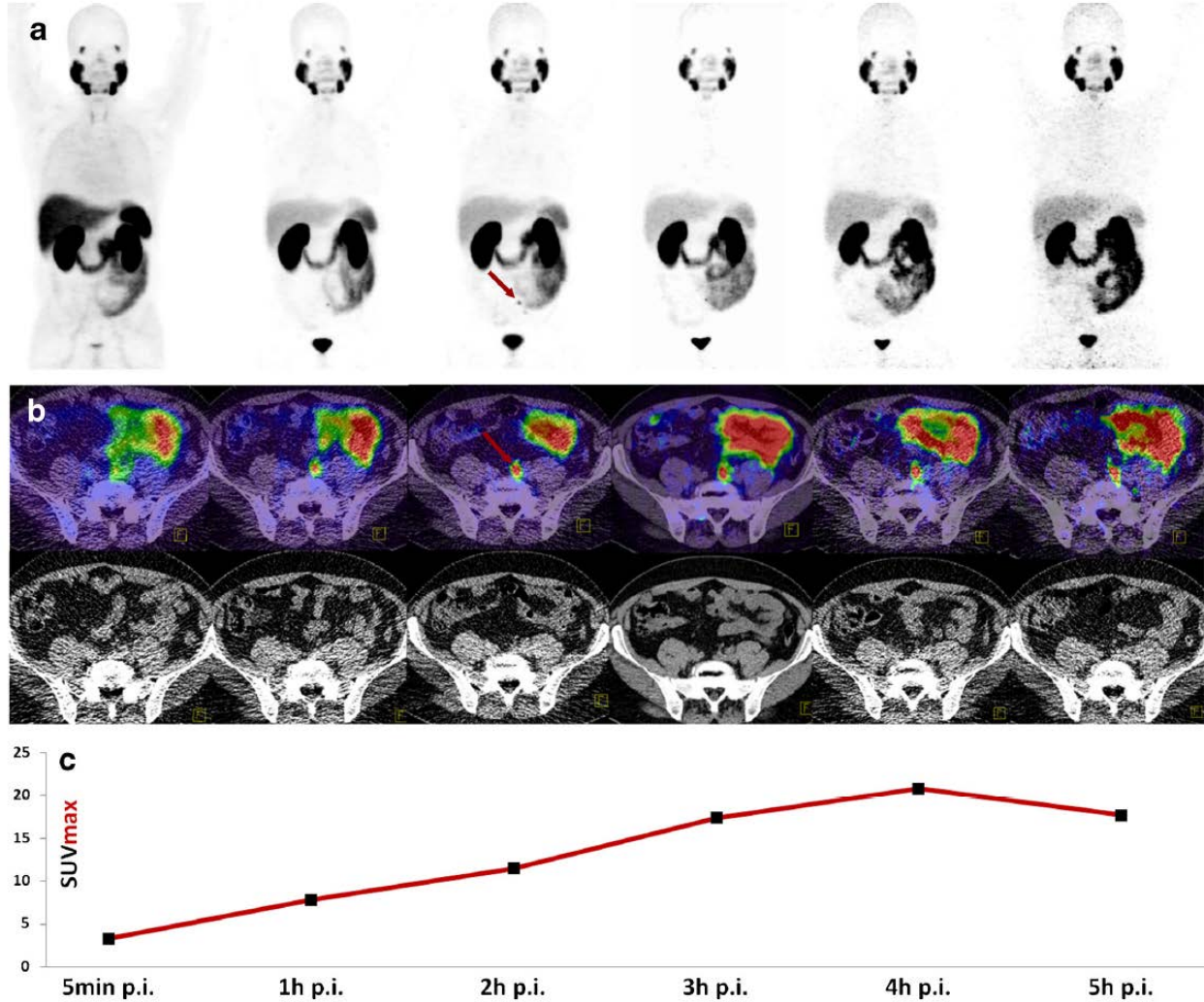
The calculated mean effective dose was 0.024 ± 0.004 mSv/MBq or 4.4 mSv for a 5 mCi of dose. The mean effective dose calculated by Sandgren et al. (2019), was 4.1 mSv for a dose of 5 mCi.

The authors stated that their analysis confirmed that prostate cancer metastases demonstrate an increase of ⁶⁸Ga-PSMA-11 uptake over time. Overall, in this study, most prostate cancer metastases were visible on ⁶⁸Ga-PSMA-11 PET conducted beyond 1 hour post-injection, with the best imaging time point being at 3 hours post-injection, per the authors. Most tumor lesions (n=16) were visible at 3 hours post-injection, while at all other time points many were not qualitatively present (10/16 visible at 1 hour post-injection).

[Figure 8](#) shows sequential PET/CT of a patient over time following the injection of 170 MBq ⁶⁸Ga-PSMA-11. Panel 8A shows maximum intensity projections of the sequential PET, Panel 8B

shows corresponding PET/CT fusion and low-dose CT images, and Panel 8C shows increasing SUVmax of a lymph node metastasis (red arrow in A and B) with time.

Figure 8. Sequential PET/CT of a Patient Following the Injection of 170 MBq ^{68}Ga -PSMA-11



Source: (Afshar-Oromieh et al. 2016).

Abbreviations: p.i. = post-injection, PET/CT = positron emission tomography/computed tomography, SUV_{max} = maximum standardized uptake value

In another study, 70% of prostate cancer lesions had increased uptake and contrast at 3 hours post-injection compared to 1 hour post-injection (Afshar-Oromieh et al. 2013). However, the 1-hour time point for PSMA-11 PET/CT imaging is consistent with clinical routine for multiple other radiopharmaceutical PET scans (e.g., ^{18}F -fludeoxyglucose, ^{18}F -DOPA, ^{68}Ga -dotatoc).

6.3.2. Clinical Pharmacology Questions

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Patients with prostate cancer can be divided into hormone-sensitive and castrate-resistant groups. Certain patients with prostate cancer receive ADT or other treatments that target the androgen pathway, such as androgen receptor antagonists and androgen synthesis inhibitors. It is suspected that the concomitant use of these therapies could impact the efficacy of ⁶⁸Ga-PSMA-11, depending on hormone-sensitive or castrate-resistant prostate cancer status.

A publication evaluated the influence of long-term use of ADT on PSMA PET/CT findings (Afshar-Oromieh et al. 2018). The authors performed a retrospective analysis of all 1,704 patients who underwent a ⁶⁸Ga-PSMA-11 PET/CT scan at their institution from 2011 to 2017 to detect prostate cancer. Of 306 patients scanned at least twice, 10 had started and continued ADT with a clinical response between the two ⁶⁸Ga-PSMA-11 scans. In these 10 patients the authors compared the tracer uptake intensity and volume of prostate cancer lesions on ⁶⁸Ga-PSMA-11 PET/CT before and during ongoing ADT.

Overall, 31 prostate cancer lesions were visible in all 10 patients before initiation of ADT. However, during ongoing ADT (duration 42–369 days, median 230 days), only 14 lesions were visible in 8 of the 10 patients. The average tracer uptake values decreased in 71% and increased in 13% of the prostate cancer lesions. Of all lesions, 33% were still visible in six patients with a complete PSA response (≤ 0.1 ng/ml). The authors concluded that continuous long-term ADT reduces the visibility of hormone-sensitive prostate cancer on ⁶⁸Ga-PSMA-11 PET/CT and recommended PSMA PET/CT scanning before starting ADT.

Another study evaluated the effect of various treatments targeting the androgen pathway on ⁶⁸Ga-PSMA-11 imaging in men with hormone-naïve (starting therapy with luteinizing hormone-releasing hormone [LHRH] $\pm$ bicalutamide) and castrate-resistant (starting therapy with enzalutamide or abiraterone) metastatic prostate cancer (Emmett et al. 2019).

Serial ⁶⁸Ga-PSMA-11 PET was performed at baseline and on days 9, 18, and 28 in eight men with metastatic hormone-sensitive prostate cancer commencing LHRH $\pm$ bicalutamide (cohort 1) and seven men with metastatic castrate-resistant prostate cancer commencing either enzalutamide or abiraterone (cohort 2). Gleason score, age, time since diagnosis, and prior treatments were documented. Testosterone and PSA were measured at baseline and all imaging time points. ⁶⁸Ga-PSMA-11 PET/CT was quantitatively analyzed for SUV_{max}, SUV_{mean}, and total tumor volume.

In cohort 1, a reduction in SUV_{max} was recorded by day 9 after treatment. A reduction from baseline SUV_{max} occurred in 86% (6/7) of patients by day 9, with an associated PSA response in all patients. Total tumor volume decreased in all patients (interquartile range= 27 to 97%). After

day 9, PSMA response heterogeneity was noted, with persistently high or increasing SUVmax in 38% (3/8) and marked reduction in 62% (5/8).

In cohort 2, an increase in intensity of ⁶⁸Ga-PSMA-11 SUV was recorded by day 9 after treatment. All patients demonstrated an increase in SUVmax and SUVmean on PSMA PET compared with baseline. PSA responses were more delayed in cohort 2, with two of seven men demonstrating PSA progression.

The authors concluded that ⁶⁸Ga-PSMA-11 imaging is affected by the tested treatments targeting the androgen pathway in a manner that is influenced by the presence of hormone-sensitive or castrate-resistant prostate cancer status. These results may have important implications for interpretation of ⁶⁸Ga-PSMA-11 PET.

Applicant's perspective on impact of initiation and duration of ADT on ⁶⁸Ga-PSMA-11 PET

There is controversy regarding the impact of androgen receptor inhibition, such as ADT, on PSMA expression soon after initiation. ADT can result in an increase in expression of PSMA on tumor cells in animal models and in humans, potentially increasing the sensitivity of PSMA PET. However, heterogeneous effects of ADT have been observed clinically with increases in PET signal from baseline in some patients and decreases in others. This variability likely relates to the competing effects on cell death, which decreases uptake, and PSMA upregulation, which increases uptake.

In the Afshar-Oromieh et al. (2018) study on the impact of long-term ADT, the second PET study was performed during the time of therapeutic effect of ADT. In that study, the average PSA at time of the pre-ADT imaging study was 37 ng/dL versus 1.8 ng/dL at the time of the imaging study on chronic ADT, and two patients had a negative PSA at the time of post-ADT imaging. The decrease in SUV and number of lesions on the second PSMA PET on ADT was related to decreased tumor volume due to efficacy of treatment rather than decreased sensitivity of the imaging study.

Based on these findings, the Applicant believes that ADT should not be modified prior to PSMA PET imaging.

FDA conclusion on potential drug-drug interactions

The potential effect of treatments targeting the androgen pathway is cited in the prescribing information (Drug Interactions, Section 7) to inform the prescriber about the possible impact (either reduction or increase in SUV) of these therapies on ⁶⁸Ga-PSMA-11 PET. The efficacy of ⁶⁸Ga-PSMA-11 PET in patients receiving these therapies requires further study.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 5. Listing of Clinical Trials

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Primary Endpoints	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Phase 3 studies to support efficacy and safety							
PSMA-PreRP	NCT03368547 (UCLA) NCT02919111 (UCSF)	Prospective, single arm, open label	Single ⁶⁸ Ga-PSMA-11 PET using 3-7 mCi i.v. dose	Per patient sensitivity and specificity for pelvic nodal metastases by pathology reference standard	325	Patients with intermediate- to high-risk prostate carcinoma who are candidates for initial definitive therapy	2 centers, single country (U.S.)
PSMA-BCR	NCT02940262 (UCLA) NCT02918357 (UCSF)	Prospective, single arm, open label	Single ⁶⁸ Ga-PSMA-11 PET using 3-7 mCi i.v. dose	Per patient and per region PPV for tumor by pathology reference standard	635	Patients with biochemical recurrence of prostate carcinoma after definitive therapy with prostatectomy or radiotherapy	2 centers, single country (U.S.)

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Primary Endpoints	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Other studies pertinent to the review of efficacy							
PSMA-PreRP-Meta	N/A	Literature review with meta-analysis	Varies	Per patient sensitivity and specificity for pelvic nodal metastases by pathology reference standard	266	Patients with prostate carcinoma who are candidates for initial definitive therapy	5 studies from 3 countries (Germany, Australia, China)
PSMA-BCR-Meta	N/A	Literature review with meta-analysis	Varies	Per patient PPV for tumor by pathology reference standard	256	Patients with biochemical recurrence of prostate carcinoma after definitive therapy	15 studies from 10 countries
(van Kalmthout et al. 2019)	N/A	Prospective, single arm, open label	Single ⁶⁸ Ga-PSMA-11 PET using 41 µCi/kg i.v. dose	Per patient sensitivity and specificity for pelvic nodal metastases by pathology reference standard	104	Patients with prostate carcinoma who are candidates for initial definitive therapy	2 centers, 1 country (Netherlands)

Source: FDA clinical reviewer.

Abbreviations: ⁶⁸Ga = gallium-68, BCR = biochemical recurrence, I.V. = intravenous, N/A = Not Applicable, PET = positron emission tomography, PSMA = prostate-specific membrane antigen, UCLA = University of California, Los Angeles, UCSF = University of California, San Francisco, U.S.= United States of America

7.2. Review Strategy

Primary evidence of effectiveness and safety for ⁶⁸Ga-PSMA-11 PET for imaging of prostate cancer was provided in two prospective trials, PSMA-PreRP and PSMA-BCR. These trials were conducted in two distinct populations, patients with new diagnoses of prostate cancer who were candidates for initial definitive therapy and patients with biochemical recurrence of disease. The Applicants for NDA 212642 and NDA 212643 collaborated to perform these studies and the Module 5 data presented in each application were identical.

Unless otherwise specified, all analyses of these trials reported in Section 8 of the review were performed by the clinical and statistical team using data submitted by the Applicant. Any substantial differences in results from the Applicant's analyses are discussed in the relevant section. Analyses performed by the clinical reviewer were derived from the updated fulldata.xpt (PSMA-PreRP) or fac.xpt (PSMA-BCR) datasets received as an amendment to the

applications on January 24, 2020, along with the fab.xpt and fap.xpt (PSMA-BCR) datasets submitted with the initial applications, using SAS Enterprise Guide version 8.1. The 95% confidence intervals for proportions used the method of Wald without continuity correction, unless the sample size was small (defined as $np < 5$ or $n(1-p) < 5$), in which case Clopper-Pearson confidence intervals were reported. Evaluations for difference used t-test for continuous variables and Fisher's exact test for proportions. All tests were two-sided.

Because ^{68}Ga -PSMA-11 has been widely used experimentally for several years, the Applicant included two meta-analyses from the scientific literature in similar populations as those of the prospective trials, PSMA-PreRP-Meta and PSMA-BCR-Meta, as evidence of effectiveness. The statistical and clinical teams have reviewed these sources, but due to the retrospective nature of most of the literature, the potential for bias was assessed as high. As such, the meta-analyses were considered as secondary supportive evidence and are briefly reviewed in Section [8](#).

After the NDA was submitted, the results of a prospective study of ^{68}Ga -PSMA-11 in patients with prostate carcinoma who were candidates for initial definitive therapy (van Kalmthout et al. 2019) were published. The study design and patient population were very similar to the PSMA-PreRP trial, and the results directly addressed the effectiveness of the radiotracer in that population. However, because of the lack of access to the source data, this study was also considered supportive evidence and is briefly reviewed in Section [8](#).

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. PSMA-PreRP

Trial Design

PSMA-PreRP was a prospective, single-arm, open-label study of ^{68}Ga -PSMA-11 PET for imaging of PSMA expressing prostate carcinoma performed at two sites, UCLA and UCSF. It enrolled adult males with biopsy-proven intermediate or high risk prostate carcinoma. Patients had not yet received definitive therapy (including prostatectomy, radiation therapy, or focal gland therapy), and were planned to undergo prostatectomy with pelvic lymph node dissection. Patients were required to have a Karnofsky performance status of at least 50. Patients with lower performance status could certainly tolerate the PET scan, but they would be less likely to tolerate the prostatectomy.

After enrollment, each patient received 3 to 5 mCi (UCLA) or 3 to 7 mCi (UCSF) of ^{68}Ga -PSMA-11 intravenously followed 45 to 60 min (UCLA) or 50 to 100 min (UCSF) later by PET/CT or PET/MR from mid-thigh to skull base. Unless advanced scatter correction algorithms were available on

the scanner, patients received 20 mg of furosemide intravenously with the radiotracer to reduce scatter and scatter correction artifact related to urinary excretion of radiotracer. As discussed in Section 6 of this review, the selection of ⁶⁸Ga-PSMA-11 dose was supported by reports of successful imaging at similar doses that were published prior to study initiation.

Three to five readers from a centralized pool of six nuclear medicine physicians and radiologists independently interpreted each ⁶⁸Ga-PSMA-11 PET scan. These central readers also had access to the anatomic images (CT or MR) obtained with the PET scan for attenuation correction. The readers were blinded to all other information except the history of pre-prostatectomy status. Training was required for the readers prior to participation in the study. Each reader rated multiple predefined regions as positive or negative based on the presence or absence of focal radiotracer uptake greater than physiologic background activity. A single result for each scan was generated by assigning the majority read result in each region, as further described in the Study Endpoints section below. No contract research organization was utilized.

A local read of each PET scan was performed by a single unblinded site reader promptly after the scan, and the result was made available to the physicians caring for the patient, including the urologist performing the prostatectomy. If the local read demonstrated PET positive pelvic lymph nodes, the prostatectomy and pelvic lymph node dissection was to proceed as planned. If the local read demonstrated PET positive bone or extrapelvic soft tissue lesions, correlative imaging or biopsy was to be performed and the treating urologist would determine whether prostatectomy and pelvic lymph node dissection should be performed.

Urologists performed the pelvic lymph node dissections using standard of care template technique guided by surgical anatomy rather than imaging. The reference standard for the PET result was the pathology report from this template pelvic lymph node dissection. The identity and number of separate lymph node groups sent to pathology was to be determined by the usual practice of the urologist performing the surgery. If nodes were read as positive on PET but none were found by histopathology, a pelvic CT or MRI would be performed to determine whether the PET positive nodes were removed.

Table 6. PSMA-PreRP Schedule of Events

	Pre-Study	Week 1	12 Months
Informed consent	X		
Demographics	X		
Medical history	X		
⁶⁸ Ga-PSMA		X	
Data analysis			X

Source: UCLA PSMA-PreRP protocol version 5, section 2.2.6.4.

Abbreviations: ⁶⁸Ga = gallium-68, PSMA = prostate-specific membrane antigen, UCLA = University of California, Los Angeles

Vital signs and adverse event data were collected before and after the PET visit during Week 1. In addition to the events listed in the table above, there was a phone call 1-3 days after the PET visit to assess for adverse events and there was a visit for the surgery. No predefined time range was provided for the surgery visit.

Study Efficacy Endpoints

The primary endpoints were “sensitivity and specificity of ⁶⁸Ga-PSMA-11 PET for the detection of regional nodal metastases compared to pathology at radical prostatectomy on a per patient basis.” These endpoints were discussed with FDA in a meeting and follow up communications spanning August 10, 2016, to January 9, 2017, and agreement was reached. FDA advised that the same two of three readers should meet the predefined sensitivity and specificity goals; this advice was incorporated into the protocol, but ultimately was not implemented in a manner that allowed optimal per-reader analyses.

Current standard of care therapy for prostate cancer localized to the prostate gland most often includes observation, radiotherapy, or prostatectomy, depending in part on the underlying extent of disease. If disease has spread beyond the prostate gland, prostatectomy has traditionally been considered futile, and the substantial morbidity associated with prostatectomy is generally avoided in this situation. However, the potential option of directed therapy of oligometastatic disease is also currently being explored clinically. In either case, management decisions often rely on accurate detection and localization of extraprostatic lesions. Unfortunately, current imaging techniques have limited sensitivity and specificity for detection of pelvic nodal metastases and distant metastatic disease. Thus, there is an unmet need for agents that can better detect extraprostatic disease.

Because prostate cancer most often spreads to the pelvic lymph nodes before becoming widely metastatic, and because pelvic nodal dissection is frequently performed along with prostatectomy for staging and prognostic purposes, assessing performance of ^{68}Ga -PSMA-11 PET in detection of pelvic lymph node metastases as an endpoint is both clinically relevant and practical. However, it does not directly assess the ability of the PET to detect all extraprostatic disease, and it is not certain that the PET will have equal performance for pelvic lymph nodes and distant metastatic disease.

During PET reads, pelvic lymph nodes were assigned to one of nine regions: right common iliac, right external iliac, right internal iliac, right obturator, left common iliac, left external iliac, left internal iliac, and other. Any PET positive node in a region led to a PET positive classification for that respective region. The number of PET positive nodes was not recorded. Note that it is not possible to precisely colocalize PET positive lymph nodes with histopathologically positive lymph nodes due to current surgical methods that use regional anatomy to guide template dissection. Instead, the pelvic regions were condensed into 3 groups (right, left, and other) for both PET read results and the reference standard surgical histopathology results. Any PET positive region contained within a group led to a PET positive classification for that group. Similarly, any histopathology positive lymph nodes within a group led to reference standard positive classification for that group. The node groups were then determined to be true positive, true negative, false positive, or false negative by comparing the PET and histopathology classifications. Patients were then categorized using the rule that the first matching node group from the following ordered list defined the patient status: TP, FP, FN, TN. For example, if a patient had groups that were FP, FP, and TP, the patient would be TP, while if they had groups that were TN, TN, and FN, they would be FN.

An important secondary endpoint was “positive and negative predictive value of ^{68}Ga -PSMA-11 PET for the detection of regional nodal metastases compared to pathology at radical prostatectomy on a per patient basis.” While the study population must closely match the intended population of clinical use for the result to be applicable, if this is fulfilled, then the PPV will accurately reflect the likelihood that a PET positive patient has pelvic lymph node metastasis. Identification of patients with pelvic lymph node metastases without an unduly large number of false positive results is anticipated to be one important use of ^{68}Ga -PSMA-11 PET in this patient population. The data for the PPV and negative predictive value (NPV) endpoints were derived in the same manner as for the primary endpoints.

Statistical Analysis Plan

A detailed statistical analysis plan was not submitted with the protocol. Much of the following is taken from the clinical study report (CSR) and the response to the biostatistics information request received on October 7, 2019.

All enrolled patients who successfully completed the ^{68}Ga -PSMA-11 PET scan were termed study completers. The other patient groups defined by the Applicant include:

- Full Data Analysis Set consists of all patients enrolled and who received a ^{68}Ga -PSMA-11

- injection and subsequently underwent prostatectomy and pelvic lymph node dissection.
- Safety Data Set consists of all patients enrolled who received a ⁶⁸Ga-PSMA-11 injection.
 - The Efficacy Analysis Set consists of all patients who received a ⁶⁸Ga-PSMA-11 injection and had their ⁶⁸Ga-PSMA-11 scan independently and blindly interpreted on a per region basis.
 - The Inter-Reader Set consists of patients who participated in the two prospective studies, received a ⁶⁸Ga-PSMA-11 injection, and had their ⁶⁸Ga-PSMA-11 scan independently and blindly interpreted by three physicians.

The primary endpoints were analyzed using the patients from the intersection of the Full Data Analysis Set and the Efficacy Analysis Set. Goals for sensitivity and specificity were predefined at 65% and 90%, respectively. The 95% confidence intervals for sensitivity, specificity, PPV and NPV were calculated by the Applicant using the Wilson score method.

The Applicant's power analysis was based on the comparison of sensitivity between conventional imaging and ⁶⁸Ga-PSMA-11. With a power of 80% and a significance level of 0.01, a sample size of 61 patients with nodal metastases would be required. The study planned to enroll a total of 271 patients, although only those undergoing prostatectomy were to be included for efficacy analysis (203 patients), given the assumptions below:

- 30% of intermediate to high-risk patients have nodal metastases at prostatectomy.
- An anticipated 25% of patients would not undergo prostatectomy.
- Conventional imaging has a 45% detection sensitivity for nodal metastases on a per patient basis.
- PSMA PET has a 65% detection sensitivity for nodal metastases on a per patient basis.

An unplanned interim analysis performed by the Applicant in early 2018, prior to implementation of UCLA protocol version 5 and UCSF protocol version 4 (see tables below), determined that they had not yet met their goal sample size of 203 patients who had undergone prostatectomy. At that time, 325 patients had been enrolled, of whom 127 had subsequently undergone prostatectomy. The study remained open to enrollment after that point, but all data submitted to this application were already collected at the time of the interim analysis. Accordingly, no statistical corrections were applied by the Applicants.

Protocol Amendments

[Table 7](#) lists the study protocol versions submitted to the UCLA IND and the number of patients scanned at UCLA under each version.

Table 7. Patients Scanned in the PSMA-PreRP Study Under Each UCLA Protocol Version

Protocol Version	FDA Receipt Date	Patients Scanned at UCLA	FAS Patients Scanned at UCLA	Patients Scanned at All Sites
1	10/5/2016	5	1	133
2	2/14/2017	51	22	135
3	10/18/2017	23	10	23

Protocol Version	FDA Receipt Date	Patients Scanned at UCLA	FAS Patients Scanned at UCLA	Patients Scanned at All Sites
4	12/21/2017	34	6	34
5	4/23/2018	0	0	0

Source: FDA clinical reviewer analysis.

Abbreviations: FAS = full analysis set, FDA = Food and Drug Administration, PSMA = prostate-specific membrane antigen, UCLA = University of California, Los Angeles

Version 2: The key change in this version was removal of the exclusion criterion for ADT or other neoadjuvant treatments.

Version 3: This amendment increased the planned patient number at UCLA from 80 to 150 because the expected increase in number of sites participating in the trial had not occurred. There was also an increase in projected accrual rate based on prior experience.

Version 4: PPV and NPV were changed from primary endpoints to secondary endpoints. A goal for specificity, which was not present in earlier versions, was set at 90%.

Version 5: This amendment was submitted after the unplanned interim analysis, which showed a lower prostatectomy rate than expected (28% versus 75%). Accordingly, the sample size at UCLA was increased from 150 to 400.

[Table 8](#) lists the study protocol versions submitted to the UCSF IND and the number of patients scanned at UCSF under each version.

Table 8. Patients Scanned in the PSMA-PreRP Study Under Each UCSF Protocol Version

Protocol Version	Version Date	Patients Scanned at UCSF	FAS Patients Scanned at UCSF	Patients Scanned at All Sites
1	8/26/2016	128	65	133
2	2/18/2017	72	21	116
3	9/6/2017	12	2	76
4	6/8/2018	0	0	0

Source: FDA clinical reviewer analysis.

Abbreviations: FAS = full analysis set, PSMA = prostate-specific membrane antigen, UCSF = University of California, San Francisco

Version 2: This version added safety as a secondary endpoint and defined methods for safety data collection. It also further defined the methods of analysis for multiple endpoints, added age >18 as an inclusion criterion, allowed patients with sulfa allergy to be enrolled if furosemide was omitted, and added institution specific template language for study management procedures.

Version 3: The total study sample size remained unchanged at 271, but this version added that 250 patients would be enrolled at UCSF.

Version 4: This version increased the total study sample size and UCSF enrollment to 300.

8.1.2. Study Results – PSMA-PreRP

Compliance with Good Clinical Practices

The Applicant indicated that the study was performed in compliance with good clinical practice (GCP) and with oversight from the local IRB. The study was performed exclusively within the

United States.

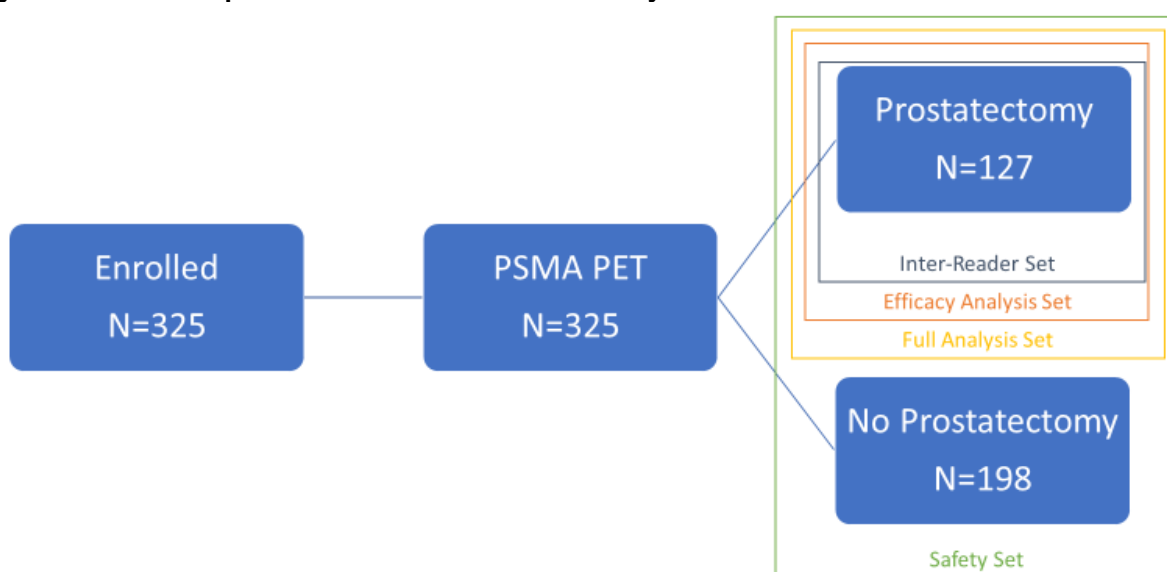
Financial Disclosure

No relevant financial disclosures were reported by the Applicant or per the Applicant, by the clinical investigators.

Patient Disposition

Among the 325 patients enrolled and scanned, a total of 127 patients underwent prostatectomy (see [Figure 9](#) below).

Figure 9. Patient Disposition in the PSMA-PreRP Study



Source: FDA clinical reviewer, using data and set definitions from the PSMA-PreRP clinical study report.
 Abbreviations: N = number of patients, PET = positron emission tomography, PSMA = prostate-specific membrane antigen

The majority of patients in the PSMA-PreRP study who did not receive prostatectomy went on to have radiation therapy (see [Table 9](#) below). A substantial fraction proceeded to ADT. As ADT is not a common first line therapy for patients with intermediate to high risk localized prostate cancer, it is likely that many patients in this group were found to have extra-prostatic disease on the PET scan.

Table 9. Management of Patients Who Did Not Proceed to Radical Prostatectomy After ⁶⁸Ga PSMA-11 PET in the PSMA-PreRP Study

	Combined N=198 N (%)	UCLA N=124 N (%)	UCSF N=74 N (%)
Management			
Active surveillance	5 (3%)	4 (3%)	1 (1%)
Radiation therapy	116 (59%)	82 (66%)	34 (46%)
Androgen deprivation therapy	28 (14%)	16 (13%)	12 (16%)
Chemotherapy	7 (4%)	4 (3%)	3 (4%)

Management	Combined N=198 N (%)	UCLA N=124 N (%)	UCSF N=74 N (%)
Unknown	35 (18%)	12 (10%)	23 (31%)
Other	7 (4%)	6 (5%)	1 (1%)

Source: Table 12 of the PSMA-PreRP clinical study report.

Abbreviations: ⁶⁸Ga = gallium-68, N = number of patients, PET = positron emission tomography, PSMA = prostate-specific membrane antigen, UCLA = University of California, Los Angeles, UCSF = University of California, San Francisco

Protocol Deviations

Several protocol deviations were reported by the Applicant. Except for the delay in the post-scan follow up call as described in 1 below, the impact of these deviations on the study results was likely minimal.

- 1) Post-scan follow up call: All patients were to receive a follow up telephone call from 1 to 3 days after the PET scan to screen for adverse events. The call was made more than 3 days after the scan for 113 patients (35%), all enrolled at UCLA. As described in later sections, similar late follow up also occurred for patients at UCLA participating in PSMA-BCR. The late follow up likely explains the lower adverse event rate at UCLA compared to UCSF (0.8% versus 4.2%, respectively).
- 2) Radiotracer dose: A total of 16 patients (5%), all from the UCSF site, received ⁶⁸Ga-PSMA-11 doses outside the prescribed range of 3-7 mCi. Fourteen patients received doses >7 mCi, up to 7.5 mCi. Two patients received doses <3 mCi, as low as 2.84 mCi.
- 3) PSA: Per protocol, PSA was to be measured within 30 days prior to the PET scan. PSA was measured outside of this time window in 244 patients (75%). The Applicant notes that the PSA value at prostate cancer diagnosis, rather than any subsequent PSA value, is used for risk stratification, therefore subsequent measurements are of limited utility.
- 4) Performance status: Performance status at enrollment was to have been documented by a physician for all patients. This documentation was instead performed by a clinical research coordinator for 43 patients in the Full Analysis Set (34%), all enrolled at UCSF. It was not reported whether similar deviations occurred for patients who did not receive prostatectomy.
- 5) Vital signs: Patients were to have heart rate and blood pressure recorded before and after the PET scan. Three patients (1%) did not have complete recording. Two patients lacked post-scan vital signs, while one lacked vital signs both before and after PET.
- 6) Informed consent: Two patients from UCLA lacked signed informed consent documents. The Applicant described this violation as an administrative error in the informed consent process that was otherwise routinely performed.

Demographic Characteristics

The full analysis set consisted of 127 patients, 39 of whom were enrolled at the UCLA site and 88 at the UCSF site. The mean age of the 127 patients was 65 years, ranging from 44 to 76 years. All patients were diagnosed with intermediate to high risk prostate cancer, and were imaged prior to definitive therapy. The majority of patients were white (n= 108; 85%). Gleason

score at time of diagnosis was 7 for 56 patients (44%), 8 for 26 patients (20%), and 9 for 39 patients (31%). The median PSA at the time of imaging was 18.5 ng/mL (range: 0.035 to 147 ng/mL).

[Table 10](#) summarizes patient demographics in the full analysis set overall and by site. Demographic data were similar between UCSF and UCLA, with a slightly higher incidence of white Americans at the UCLA site compared to UCSF. Patient risk factors (PSA and Gleason score) were similar between the sites.

Table 10. Demographic Characteristics of Patients in the PSMA-PreRP Full Analysis Set

Characteristic	Overall (N=127)	UCSF	UCLA
Age (years)			
Median (SD)	65 (8)	66 (8)	62 (7)
Range	44-76	44-76	44-72
Ethnicity and Race			
White American, n (%)	108 (85)	71 (81)	37 (95)
Black or African American, n (%)	1 (1)	1 (1)	0 (0)
Native American and Alaska Native, n (%)	0 (0)	0 (0)	0 (0)
Asian American, n (%)	4 (3)	2 (2)	2 (5)
Native Hawaiian, n (%)	1 (1)	1 (1)	0 (0)
Other Pacific Islander, n (%)	0 (0)	0 (0)	0 (0)
Other, n (%)	8 (6)	8 (9)	0 (0)
Missing data, n (%)	5 (4)	5 (7)	0 (0)
Gleason Score at time of diagnosis			
6	3 (2)	3 (3)	0 (0)
7	56 (44)	39 (44)	17 (44)
8	26 (20)	14 (16)	12 (31)
9	39 (31)	30 (34)	9 (23)
10	3 (2)	2 (2)	1 (3)
Missing data	0 (0)	0 (0)	0 (0)
PSA at time of imaging			
Mean (SD)	18.5 (19.1)	18.8 (16.5)	17.8 (24.2)
Range	0.035-147	0.036-83.1	2.4-147
T-stage at diagnosis			
6, n (%)	17 (13)	12 (14)	5 (13)
7, n (%)	47 (37)	39 (44)	8 (21)
8, n (%)	39 (31)	26 (30)	13 (33)
9, n (%)	2 (2)	1 (1)	1 (3)
Missing, n (%)	22 (17)	10 (11)	12 (31)

Source: Applicant's Table 3 in CSR of PSMA-PreRP.

Abbreviations: N or n = number of patients, PSA = prostate-specific antigen, PSMA = prostate-specific membrane antigen, SD = standard deviation, UCLA = University of California, Los Angeles, UCSF = University of California, San Francisco

[Table 11](#) summarizes patient demographics for the full analysis set and safety set as well as for patients who did not undergo prostatectomy.

Table 11. Comparison of Demographic Characteristics Among Several PSMA-PreRP Patient Sets

Demographic Characteristics	Full Analysis Set (N=127) N (%)	No Prostatectomy (N=198) N (%)	Safety Set (N=325) N (%)
Age			
Mean years (SD)	65 (7.6)	69 (8.4)	68 (8.4)
Median (years)	67	70	69
Min, max (years)	45, 76	40, 93	40, 93
Age group			
< 65 years	53 (42%)	48 (24%)	101 (31%)
≥ 65 years	74 (58%)	150 (76%)	224 (69%)
Race			
White	108 (85%)	161 (81%)	269 (83%)
Black or African American	1 (<1%)	5 (3%)	6 (2%)
Asian	4 (3%)	14 (7%)	18 (6%)
American Indian or Alaska Native	0	1 (<1%)	1 (<1%)
Native Hawaiian or Other Pacific Islander	1 (<1%)	3 (2%)	4 (1%)
Other	8 (6%)	12 (6%)	20 (6%)
Missing	5 (4%)	2 (1%)	7 (2%)
Ethnicity			
Hispanic or Latino	5 (4%)	7 (4%)	12 (4%)
Not Hispanic or Latino	115 (91%)	182 (92%)	297 (91%)
Missing	7 (5%)	9 (5%)	16 (5%)
PSA			
Median (ng/mL)	11.8	14.3	13.6
Min, max (ng/mL)	0.04, 147.0	0.42, 577.2	0.04, 577.2
Sum Gleason score			
6	3 (2%)	N/A	N/A
7	56 (44%)	N/A	N/A
8	26 (20%)	N/A	N/A
9	39 (31%)	N/A	N/A
10	3 (2%)	N/A	N/A
D'Amico risk group			
High	96 (76%)	N/A	N/A
Baseline conventional imaging status			
Baseline imaging present	82 (65%)	154 (78%)	236 (73%)
N1 by baseline imaging	25 (20%)	30 (15%)	55 (17%)
M1 by baseline imaging	9 (7%)	24 (12%)	33 (10%)

Source: FDA clinical reviewer analysis.

Abbreviations: M1 = distant metastatic disease, N = number of patients, N1 = regional lymph node metastasis, PSMA = prostate-specific membrane antigen, PSA = prostate-specific antigen, SD = standard deviation

While the age distribution overall appears to be representative of the primary prostate cancer population, there was a trend to older age in the patients who did not proceed to prostatectomy. This trend becomes more apparent when age is grouped using 65 years as a cutoff. Two factors that may have contributed to this difference are the likelihood that older patients were less able to tolerate surgery due to general health status and the possibility that older patients were considered less likely to benefit from surgery due to shorter life expectancy.

The enrolled patients were mostly white; patients who were black were few in number. This observation may reflect the limited geographic availability of the trial, which enrolled only in Los Angeles, CA and San Francisco, CA. The review team was unable to find data to suggest that

the test will perform less well in black patients than in white patients. There are some published data that suggest the test could perform better in black South Africans than white South Africans (Sathekge et al. 2018), presumably due to differences in PSMA expression on prostate cancer cells.

Other Baseline Characteristics

As shown in [Table 11](#), there was a trend toward higher PSA levels in the no prostatectomy group that was excluded from the primary endpoint analysis, however the clinical significance of this trend is questionable due to the small magnitude of the difference. Data were not available for Gleason score in the no prostatectomy group. In the full analysis set, 53% of patients had summed Gleason score of at least 8, and 76% were considered high risk for recurrence by D'Amico criteria.

Baseline conventional imaging defined as performed within 6 months of enrollment was available for 65% of the full analysis set, which is somewhat lower than expected in an intermediate to high risk population. However, the Applicant indicated that many patients were referred to the study from outside institutions and imaging was likely performed elsewhere but not made available. The baseline imaging modalities commonly available in the full analysis set included MR in 43% of patients, bone scan in 41% of patients, and CT in 35% of patients; some patients had multiple modalities available. Of note, the anatomic coverage and individual test results for the baseline conventional imaging were not captured in detail. The no prostatectomy group had a higher rate of conventional imaging availability than the full analysis set. In part, this is explained by a higher rate of distant metastatic disease seen on conventional imaging, which likely contributed to exclusion from prostatectomy.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study drug was administered at the clinical sites; therefore, drug compliance is not applicable. Information about prior and concomitant medications was not collected other than ADT exposure.

All enrolled patients successfully completed a ⁶⁸Ga-PSMA-11 PET scan in this single arm study. However only 127 of 325 patients (39%) proceeded to prostatectomy and pelvic lymph node dissection, which was needed for reference standard determination. It was anticipated in the protocol that the surgery rate would be about 75%; this value is less than 100% due to the expectation that there would be identification of new findings on the PET scan as well as miscellaneous other factors. The protocol specified that if PET positive pelvic lymph nodes were found, the treating urologist would be notified and the patient would still proceed to surgery. If PET positivity for distant metastatic disease was found, the lesions would be further evaluated using other imaging techniques or by biopsy before deciding whether prostatectomy and pelvic lymph node dissection were appropriate.

Based on the plan in the protocol, the rate of ⁶⁸Ga-PSMA-11 PET positive lesions in the extrapelvic soft tissues and in the bones should be higher in the group of patients who did not proceed to prostatectomy and pelvic lymph node dissection. This was the case, as shown in [Table 12](#). However, suspected distant metastatic disease accounted for only 14 to 32% of the patients without surgery, depending on the number of patients with both soft tissue and bone lesions. While the presence of PET positive lymph nodes was not anticipated to influence the decision to proceed to surgery according to the protocol, it appears to have had a substantial effect as reflected in the much higher incidence of PET positive pelvic lymph nodes in the no prostatectomy group. The finding of pelvic nodal disease as determined by PET has not been shown to be equivalent to the finding of pelvic nodal disease revealed by conventional imaging for the purpose of patient management. However, the historically poor performance of prostatectomy in the setting of conventionally identified extraprostatic disease likely led to a similar influence of PET on treatment decisions in the PSMA-PreRP study population. If all patients with potential extraprostatic disease by PET are excluded from the sample, the adjusted rate of prostatectomy becomes 56%.

Table 12. ⁶⁸Ga-PSMA-11 PET Positivity Rates in Patients Who Did (FAS) or Did Not Proceed to Surgery

Region	Full Analysis Set (N=127) N (%)	No Prostatectomy (N=198) N (%)
Prostate	125 (98%)	193 (98%)
Pelvic lymph nodes	22 (17%)	88 (44%)
Extrapelvic soft tissues	0	27 (14%)
Bone	1 (1%)	36 (18%)
Any outside prostate	23 (18%)	99 (50%)

Sources: No prostatectomy results from Table 11 of the PSMA-PreRP CSR. Full analysis set results from FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, FAS = full analysis set, N = number of patients, PET = positron emission tomography, PSMA = prostate-specific membrane antigen

Note that in [Table 12](#), the full analysis set results are derived from a consensus read while the no prostatectomy results reflect a single local read. PET scans for patients who did not have surgery were not read by the blinded central readers and local read results were not available for surgical patients.

In a response to an information request on the potential for bias caused by selection of patients for reference standard determination based on the result of the ⁶⁸Ga-PSMA-11 scan, the Applicant suggested that the bias introduced would decrease the chance of success of the study. The rationale is that patients with disease more readily detected by PET would also tend to have larger and more numerous metastatic lesions and would be less likely to proceed to prostatectomy. The full analysis set would then be enriched for patients with harder to detect disease, decreasing the number of true positive patients and thereby reducing measured sensitivity and PPV. This argument seems reasonable and was considered when reviewing the primary endpoint results. Note, however, that other types of bias could exist, and the argument does not explain why the adjusted rate of prostatectomy remained substantially below target.

The full analysis set and no prostatectomy group were also examined for differences in the proportion of patients receiving ADT, proportion of patients receiving furosemide with the PET scan, dose of ⁶⁸Ga-PSMA-11 administered, dose to scan time, and date of PET scan. Patients in the full analysis set were more likely to have been scanned earlier in the study than patients who did not proceed to surgery (days from first scan performed in study [mean ± SD] 396 ± 220 versus 488 ± 194; proportion of patients scanned in the first half of the study 57% versus 44%). This finding suggests that the enrollment criterion of planned prostatectomy was less strictly enforced as the trial proceeded. However, such a trend seems unlikely to bias the study results. No substantial differences were found for the other tested variables.

In the full analysis set, there were four patients who had a value of 0 or no data recorded for the number of lymph nodes surgically removed. The Applicant indicated that no lymph nodes were described in the pathology reports for any of these four patients. These patients were therefore excluded from the primary endpoint analysis due to lack of reference standard data.

Efficacy Results – Primary Endpoint

FDA analysis of the Applicant’s data excluded four patients who had no lymph nodes identified in their pathology reports as mentioned above, incorporated additional reader results into the majority read determination for 19 patients who had more than three central readers interpret their PET scans, and corrected an error in coding of the “other” pelvic lymph node group PET results. In cases where four central readers interpreted a PET scan, ties in a region were considered positive results. The Applicant agreed with these modifications. The tables that follow present data and results using this FDA analysis.

Table 13. Patient-Level Comparison of ⁶⁸Ga-PSMA-11 PET Majority Read Versus Histopathology for Detection of Pelvic Lymph Node Metastases

PET Majority Read	Pathology Positive	Pathology Negative	Total
PET positive	14 (true positive)	9 (false positive)	23
PET negative	16 (false negative)	84 (true negative)	100
Total	30	93	123

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, PET = positron emission tomography, PSMA = prostate-specific membrane antigen

The results differ minimally from those the Applicant presented in Table 4 of the CSR. The four patients who had no lymph nodes identified on pathology were categorized as true negative in the Applicant’s analysis. Several of the patients with additional reader data incorporated in this analysis were recategorized from the Applicant’s results with the net effect of changing one true negative patient to false positive.

Table 14. Patient-Level Performance of ⁶⁸Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases

Diagnostic Performance Measure (N=123)	Point Estimate	95% CI	Goal
Sensitivity	47%	29%, 65%	65%
Specificity	90%	84%, 96%	90%
PPV	61%	41%, 81%	-
NPV	84%	77%, 91%	-
% pathology +	24%	17%, 32%	-

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, N = number of patients, NPV = negative predictive value, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen

Neither the sensitivity nor the specificity, as defined by the lower bound of the 95% confidence interval, met its prespecified goal. Note that a histopathology reference standard can detect micrometastatic disease in the pelvic lymph nodes. While this is a clinically meaningful standard, it is also challenging for any imaging test to meet and likely negatively impacted the observed sensitivity.

Table 15. Patient-Level Performance of ⁶⁸Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases, Stratified by Patient Age

Diagnostic Performance Measure (N=123)	Combined N=123	Age < 65 N=52	Age ≥ 65 N=71
TP	14	6	8
FP	9	4	5
FN	16	10	6
TN	84	32	52
Sensitivity, point estimate (95% CI)	47% (29%, 65%)	38% (14%, 61%)	57% (31%, 83%)
Specificity, point estimate (95% CI)	90% (84%, 96%)	89% (76%, 97%)	91% (84%, 99%)
PPV, point estimate (95% CI)	61% (41%, 81%)	60% (26%, 88%)	62% (35%, 88%)
NPV, point estimate (95% CI)	84% (77%, 91%)	76% (63%, 89%)	90% (82%, 97%)
% pathology +, point estimate (95% CI)	24% (17%, 32%)	31% (18%, 43%)	20% (10%, 29%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, FN = false negative, FP = false positive, N = number of patients, NPV = negative predictive value, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen, TN = true negative, TP = true positive

A trend towards numerically lower sensitivity was seen in patients <65 years old compared to the older patients in the group, which is more pronounced in the Applicant's analysis (point estimate 35% versus 62% for <65 and ≥ 65, respectively).

The results are not stratified by race due to the very small number of non-white patients.

Table 16. Patient-Level Performance of ⁶⁸Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases, Stratified by Risk Factors

Diagnostic Performance Measure (N=123)	PSA (ng/mL)		Tumor Stage		Gleason Score	
	<11.8 N=61	≥11.8 N=62	<T2c N=52	≥T2c N=49	<8 N=58	≥8 N=65
TP	4	10	4	9	2	12
FP	3	6	3	4	4	5

NDA/BLA Multi-Disciplinary Review and Evaluation NDA 212643
Gallium Ga 68 PSMA-11 Injection

Diagnostic Performance Measure (N=123)	PSA (ng/mL)		Tumor Stage		Gleason Score	
	<11.8 N=61	≥11.8 N=62	<T2c N=52	≥T2c N=49	<8 N=58	≥8 N=65
FN	6	10	3	8	6	10
TN	48	36	42	28	46	38
Sensitivity, point estimate (95% CI)	40% (12%, 74%)	50% (28%, 72%)	57% (18%, 90%)	53% (29%, 77%)	25% (3%, 65%)	55% (34%, 75%)
Specificity, point estimate (95% CI)	94% (84%, 99%)	86% (75%, 96%)	93% (82%, 99%)	88% (71%, 96%)	92% (81%, 98%)	88% (79%, 98%)
PPV, point estimate (95% CI)	57% (18%, 90%)	63% (39%, 86%)	57% (18%, 90%)	69% (39%, 91%)	33% (4%, 78%)	71% (49%, 92%)
NPV, point estimate (95% CI)	89% (81%, 97%)	78% (66%, 90%)	93% (82%, 99%)	78% (64%, 91%)	88% (80%, 97%)	79% (68%, 91%)
% pathology +, point estimate (95% CI)	16% (7%, 26%)	32% (21%, 44%)	13% (4%, 23%)	35% (21%, 48%)	14% (5%, 23%)	34% (22%, 45%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, FN = false negative, FP = false positive, N = number of patients, NPV = negative predictive value, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen, TN = true negative, TP = true positive

As expected, more patients had histopathologically cancer-positive lymph nodes (% pathology + in [Table 16](#)) in cohorts with higher PSA level, tumor stage, and Gleason score, all of which are well established markers for risk of regional lymph node metastases. The high Gleason score cohort appeared to have numerically higher sensitivity and PPV than the low Gleason score cohort.

Table 17. Patient-Level Performance of ⁶⁸Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases, Stratified by Study Site

Diagnostic Performance Measure	Combined N=123	UCSF N=86	UCLA N=37
TP	14	11	3
FP	9	6	3
FN	16	10	6
TN	84	59	25
Sensitivity, point estimate (95% CI)	47% (29%, 65%)	52% (31%, 74%)	33% (7%, 70%)
Specificity, point estimate (95% CI)	90% (84%, 96%)	91% (84%, 98%)	89% (72%, 98%)
PPV, point estimate (95% CI)	61% (41%, 81%)	65% (42%, 87%)	50% (12%, 88%)
NPV, point estimate (95% CI)	84% (77%, 91%)	86% (77%, 94%)	81% (67%, 95%)
% pathology +, point estimate (95% CI)	24% (17%, 32%)	24% (15%, 33%)	24% (10%, 38%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, FN = false negative, FP = false positive, N = number of patients, NPV = negative predictive value, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen, TN = true negative, TP = true positive, UCLA = University of California, Los Angeles, UCSF = University of California, San Francisco

Within the limitations imposed by sample size, there did not appear to be any meaningful difference in the results obtained at the two trial sites.

Table 18. Patient-Level Performance of ⁶⁸Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases, Stratified by PET Scan Date

Diagnostic Performance Measure	Combined N=123	First Half of Patients N=61	Last Half of Patients N=62
TP	14	11	3
FP	9	6	3
FN	16	9	7
TN	84	35	49
Sensitivity, point estimate (95% CI)	47% (29%, 65%)	55% (33%, 77%)	30% (7%, 65%)
Specificity, point estimate (95% CI)	90% (84%, 96%)	85% (75%, 96%)	94% (84%, 99%)
PPV, point estimate (95% CI)	61% (41%, 81%)	65% (42%, 87%)	50% (12%, 88%)
NPV, point estimate (95% CI)	84% (77%, 91%)	80% (68%, 91%)	88% (79%, 96%)
% pathology +, point estimate (95% CI)	24% (17%, 32%)	33% (21%, 45%)	16% (7%, 25%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, FN = false negative, FP = false positive, N = number of patients, NPV = negative predictive value, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen, TN = true negative, TP = true positive

Analysis was performed to search for an effect of time of enrollment on test performance using PET scan date as the index because of the difference in PET scan date between patients who did and did not proceed to prostatectomy. Note there was substantial interaction between this analysis and the analysis by trial site because 60/86 (70%) of the UCSF patients were among the first half of the study population to be scanned while only 1/37 (3%) of the UCLA patients were scanned in the first half. Small sample sizes and low PET positivity rate again combined to create wide confidence intervals, and the only clearly appreciable trend was a higher percentage of pathology-positive patients in the first half of the group scanned at UCSF (37% first half, 12% second half). This trend might be explained by changing referral patterns of patients to the study or by changes in management patterns that altered the decision of whether to proceed to prostatectomy.

Data Quality and Integrity

FDA OSI audits of the UCLA and UCSF sites revealed no significant GCP deficiencies.

The datasets provided by the Applicant revealed a large number of missing values for many variables. The issue primarily applied to binary variables, and when data was provided it was usually positive, suggesting that negative results often were not entered into the dataset. The Applicant confirmed the reviewers' interpretation in discussions and in written replies to information requests. For this review, where appropriate, missing data from binary variables were assumed to be negative.

Efficacy Results – Secondary and other relevant endpoints

Secondary endpoints included evaluation of inter-reader reproducibility.

Table 19. Per Reader Comparison of ⁶⁸Ga-PSMA-11 PET Versus Pathology for Detection of Pelvic Lymph Node Metastases in the PSMA-PreRP Study

Detection	Reader 1 (N=83)	Reader 2 (N=64)	Reader 3 (N=63)	Reader 4 (N=64)	Reader 5 (N=65)	Reader 6 (N=63)
True positive	7	9	6	8	10	5
False positive	11	4	7	2	3	8
False negative	12	6	10	7	7	9
True negative	53	45	40	47	45	41
Sensitivity	37%	60%	38%	53%	59%	36%
Specificity	83%	92%	85%	96%	94%	84%
PPV	39%	69%	46%	80%	77%	38%
NPV	82%	88%	80%	87%	87%	82%
% pathology +	23%	23%	25%	23%	26%	22%

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, N = number of patients, NPV = negative predictive value, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen

The above performance data cannot be reliably compared among readers since they interpreted different subsets of the PET scans. The number of cases interpreted by each reader was also relatively small. Among the pool of six readers used in the study, point estimates of sensitivity ranged from 36 to 60%, specificity from 83 to 96%, positive predictive value from 38 to 80%, and negative predictive value from 80 to 88%. These ranges are broad, but they closely reflect the 95% confidence intervals reported in the primary analysis.

Table 20. Measures of Inter-Reader Agreement for ⁶⁸Ga-PSMA-11 PET in the 123 Patients Used for Primary Endpoint Analysis

Node Group Evaluated (N=123 Patients)	Patients With All Readers	
	Concordant N (%)	Kappa Point Estimate (95% CI)
All pelvic lymph nodes	96 (78%)	0.79 (0.68, 0.9)
Left pelvic lymph nodes	102 (83%)	0.78 (0.65, 0.91)
Right pelvic lymph nodes	109 (89%)	0.66 (0.48, 0.85)
Other pelvic lymph nodes	121 (98%)	0.85 (0.64, 1)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, N = number of patients, PET = positron emission tomography, PSMA = prostate-specific membrane antigen

Although direct comparison of per reader performance for the major endpoints of the study was not possible, reader concordance rate and Fleiss' kappa were calculated to provide some estimate of the degree of inter-reader agreement. The concordance rate was based on region-level data and required identical reads among all readers of each region in a node group to call the group concordant. Most PET scans were read by various combinations of three readers selected from a pool of six readers, although some scans were read by four or five readers. Regions were combined into node groups using the rule that any positive region defines a positive group before calculating kappa. Thus, concordance rate and kappa are not directly comparable.

Because the “all pelvic lymph nodes” group requires agreement of all readers in all nine pelvic lymph node regions to be deemed concordant, the measured rate of 78% suggests relatively high reproducibility between readers. The left and right node groups showed similar rates of concordance to each other. The “other” node group had much higher concordance results because this group contained only one region, versus four each for the left and right groups.

Dose/Dose Response

A single dose range of 3 to 7 mCi was studied with injected activities averaging 5.4 ± 1.1 mCi in the 123 patients included in analyses and 5.3 ± 1.1 mCi in the 325 enrolled patients.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Efficacy Results – Secondary or exploratory COA patient reported outcome (PRO) endpoints

Not applicable.

Additional Analyses Conducted on the Individual Trial

A post hoc analysis of the primary endpoint data was conducted by the Applicant due to the lower than expected test performance. Post-surgical follow up results for the eight patients who were categorized as false positive by the Applicant were examined and brief narratives were submitted for seven of them.

Table 21. Patients Included in the Applicant’s Post Hoc Analysis

Case Name	Narrative	Categorization by Applicant		Categorization by Reviewer	
		Initial	Post Hoc	Initial	Post Hoc
Ucla ^{(b) (6)}	Patient had positive left perirectal node that was called positive by all 3 central readers. Note the patient was treated with neo-adjuvant ADT after PSMA PET and prior to RP. Pathology including left peri-rectal fat did not demonstrate a positive node. CT at time of PSMA PET demonstrates a clear nodal metastasis, and likely the node resolved while the patient was treated with ADT.	FP	TP	FP	FP

NDA/BLA Multi-Disciplinary Review and Evaluation NDA 212643
Gallium Ga 68 PSMA-11 Injection

Case Name	Narrative	Categorization by Applicant		Categorization by Reviewer	
		Initial	Post Hoc	Initial	Post Hoc
Ucsf-Prerp-(b) (6)	Patient had multiple presacral nodes / common iliac nodes that were called positive by all 3 central readers. Pathology did not demonstrate any positive node. The patient developed immediate BCR after surgery (PSA of 1.7 ng/mL) and follow-up imaging demonstrated that these nodes were not removed at time of surgery.	FP	TP	FP	ND
Ucsf-Prerp-(b) (6)	Patient had two left external iliac nodes and a small obturator node which was called positive by two of three central readers. The patient had immediate BCR after surgery (PSA of 0.8 ng/mL) indicating that tumor lesions were left behind. No repeat imaging was available.	FP	TP	FP	FP
Ucsf-Prerp-(b) (6)	Patient had a left internal iliac / perirectal node that was called by two of three central readers. Pathology at time of prostatectomy was positive for two right sided nodes. It is unclear if there was an error in bagging of the pathology samples, as the nodes were clearly on the left on imaging. The patient developed immediate BCR after surgery (PSA of 3.8 ng/mL) and follow-up imaging demonstrated that these nodes were not removed at time of surgery.	FP	TP	FP	ND
Ucsf-Prerp-(b) (6)	Patient had left internal iliac, left obturator and left common iliac nodes that were called positive by all 3 central readers. Pathology did not demonstrate any positive nodes. The patient developed immediate BCR (PSA of 1.8 ng/mL) after surgery and follow-up imaging demonstrated that these nodes were not removed at time of surgery.	FP	TP	FP	ND
Ucsf-Prerp-(b) (6)	Patient had a right obturator node called positive by reader 2 and a right internal iliac node called by reader 3 (most likely the same node). Pathology did not demonstrate any positive nodes. The patient developed immediate BCR (PSA of 0.06 ng/mL) after surgery and follow-up imaging demonstrated that this node was not removed at time of surgery.	FP	TP	TN	TN
Ucsf-Prerp-(b) (6)	Patient had a left internal iliac node that was called positive by all 3 central readers. Pathology did not demonstrate any positive nodes. The patient developed immediate BCR after surgery (PSA of 0.4 ng/mL) and follow-up imaging demonstrated that these nodes were not removed at time of surgery.	FP	TP	FP	ND

Source: Section 11.4.8 of the PSMA-PreRP CSR.

Abbreviations: BCR = biochemical recurrence, FP = false positive, ND = Not determinable, PSA = prostate-specific antigen, TN = true negative, TP = true positive

It seems reasonable to consider four false positive patients as lacking sufficient reference standard information in the cases where there was imaging evidence that PET positive lesions were not removed. An analysis excluding these patients is shown in [Table 22](#).

Table 22. Result of Post-Hoc Analysis for Patient-Level Performance of ⁶⁸Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases

Diagnostic Performance Measure	Initial Categorization N=123	Post Hoc Categorization N=119
TP	14	14
FP	9	5
FN	16	16
TN	84	84
Sensitivity, point estimate (95% CI)	47% (29%, 65%)	47% (29%, 65%)
Specificity, point estimate (95% CI)	90% (84%, 96%)	94% (90%, 99%)
PPV, point estimate (95% CI)	61% (41%, 81%)	74% (54%, 93%)
NPV, point estimate (95% CI)	84% (77%, 91%)	84% (77%, 91%)
% pathology +, point estimate (95% CI)	24% (17%, 32%)	25% (17%, 33%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, FN = false negative, FP = false positive, N = number of patients, NPV = negative predictive value, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen, TN = true negative, TP = true positive

Sensitivity is unchanged and remains below the goal of 65% by this analysis, however specificity has increased and now reaches the target of 90%. Accordingly, the PPV is substantially increased.

While patient-level test performance has strong clinical relevance in the context of prostate cancer imaging before definitive therapy, increased use of anatomically targeted therapy stresses the importance of accurate localization of cancer. Accordingly, test performance was evaluated at the node group- and region-levels ([Table 23](#)).

Table 23. Patient-Level, Node Group-Level, and Region-Level Performance of ⁶⁸Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases

Diagnostic Performance Measure	Patient-Level N=123	Node Group-Level* N=369	Region-Level* N=999
TP	14	16	9
FP	9	13	14
FN	16	29	20
TN	84	311	956
Sensitivity, point estimate (95% CI)	47% (29%, 65%)	36% (22%, 50%)	31% (14%, 48%)
Specificity, point estimate (95% CI)	90% (84%, 96%)	96% (94%, 98%)	99% (98%, 99%)
PPV, point estimate (95% CI)	61% (41%, 81%)	55% (37%, 73%)	39% (19%, 59%)
NPV, point estimate (95% CI)	84% (77%, 91%)	91% (89%, 94%)	98% (97%, 99%)
% pathology +, point estimate (95% CI)	24% (17%, 32%)	12% (9%, 16%)	3% (2%, 4%)

Source: FDA clinical reviewer analysis.

*Assuming observed lesions are independent

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, FN = false negative, FP = false positive, N = number, NPV = negative predictive value, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen, TN = true negative, TP = true positive

Because the patient-level data uses the rule that any true positive node group defines a true positive patient, it is not surprising that sensitivity trends lower at the node group- and region-levels compared to the patient-level. The higher specificity at the more granular levels can be explained by the increased number of true negatives in the setting of low PET positivity rate.

Note that the region-level analysis is limited by lack of reference standard data for 108 regions (12 patients) where the pathologist reported only at the node group-level. This limitation only affects patients with positive histopathology, as a negative node group can be reliably translated to the region-level, and it explains in part the decrease in percentage of positive histopathology at the region-level. At all levels, the 95% confidence interval of PPV shows no overlap with that of the percentage of positive histopathology.

One possible explanation for the lower than expected sensitivity reported in this trial is selection of patients who are harder to diagnose than was anticipated during study design. The majority of patients had conventional imaging available at enrollment. Under current treatment guidelines, the presence of pelvic nodal or distant metastatic disease typically prompts therapy other than surgery. Thus, it seems likely that some patients with suspicion of pelvic nodal disease on conventional imaging would have been discouraged from entering the trial. In clinical practice, ⁶⁸Ga-PSMA-11 PET might be performed in place of conventional imaging studies, and patients with more advanced disease that is presumably more detectable would then be included in the population of use. To investigate this possibility, diagnostic performance was calculated for patients with and without conventional imaging at enrollment. As shown in [Table 24](#), consistent with such reasoning, there was a trend toward higher sensitivity in patients without conventional imaging.

Table 24. Patient-Level Performance of ⁶⁸Ga-PSMA-11 PET for Detection of Pelvic Lymph Node Metastases, Stratified by Availability of Conventional Imaging at Enrollment

Diagnostic Performance Measure	Combined N=123	Imaging Available N=78	Imaging Not Available N=45
TP	14	9	5
FP	9	6	3
FN	16	14	2
TN	84	49	35
Sensitivity, point estimate (95% CI)	47% (29%, 65%)	39% (19%, 59%)	71% (29%, 96%)
Specificity, point estimate (95% CI)	90% (84%, 96%)	89% (81%, 97%)	92% (79%, 98%)
PPV, point estimate (95% CI)	61% (41%, 81%)	60% (35%, 85%)	63% (24%, 91%)
NPV, point estimate (95% CI)	84% (77%, 91%)	78% (68%, 88%)	95% (82%, 99%)
% pathology +, point estimate (95% CI)	24% (17%, 32%)	29% (19%, 40%)	16% (5%, 26%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, FN = false negative, FP = false positive, N = number of patients, NPV = negative predictive value, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen, TN = true negative, TP = true positive

Results of ⁶⁸Ga-PSMA-11 PET were compared to those of conventional imaging for the 67 patients in whom non-equivocal conventional imaging results were available or could be reliably assumed. Patients were categorized as true positive, false positive, true negative, or false negative for both ⁶⁸Ga-PSMA-11 PET and conventional imaging using the pelvic lymph node histopathology reference standard. Because the node group or region assignment was not available for conventional imaging, location matching was also not performed for the PET.

When location matching was removed from the PET analysis, the resulting sensitivity was 50% (95% CI: 33-67%), specificity was 92% (87-98%), and PPV was 70% (51-88%).

Table 25. Patient-Level Comparison of ⁶⁸Ga-PSMA-11 PET to Conventional Imaging Results for Pelvic Nodal Metastases Using a Histopathology Reference Standard (N=67)

Conventional Imaging	⁶⁸ Ga-PSMA-11 PET			
	TP	FP	FN	TN
TP	5		4	
FP		1		14
FN	4		9	
TN		0		30

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, FN = false negative, FP = false positive, N = number of patients, PET = positron emission tomography, PSMA = prostate-specific membrane antigen, TN = true negative, TP = true positive

As shown in Table 25 above, this analysis demonstrates moderate agreement between PET and conventional imaging, with 67% of patients being assigned the same category for both techniques. For the remaining 22 patients who had discordant results, 18 were correctly categorized by PET (green boxes) and four were correctly categorized by conventional imaging (red boxes). This exploratory analysis suggests that ⁶⁸Ga-PSMA-11 PET performs favorably compared to current commonly used imaging techniques for detecting prostate cancer in the pelvic lymph nodes and may add value to such imaging or even provide a suitable first-line imaging option.

While PSMA-PreRP was designed to evaluate detection of prostate cancer in pelvic lymph nodes, the prostate gland itself was also evaluated by the central readers. Abnormal focal uptake was found by majority read in the prostate gland of 125 out of 127 patients (98%) in the Full Analysis Set. Note that it was not practical to blind the readers to the knowledge that all patients were known to have primary prostate cancer in this study design, allowing the potential for reader bias to affect this result.

8.1.3. PSMA-BCR

Trial Design

PSMA-BCR was a prospective, single-arm, open-label study of ⁶⁸Ga-PSMA-11 PET for localization of biochemically recurrent prostate cancer. The study was performed at two sites in the United States, UCLA and UCSF. It enrolled men who developed biochemically recurrent prostate cancer after definitive therapy with prostatectomy or radiotherapy. Patients who had received focal gland therapies such as cryoablation were not included. The definition of biochemical recurrence was serum PSA of >0.2 ng/mL more than 6 weeks after prostatectomy or serum PSA > 2 ng/ml over nadir after radiotherapy alone. The recurrence criterion for patients following prostatectomy is a modification of the American Urological Association definition to eliminate the requirement for a repeat PSA measurement (Cookson et al. 2007). The recurrence criterion

for patients following radiotherapy is from the widely used American Society for Radiation Oncology-Phoenix definition (Roach et al. 2006). Patients were required to have a Karnofsky performance status of at least 50. Patients with lower performance status could certainly tolerate the PET scan, but it could be argued that these patients are not in the intended population of use as they may not be able to tolerate therapy.

After enrollment, each patient received 3-5 mCi (UCLA) or 3-7 mCi (UCSF) ⁶⁸Ga-PSMA-11 intravenously followed 45-60 (UCLA) or 50-100 (UCSF) minutes later by PET/CT from mid-thigh to skull base. Unless advanced scatter correction algorithms were available on the scanner, patients received oral hydration and 20 mg furosemide intravenously with the radiotracer to reduce artifact from scatter and its correction in the pelvis related to urinary excretion of radiotracer. As discussed in Section 6 of this review, the selection of ⁶⁸Ga-PSMA-11 dose was supported by reports of successful imaging at similar doses that were published prior to study initiation.

Three readers from a centralized pool of nine nuclear medicine physicians and radiologists independently interpreted each ⁶⁸Ga-PSMA-11 PET scan. These central readers also had access to the anatomic images (CT or MR) obtained with the PET scan for attenuation correction. The readers were blinded to all other information except the type of primary therapy and the most recent serum PSA level. Training was required for the readers prior to participation in the study. Multiple anatomic regions and subregions were defined as listed in Table 26, and each was evaluated by the readers for PET positive lesions through visual assessment of intensity. Regions/subregions containing at least one PET positive lesion were categorized as positive; regions/subregions lacking any PET positive lesions were categorized as negative. A lesion count was not performed. A majority read result was assigned for each region and subregion. No contract research organization was utilized.

Table 26. List of Regions and Subregions to Be Evaluated by ⁶⁸Ga-PSMA-11 PET

Region	Subregions
Prostate bed/prostate	-
Pelvic lymph nodes	Right Left Presacral/mesorectal Other
Soft tissues	Retroperitoneal node Mediastinal/thoracic/axillary node Supraclavicular/cervical node Inguinal node Lung Liver Kidney/pancreas/spleen Stomach/intestine/mesentery/peritoneum Other

NDA/BLA Multi-Disciplinary Review and Evaluation NDA 212643
Gallium Ga 68 PSMA-11 Injection

Region	Subregions
Bone	Spine Rib/clavicle/sternum Pelvis Extremity Skull Other

Source: PSMA-BCR Analysis Dataset Definition file.

Abbreviations: ⁶⁸Ga = gallium-68, PET = positron emission tomography, PSMA = prostate-specific membrane antigen

The PET scans were also read locally by a single nuclear medicine physician or radiologist, with results presumably made available to the physicians treating the patient as there is mention of assessing impact of the PET result on clinical management. The central readers were blinded to the local read result as stated in the Applicant's response to an IR from January 24, 2020.

Reference standard determination was based on a composite of histopathology, follow up conventional imaging, baseline conventional imaging, and PSA follow up. The protocol states that PET positive findings were to be assessed by biopsy if clinically feasible and that all patients would be followed up at 3 to 12 months with conventional imaging in the form of CT, MRI, and/or bone scan. Pathology results took precedence over imaging results in most cases, with the exception of negative bone biopsies or biopsies where the lesion of interest was not correctly targeted.

For imaging and PSA reference standard follow up, the criteria used to define positivity for prostate cancer varied by location in the body. For prostate bed, lymph node, and non-node soft tissue, prostate cancer positivity and negativity were defined through changes in size and/or PSA level that depended upon treatment status (i.e., no treatment, systemic treatment, or localized treatment). Aside from assessing change in PSA for lesions treated locally, reference standard determination in bone relied on the presence of a lesion on baseline or follow up imaging. Detailed reference standard criteria are listed below in [Table 27](#), with a single criterion required for assignment of a positive or negative result.

Table 27. Summary of Criteria Used to Classify ⁶⁸Ga-PSMA-11 PET-Positive Findings for the Composite Reference Standard of PSMA-BCR

Location	Positive for Malignancy	Negative for Malignancy
Prostate bed	>30% decrease in size with systemic or localized therapy >50% decrease in PSA with localized therapy >20% increase in size without therapy	>20% increase in size AND >50% decrease in PSA with systemic therapy >20% increase in size with localized therapy <50% decrease in PSA with localized therapy >30% decrease in size without therapy

NDA/BLA Multi-Disciplinary Review and Evaluation NDA 212643
Gallium Ga 68 PSMA-11 Injection

Location	Positive for Malignancy	Negative for Malignancy
Lymph node	>30% decrease in size AND >50% decrease in PSA with systemic therapy >20% increase in size AND >50% increase in PSA with systemic therapy <20% change in size AND >50% decrease in PSA with localized therapy >30% decrease in size with localized therapy >20% increase in size without therapy	>20% increase in size AND >50% decrease in PSA with systemic therapy >20% increase in size with localized therapy <50% decrease in PSA with localized therapy >30% decrease in size without therapy
Non-node soft tissue	>30% decrease in size AND >50% decrease in PSA with systemic therapy >20% increase in size AND >50% increase in PSA with systemic therapy >30% decrease in size with localized therapy >50% decrease in PSA with localized therapy >20% increase in size without therapy	>20% increase in size AND >50% decrease in PSA with systemic therapy >20% increase in size with localized therapy <50% decrease in PSA with localized therapy >30% decrease in size without therapy
Bone	Sclerotic lesion on attenuation correction or baseline CT Focal uptake on baseline bone scan Lesion on baseline MRI New sclerosis/focal uptake/lesion on follow up imaging >50% decrease in PSA with localized therapy	<50% decrease in PSA with localized therapy Criteria for positive lesion are not met AND follow up imaging was acquired

Source: UCLA PSMA-BCR protocol version 7, section 2.1.5.3.

Notes: Size is short axis diameter for lymph nodes and long axis diameter for all other lesions. Most criteria also specify a minimum change in size of 3 mm. At least one criterion must be met to assign a category. Lesions that do not meet criteria for positive or negative are considered unevaluable.

Abbreviations: ⁶⁸Ga = gallium-68, BCR = biochemical recurrence, CT = computed tomography, MRI = magnetic resonance imaging, PET = positron emission tomography, PSA = prostate-specific antigen, PSMA = prostate-specific membrane antigen, UCLA = University of California, Los Angeles

Reference standard determination was performed by local readers. A single reader was used per patient, and the number of local readers in the pool was not defined. The reference standard reader had access to all clinical, pathology, and imaging information, including the ⁶⁸Ga-PSMA-11 PET images and local PET read, but was blinded to the result of the central PET reads. While access of the reference standard readers to ⁶⁸Ga-PSMA-11 PET images is a potential source of bias, use of the predominantly objective criteria described in [Table 27](#) to classify PET-positive lesions as true positive or false positive is expected to have reduced such bias. Additionally, analyses conducted with only histopathology reference standard data eliminate this potential source of bias.

The result of the reference standard read was recorded at the region-level only. The subregion or subregions that were evaluated were also recorded and matched to the PET results as described below in the Study Endpoints section, however, these data cannot be reliably used to make subregion- or lesion-level assessments.

Table 28. PSA-BCR Schedule of Events

	Pre-Study	Day 1	Day 2-4	3-12 Months
Informed consent	X			
Demographics	X			
Medical history	X			
⁶⁸ Ga-PSMA PET		X		
Delayed AE follow up			X	
Histopathology/conventional imaging follow up				X

Source: UCLA PSMA-BCR protocol version 7, section 2.1.6.5.

Abbreviations: AE = adverse event, ⁶⁸Ga = gallium-68, BCR = biochemical recurrence, PET = positron emission tomography, PSMA = prostate-specific membrane antigen, UCLA = University of California Los Angeles

In addition to the events listed in the above table, vital signs and adverse event data were collected before and after the PET scan on day 1.

Study Efficacy Endpoints

The protocol-defined primary endpoints varied by protocol version and by study site. At UCLA, the primary endpoints were sensitivity, specificity, PPV, and NPV in the initial version of the protocol. In versions 2 through 4, under which most patients were enrolled, the primary endpoint was PPV on a per-patient and per-region basis using a histopathology reference standard. At UCSF, version 1 of the protocol defined the primary endpoint as sensitivity and PPV on a per-patient and per-region basis using a histopathology reference standard. Version 2 changed this to sensitivity on a per-patient and per-region basis using the composite reference standard defined in the previous section. Note however, the study execution did not allow accurate estimation of the false negative rate, and in the PSMA-BCR CSR the primary endpoint was defined as patient-level and region-level PPV using a histopathology reference standard. Patient-level sensitivity against a composite reference standard was changed to a secondary endpoint by the Applicant and was not considered a relevant endpoint for this review.

Important secondary endpoints described in various protocol versions are patient-level and region-level PPV using the composite reference standard, PET positivity rate stratified by PSA level, and inter-reader reproducibility. The PET positivity rate, also commonly referred to as the detection rate, was not validated by a reference standard. Therefore, the correct detection rate, defined as the number of true positive patients divided by the number of patients with sufficient data to classify their result, was also calculated by the review team and will be discussed with the other results of the trial.

While specificity would have been a useful endpoint, the study design does not allow accurate estimation of this parameter. Alternate study designs that would allow specificity to be

measured for this population are often not practical, and the Applicant and FDA agreed that specificity would not be assessed in a meeting held on August 10, 2016.

Patients with rising PSA after definitive therapy of prostate cancer, referred to commonly as biochemical recurrence, are typically assumed to have residual or recurrent disease. The choice of therapy for these patients depends on the location and sometimes the extent of disease. However, currently available imaging techniques including other PET agents approved for prostate cancer imaging, such as ^{18}F -fluciclovine and ^{11}C -choline, have relatively poor detection rates and high false positive rates for prostate cancer, particularly at initial recognition of biochemical recurrence when PSA levels are low. Thus, PPV and detection rate are relevant endpoints.

To compare the PET result to the reference standard, the Applicant first identified PET positive regions with available reference standard information. If the reference standard was collected from at least one PET positive subregion, the region was classified as true positive when the reference standard determination was “cancer confirmed” or as false positive when the reference standard determination was “cancer ruled out.” If none of the subregions with reference standard information was PET positive, the Applicant considered the region to be a subregion mismatch and indeterminate rather than attempting to assign true negative or false negative classification. Because of the use of PPV as the primary endpoint and the inability to consistently sample PET negative lesions, this approach is reasonable. For the patient-level analyses, if a patient had more than one region classified, the patient was categorized as true positive if there was at least one true positive region and categorized as false positive if there were only false positive regions. Of note, most patients had only one region classified, so region-level results closely matched patient-level results.

Statistical Analysis Plan

The Statistical Analysis Plan defined in the protocol is brief, and the material described in this section is derived from that source, from the PSMA-BCR CSR, and from the Applicant’s reply of October 7, 2019, to a statistics information request.

All patients who successfully underwent ^{68}Ga -PSMA-11 PET were considered study completers. Other groups defined by the Applicant include (source = section 11.1 of the PSMA-BCR CSR):

- Full Data Analysis Set consists of all patients enrolled who received a ^{68}Ga -PSMA 11 injection.
- Safety Data Set consists of all patients enrolled who received a ^{68}Ga -PSMA-11 injection.
- The Efficacy Analysis Set consists of all patients who received a ^{68}Ga -PSMA-11 injection and had their ^{68}Ga -PSMA-11 scan independently and blindly interpreted on a per patient and per region basis.
 - Efficacy Analysis Set (Histology) consists of all patients in the Efficacy Analysis Set who have histopathology data for determination of positive or negative for disease.

- Efficacy Analysis Set (Composite Endpoint) consists of all patients in the Efficacy Analysis Set who have at least one of (in descending priority) histopathology, imaging, or PSA follow-up after local therapy.
- The Change in Management Set consists of patients who received a ⁶⁸Ga-PSMA-11 injection and had a clinical treatment plan documented both before and after the ⁶⁸Ga-PSMA-11 scan.
- The Inter-Reader Set consists of patients who received a ⁶⁸Ga-PSMA-11 injection and had their ⁶⁸Ga-PSMA-11 scan independently and blindly interpreted by 3 physicians.

The efficacy analysis set (histology) was used to derive the primary PPV endpoint. The efficacy analysis set (composite endpoint) was used for the secondary sensitivity and PPV endpoints. The PET positivity rate and correct detection rate were based on the full data analysis set. Inter-reader reproducibility was assessed by calculation of Fleiss' kappa using the inter-reader set. The Applicant constructed 95% confidence intervals using the Wilson method. The goal for PPV was stated as 50% in section 9.7.2 of the PSMA-BCR CSR. The power calculation in the CSR was based on a 20% effect size and an expected PPV of 70%.

An unplanned interim analysis was performed prior to implementation of UCLA protocol version 6 (see Table 29). The analysis occurred before target accrual was reached and the study remained open. However, all data submitted as part of this application were obtained by the time of the interim analysis. Therefore, no statistical corrections have been applied.

Protocol Amendments

[Table 29](#) lists the study protocol versions submitted to the UCLA IND and the number of patients scanned at UCLA under each version.

Table 29. Patients Scanned in the PSMA-BCR Study Under Each UCLA Protocol Version

Protocol Version	FDA Receipt Date	Patients Scanned at UCLA	Efficacy Patients Scanned at UCLA	Patients Scanned at All Sites
1	4/27/2016	0	0	0
2	7/21/2016	70	39	208
3	2/14/2017	31	12	70
4	3/29/2017	135	56	335
5	9/14/2017	14	3	22
6	12/14/2018	0	0	0
7	7/9/2019	0	0	0

Source: FDA clinical reviewer analysis.

Abbreviations: BCR = biochemical recurrence, PSMA = prostate-specific membrane antigen, UCLA = University of California, Los Angeles

Note that according to the response to IR received October 7, 2019, all patients at UCLA were enrolled under version 4 or earlier. The apparent discrepancy from the table above likely reflects the difference between the date the protocol was received at FDA versus the date the protocol began to be used as well as the time from enrollment to PET scan.

Version 2: No summary of changes from version 1 or redline protocol was submitted. Notable differences identified in version 2 included removal of the inclusion criterion requiring no evidence of metastatic disease by conventional imaging, removal of the exclusion criterion prohibiting prior use of ADT or chemotherapy, and substantial revision to the reference standard.

Version 3: The major revision in this version was changing the definition of biochemical recurrence for patients with prostatectomy from American Urological Association criteria to a single PSA measurement of 0.2 ng/mL or greater. The language defining radiation therapy was also broadened to include any type of definitive radiotherapy, versus external beam radiation therapy or brachytherapy in version 2.

Version 4: This version increased the number of patients to be enrolled at UCLA from 200 to 400. It was also edited to harmonize with the UCSF protocol.

Version 5: The primary endpoint was changed from PPV to sensitivity. Additional detail was added to the protocol for how PET scans were to be read. The reference standard was expanded to define the false positive lesions by specific criteria rather than as lesions not characterized as true positive. An indeterminate category was added to include lesions not categorized as true positive or false positive.

Version 6: This version increased the number of patients to be enrolled at UCLA from 400 to 800. This change was in response to an interim analysis that revealed lower than expected availability of pathology data.

Version 7: Many changes were made in this version to harmonize the protocol with other sites and for housekeeping purposes. Key differences include increase of the dose of ⁶⁸Ga-PSMA-11 from 3 to 5 mCi to 3 to 7 mCi, increase of dose to scan time from 45 to 60 minutes to 50 to 100 minutes, and allowing patients to re-enroll in the study.

[Table 30](#) lists the study protocol versions submitted to the UCSF IND and the number of patients scanned at UCSF under each version.

Table 30. Patients Scanned in the PSMA-BCR Study Under Each UCSF Protocol Version

Protocol Version	Version Date	Patients Scanned at UCSF	Efficacy Patients Scanned at UCSF	Patients Scanned at All Sites
1	8/18/2016	150	64	235
2	3/4/2017	235	95	400

Source: FDA clinical reviewer analysis.

Abbreviations: BCR = biochemical recurrence, PSMA = prostate-specific membrane antigen, UCSF = University of California, San Francisco

Version 2: The primary objective was changed from sensitivity and PPV against a histopathology reference to sensitivity against a composite reference standard. Multiple changes were made to planned secondary endpoints. Methods for assessing adverse events were added. An inclusion criterion for age >18 years was added.

8.1.4. Study Results – PSMA-BCR

Compliance with Good Clinical Practices

In Section 5 of the PSMA-BCR CSR, the Applicant states that the study was conducted in compliance with GCP and under the oversight of local IRBs. The two study sites were within the United States.

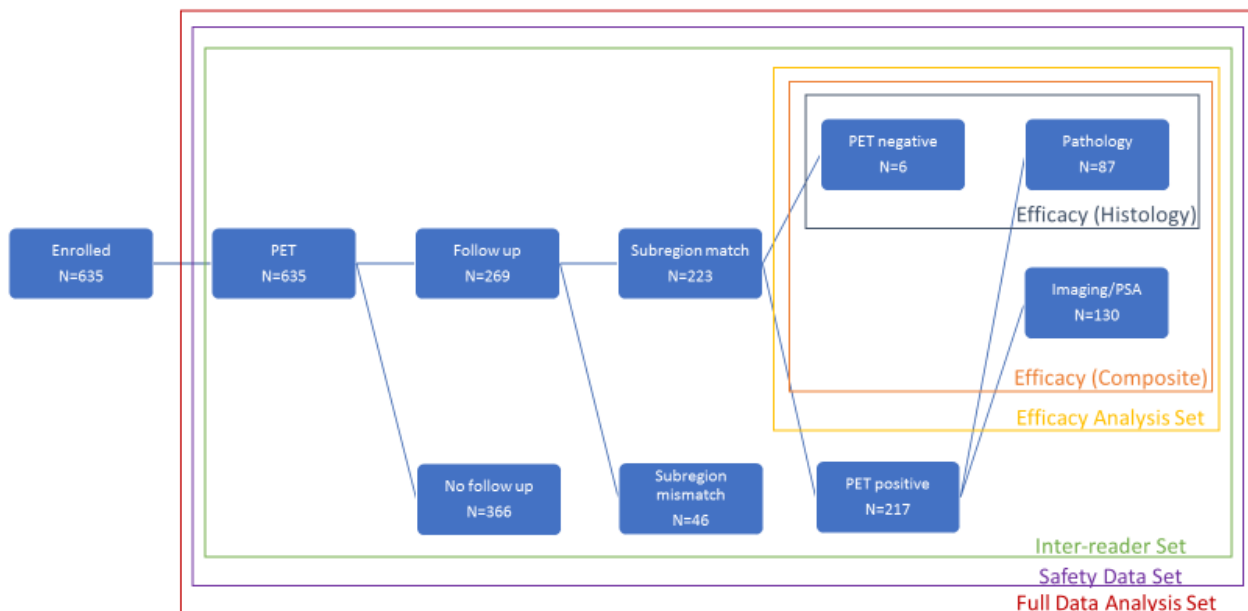
Financial Disclosure

No relevant financial disclosures were made by the Applicant or per the Applicant, by the clinical investigators.

Patient Disposition

[Figure 10](#) below shows the disposition of the 635 patients who were enrolled and underwent ⁶⁸Ga-PSMA-11 PET in PSMA-BCR, particularly in relation to the availability of follow-up information and the type of reference standard data collected.

Figure 10. Patient Disposition in the PSMA-BCR Study



Source: FDA clinical reviewer, using data and set definitions from the PSMA-BCR clinical study report.

Abbreviations: BCR = biochemical recurrence, N = number of patients, PET = positron emission tomography, PSA = prostate-specific antigen, PSMA = prostate-specific membrane antigen

The Applicant's defined patient groups are outlined in the above figure. For the purpose of this review, 3 additional groups were defined: reference standard, histopathology reference standard, and no reference standard. The reference standard group included all patients for which the Applicant assigned a value to at least one of the "Follow up result" variables (FPBR [prostate bed], FPR [pelvic lymph node], FER [soft tissue], FBR [bone]). The histopathology

reference standard group was the subset of the reference standard group for which histopathology data was available. The no reference standard group contained all patients for which no value was contained in any of the four “follow up result” variables.

Protocol Deviations

The eight reported protocol deviations are summarized below. Deviations 1 to 4 might have influenced study results as described for each item. The remaining deviations were considered unlikely to substantially influence the study results.

- 1) Lack of definitive therapy: Seven patients, six at UCSF and one at UCLA, were enrolled in the study without prior prostatectomy or definitive radiotherapy. Five of these patients had non-histopathology composite reference data, all classified as TP. Two patients had histopathology data, one TP and one FN. It is unclear whether the UCSF patients were included in the Applicant’s analysis; the UCLA patient, who was TP by the composite reference standard, was included. These patients were excluded from the FDA primary and secondary analyses below.
- 2) PSA level not meeting definition of biochemical recurrence: A total of 11 patients (9 at UCSF, 2 at UCLA) with a history of radiation therapy were enrolled without evidence of biochemical recurrence, either because they did not have PSA more than 2 ng/mL higher than their nadir or because they did not have documentation of their nadir PSA. Six of these patients had composite reference data (three TP, two FP, one FN) and four had histopathology data (one TP, two FP, one FN). The Applicant included these patients in the analyses, stating that they represent a more challenging population for the test. The clinical reviewer concurred and also included them in analyses.
- 3) Missing PSA level within 30 days: Per protocol, all patients were to have a PSA level obtained within 30 days of the PET scan. For 313 patients (49% of enrolled patients; 187 at UCSF and 126 at UCLA), the PSA level was obtained outside of this window. For patients with this protocol deviation, the median time between PSA level and PET scan was 57 days, the range was 31 to 367 days, and the interquartile range was 43 to 82 days. The Applicant stated this deviation would not affect the PPV or sensitivity endpoints and included the patients in all analyses. However, detection rate stratified by PSA level is an important measure of test performance in the biochemical recurrence setting because PSA increases with disease volume and tumor tends to be easier to detect in patients with higher volume disease. Since the PSA level was obtained before the PET scan, a longer delay could improve apparent test performance by this metric. However, the effect that such delay had in these cases was likely not extreme since a PSA doubling time of 60 days is associated with only very aggressive disease and more typical doubling times are on the order of 300 days. As such, all patients were included in analyses that stratified by PSA level, regardless of the timing of collection relative to the PET scan.
- 4) Post-scan follow up call: All patients were to receive a follow up telephone call between 1 to 3 days after the PET scan to screen for adverse events. The call was made more than 3 days after the scan for 249 patients (39%), all enrolled at UCLA. As described elsewhere, this delay also occurred for patients at UCLA participating in PSMA-PreRP.

The late follow up likely explains the lower adverse event rate at UCLA compared to UCSF (0.8% versus 4.2%).

- 5) Radiotracer dose: A total of 22 patients (3%; 21 at UCSF and one at UCLA) received radiotracer doses outside the 3 to 7 mCi range. Among these patients, 18 received more than 7 mCi, with the highest administered dose of 7.6 mCi. Four patients received less than 3 mCi, with the lowest administered dose of 2.5 mCi. Note that UCLA used a more restrictive 3 to 5 mCi dose range and thus there might be additional unreported protocol deviations related to dose. However, UCLA doses from 5 to 7 mCi would fall within allowed dosing at UCSF.
- 6) Vital signs: Patients were to have heart rate and blood pressure recorded before and after the PET scan. Six patients (1%; all from UCLA) did not have complete recording.
- 7) Performance status: Performance status at enrollment was to have been documented by a physician for all patients. A total of 160 patients (25%) had performance status documented by a non-physician. An additional 161 patients (25%) had performance status documented by a physician but outside the predefined screening window. All of these patients were enrolled at UCSF.
- 8) Sulfa allergy: Sulfa allergy was an exclusion criterion because of the theoretical risk of cross reactivity with the furosemide administered to most patients with the ⁶⁸Ga-PSMA-11 dose. A total of 14 patients with sulfa allergy were enrolled at UCSF and 13 of them received furosemide. No allergic reactions were reported.

Table of Demographic Characteristics

Table 31. Demographic Characteristics of Patients in the PSMA-BCR Study

Demographic Parameters	Full Analysis Set (N=635) N (%)	Reference Standard (N=266) N (%)	No Reference Standard (N=369) N (%)
Age			
Mean years (SD)	69 (7.7)	70 (7.1)	68 (8.0)
Median (years)	69	71	68
Min, max (years)	44-95	49-88	44-95
Age Group			
< 65 years	172 (27%)	54 (20%)	118 (32%)
≥ 65 years	463 (73%)	212 (80%)	251 (68%)
Race			
White	545 (86%)	233 (88%)	312 (85%)
Black or African American	11 (2%)	6 (2%)	5 (1%)
Asian	23 (4%)	9 (3%)	14 (4%)
American Indian or Alaska Native	1 (<1%)	1 (<1%)	0
Native Hawaiian or Other Pacific Islander	1 (<1%)	0	1 (<1%)
Other	25 (4%)	9 (3%)	16 (4%)
Missing	29 (5%)	8 (3%)	21 (6%)
Ethnicity			
Hispanic or Latino	30 (5%)	12 (5%)	18 (5%)
Not Hispanic or Latino	446 (70%)	193 (73%)	253 (69%)
Missing	159 (25%)	61 (23%)	98 (27%)

Demographic Parameters	Full Analysis Set (N=635) N (%)	Reference Standard (N=266) N (%)	No Reference Standard (N=369) N (%)
PSA			
Median (ng/mL)	2.14	3.22	1.3
Min, max (ng/mL)	0.05-1154	0.05-1154	0.2-72.5
Interquartile range (ng/mL)	0.58-5.32	1.2-7.6	0.42-4.28
Prior therapy			
Prostatectomy	466 (73%)	178 (67%)	288 (78%)
Radiotherapy	366 (58%)	181 (68%)	185 (50%)
Baseline conventional imaging status			
Conventional imaging available	277 (44%)	136 (51%)	141 (38%)
Conventional imaging positive	81 (13%)	55 (21%)	26 (7%)

Source: FDA clinical reviewer analysis.

Abbreviations: BCR = biochemical recurrence, N = number of patients, PSA = prostate-specific antigen, PSMA = prostate-specific membrane antigen, SD = standard deviation

Overall, the age distribution seemed reasonable for patients with biochemically recurrent prostate cancer. There was a slight trend, considered unimportant, towards older patients in the reference standard available group. Note that some patients received both prostatectomy and radiotherapy, therefore the percentages of patients in the prior therapy category do not sum to 100.

Most study patients were white, there were fewer black patients in the study than expected. Overall the race and ethnicity distributions were similar to those of the PSMA-PreRP study and likely reflected the limited geographic distribution of the study sites.

Other Baseline Characteristics

As shown in [Table 31](#) above, patients with reference standard data were more likely to have had radiotherapy and less likely to have had prostatectomy than patients without reference standard data. It is possible that ⁶⁸Ga-PSMA-11 PET performs differently in patients with radiotherapy versus prostatectomy. For example, there will usually be more residual, viable normal prostate tissue after radiotherapy than after prostatectomy, which could affect interpretation of the PET scan. However, the rates of each therapy in PSMA-BCR patients appeared reasonably representative of the expected population of use.

The PSA level trended higher for patients who had reference standard data than those without, and the size of this difference appeared clinically meaningful in the setting of biochemical recurrent prostate cancer, in which numerous imaging modalities have demonstrated a strong dependence of detection rate on PSA level. For example, in one study ¹⁸F-fluciclovine PET had a positivity rate of 36% when PSA was 1 ng/mL or less, but 66% for levels between 1 and 2 ng/mL (Andriole et al. 2019). As the definition of biochemical recurrence required a higher PSA level for patients with definitive radiotherapy than those with prostatectomy (nadir+2 ng/mL versus 0.2 ng/mL), it is possible that the difference in prostatectomy rate drove the difference in PSA level. Additionally, negative PET scans, which are expected to occur more often with lower PSA,

were largely located in the no reference standard group (PET positivity rate 89% in patients with reference standard data versus 63% in patients without it) as expected per study design, which emphasized biopsy or follow up of PET positive lesions. However, when both of these factors were considered by limiting analysis to patients with positive PET scans and prostatectomy, the PSA level remained slightly higher in patients with reference standard data than those without (n=154 versus n=159, median PSA 2.33 ng/mL versus 1.64 ng/mL, interquartile range 1.03 to 5.21 ng/mL versus 0.61 to 4.30 ng/mL). The probability that the portion of the study patients included in the primary efficacy analysis had easier to diagnose disease must be considered when reviewing the application.

Patients in the reference standard group were more likely to have conventional imaging available at enrollment, and this imaging was more likely to be positive. This trend persisted when analysis was limited to patients with a positive ⁶⁸Ga-PSMA-11 PET scan (n=238 with reference standard data versus n=231 without, conventional imaging available in 52% versus 42%, conventional imaging positive in 21% versus 11%). Because conventional imaging is considered relatively insensitive for localizing biochemically recurrent prostate cancer, these trends, like the trend in PSA level, raise the possibility that patients with easier to diagnose disease were selected for analysis, as compared to the general biochemical recurrence population. FDA subgroup analyses below will address this concern.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All enrolled patients completed the study by the Applicant's criterion of receiving a ⁶⁸Ga-PSMA-11 PET scan. However, many patients did not have sufficient reference standard data to allow complete endpoint analysis. In patients with negative PET scans (166 of 635, 26%), no consistent reference standard determination was planned due to practical limitations in identifying lesions for follow up. However, for the remaining patients only 215 of 469 (46%) have data for the secondary endpoint of PPV by composite reference, and 87 of 469 (19%) have data for the primary endpoint of PPV by histopathology. A low availability of biopsy data was anticipated in the protocol, with biopsy rate predicted to be 25% of accrued patients versus 18% (113/635) of accrued patients actually biopsied. For the composite reference standard, the protocol stated that all patients would be followed up at 3 to 12 months with conventional imaging using dedicated CT, MRI and/or bone scan. In response to information requests, the Applicant indicated that they interpreted the protocol to define a follow up period over which the results of any standard of care imaging that was performed would be collected. This methodology seems to explain the relatively low number of patients with composite reference standard information.

A critical issue raised by the lack of reference standard data for many of the patients is whether those who had such data are otherwise the same as those who did not. Because standard of care was used for determining whether or not a patient underwent biopsy or follow up, the decision of whether to obtain reference standard information was left to the treating physician. No data were available to directly ascertain how this decision was made for each patient. The

treating physician was also aware of the ⁶⁸Ga-PSMA-11 PET scan result via the local read, though the central read was not made available. This created an unavoidable potential for bias. It seems likely that the differences described in the previous section for conventional imaging availability, conventional imaging positivity, and PSA level between patients with and without reference standard data indicate that such bias existed.

Efficacy Results – Primary Endpoint

Except where specified, all analyses in this primary endpoint section were performed on the histopathology reference standard set, excluding two patients with protocol deviations for lack of definitive therapy at enrollment. If a patient had both histopathology and non-histopathology reference standard data, only the histopathology data was considered.

Table 32. Patient-Level Comparison of ⁶⁸Ga-PSMA-11 PET Majority Read Versus Histopathology Reference for Detection of Recurrent Prostate Cancer

PET Majority Read	Pathology Positive	Pathology Negative	Total
PET positive patients	71 (true positive)	15 (false positive)	86
PET negative patients	8 (false negative)	17 (true negative)	25
Total	79	32	111

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, PET = positron emission tomography, PSMA = prostate-specific membrane antigen

The patient level PPV was 83%, with a 95% confidence interval of 75-91%. This result exceeded the goal PPV of 70%. Because PET negative patients were not systematically sampled, sensitivity and specificity were not calculated.

Table 33. Region-Level Comparison of ⁶⁸Ga-PSMA-11 PET Majority Read Versus Histopathology Reference for Detection of Recurrent Prostate Cancer*

PET Majority Read	Pathology Positive	Pathology Negative	Total
PET positive regions	74 (true positive)	15 (false positive)	89
PET negative regions	9 (false negative)	19 (true negative)	28
Total	83	34	117

Source: FDA clinical reviewer analysis.

*No correction for multiple regions per patient was applied.

Abbreviations: ⁶⁸Ga = gallium-68, PET = positron emission tomography, PSMA = prostate-specific membrane antigen

For patients with histopathology data, very few patients received more than one biopsy. Accordingly, the region-level and patient-level analyses were very similar and the region-level PPV was the same as the patient-level PPV of 83% (75-91%). FDA primary endpoint results were very similar to those provided by the Applicant.

Table 34. Distribution of Regions Evaluated in the Primary Analysis of PPV for ⁶⁸Ga-PSMA-11 PET Versus Histopathology Reference

Region	PET Positive Regions With Reference (N=89) N (%)	True Positive Regions (N=74) N (%)	False Positive Regions (N=15) N (%)	Regional PPV % (95% CI)
Prostate/prostate bed	50 (68%)	37 (50%)	13 (87%)	74% (62%, 86%)
Pelvic lymph node	19 (21%)	19 (26%)	0	100% (82%, 100%)
Soft tissue	19 (21%)	17 (23%)	2 (13%)	89% (67%, 99%)
Bone	1 (1%)	1 (1%)	0	100% (3%, 100%)
All regions	89 (100%)	74 (100%)	15 (100%)	83% (75%, 91%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, N = number of regions, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen

The primary analysis was weighted towards samples obtained from the prostate or prostate bed, representing 68% of the sampled regions. Only a single sample was obtained from bone. This distribution reflects the relative accessibility of different regions for biopsy, as well as the difficulty in obtaining accurate results from bone biopsies. Note that this distribution of regions with histopathology data differs from the distribution of PET positive regions in the studied patients. Among all 635 patients in the study, there were a total of 698 PET positive regions, of which 167 (24%) were prostate, 234 (34%) were pelvic lymph node, 148 (21%) were soft tissue, and 149 (21%) were bone.

There appeared to be a trend towards lower PPV in the prostate/prostate bed than in other regions (74% [62-86%] for prostate versus 95% [88-100%] for pooled non-prostate).

Table 35. Patient-Level Performance of ⁶⁸Ga-PSMA-11 PET Versus Histopathology for Detection of Recurrent Prostate Cancer, Stratified by Patient Age

Diagnostic performance measure	Combined N=86	Age < 65 N=13	Age ≥ 65 N=73
TP	71	11	60
FP	15	2	13
PPV, point estimate (95% CI)	83% (75%, 91%)	85% (55%, 98%)	82% (73%, 91%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, FP = false positive, N = number of patients, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen, TP = true positive

The PPV of patients aged 65 or older and those less than 65 years old appeared to be similar. Due to the relatively small number of non-white patients, meaningful subgroup analyses for race and ethnicity were precluded.

Table 36. Patient-Level PPV of ⁶⁸Ga-PSMA-11 PET Versus Histopathology Reference for Detection of Recurrent Prostate Cancer, Stratified by Study Site

Diagnostic Performance Measure	Combined N=86	UCSF N=57	UCLA N=29
TP	71	45	26

NDA/BLA Multi-Disciplinary Review and Evaluation NDA 212643
Gallium Ga 68 PSMA-11 Injection

Diagnostic Performance Measure	Combined N=86	UCSF N=57	UCLA N=29
FP	15	12	3
PPV, point estimate (95% CI)	83% (75%, 91%)	79% (68%, 90%)	90% (73%, 98%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, FP = false positive, N = number of patients, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen, TP = true positive, UCLA = University of California Los Angeles, UCSF = University of California San Francisco

There appeared to be a trend towards numerically higher point estimates for PPV in patients enrolled at UCLA compared to patients enrolled at UCSF with overlapping confidence intervals. The small sample size in the two subgroups is noted.

Table 37. Patient-Level PPV of ⁶⁸Ga-PSMA-11 PET Versus Histopathology Reference for Detection of Recurrent Prostate Cancer, Stratified by PET Scan Date

Diagnostic Performance Measure	Combined N=86	First Half of Patients N=44	Last Half of Patients N=42
TP	71	35	36
FP	15	9	6
PPV, point estimate (95% CI)	83% (75%, 91%)	80% (68%, 91%)	86% (75%, 96%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, FP = false positive, N = number of patients, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen, TP = true positive

No substantial difference was seen when comparing PPV between patients who were scanned in the first half of the study and patients scanned in the last half. The median number of days between the first patient PET scan and subsequent PET scans for all 635 patients in the study was 208 days, with a maximum of 380 days.

Table 38. Patient-Level PPV of ⁶⁸Ga-PSMA-11 PET Versus Histopathology Reference for Detection of Recurrent Prostate Cancer, Stratified by Possible Confounding Variables

Diagnostic Performance Measure	PSA (ng/mL)		Prostatectomy		Conventional Imaging	
	<3.88 N=43	≥3.88 N=43	No N=48	Yes N=38	No N=44	Yes N=42
TP	36	35	38	33	33	38
FP	7	8	10	5	11	4
PPV, point estimate (95% CI)	84% (73%, 95%)	81% (70%, 93%)	79% (68%, 91%)	87% (76%, 98%)	75% (62%, 88%)	90% (77%, 97%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, FP = false positive, N = number of patients, PET = positron emission tomography, PPV = positive predictive value, PSA = prostate-specific antigen, PSMA = prostate-specific membrane antigen, TP = true positive

The median PSA among patients with a positive PET scan and histopathology data was 3.88 ng/mL. No appreciable difference was found in PPV between patients above and below the median PSA. There was a trend towards improved PPV in patients who had a history of prostatectomy compared to those without this history. Similarly, there was a trend towards

improved PPV in patients who had baseline conventional imaging available than those without it.

Data Quality and Integrity

OSI audits of the UCLA and UCSF clinical study sites were conducted and revealed no significant GCP deficiencies.

The datasets provided by the Applicant revealed numerous missing values for many variables. This issue primarily applied to binary variables and when data were provided they were usually positive, suggesting that negative results often were not entered into the dataset. The Applicant confirmed this interpretation. This issue was also mentioned in part in the Applicant's reply to a statistics information request. For this review, where appropriate, missing data from binary variables were assumed to be negative.

Efficacy Results – Secondary and other relevant endpoints

Except where specified, all analyses in this section for secondary and other endpoints were performed on the reference standard set, which contains the PET positive patients for which the Applicant assigned a follow up result based on histopathology, imaging, and/or PSA value, excluding five patients with protocol deviations for lack of definitive therapy at enrollment.

Table 39. PPV of ⁶⁸Ga-PSMA-11 PET Versus Composite Reference for Detection of Recurrent Prostate Cancer

Diagnostic Performance Measure	Patient-Level N=210	Region-Level N=239
TP	192	218
FP	18	21
PPV, point estimate (95% CI)	91% (88%, 95%)	91% (88%, 95%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, FP = false positive, N = number, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen, TP = true positive

The PPV results shown in Table 39 were very similar to those provided by the Applicant. PPV was identical for the per patient and per region analyses. This largely reflects the fact that the average number of PET positive regions in each of the 210 patients with composite reference standard data was only 1.14. For comparison, there were on average 1.49 PET positive regions per patient in the 469 patients with a positive PET scan.

The PPV by the composite reference standard was higher than the PPV by the histopathology reference standard, 88% versus 75% for the lower bound of the 95% confidence interval. To explore possible reasons for this difference, analyses of the regional composition and lesion characterization methods used in the composite reference standard were performed as shown in Table 40 and Table 41.

Table 40. Distribution of Regions Evaluated in the Secondary Analysis of PPV for ⁶⁸Ga-PSMA-11 PET Versus Composite Reference

Region	PET Positive Regions With Reference (N=239) N (%)	True Positive Regions (N=218) N (%)	False Positive Regions (N=21) N (%)	Regional PPV % (95% CI)
Prostate/prostate bed	59 (25%)	45 (21%)	14 (67%)	76% (65%, 87%)
Pelvic lymph node	43 (18%)	41 (19%)	2 (10%)	95% (84%, 99%)
Soft tissue	30 (13%)	26 (12%)	4 (19%)	87% (69%, 96%)
Bone	107 (45%)	106 (49%)	1 (5%)	99% (95%, 100%)
All regions	239 (100%)	218 (100%)	21 (100%)	91% (88%, 95%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, N = number of regions, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen

Compared to the histopathology reference standard, the composite reference standard data contained a much higher proportion of bone regions and relatively fewer prostate regions. Thus, the primary and secondary PPV results could be considered complementary, as they are focusing on different sub-populations. The PPVs within each region follow a similar pattern for both reference standards, with PPV for the prostate/prostate bed trending lower than other regions.

Table 41. Utilization of Criteria to Characterize Lesions Under the Composite Reference Standard

Criterion	Pelvic Lymph				Total (N=268) N (%)
	Prostate (N=63) N (%)	Node (N=44) N (%)	Soft Tissue (N=32) N (%)	Bone (N=129) N (%)	
Histopathology	50 (79%)	19 (43%)	19 (59%)	2 (2%)	90 (34%)
PSA with treatment	8 (13%)	7 (16%)	1 (3%)	2 (2%)	18 (7%)
Size with treatment	5 (8%)	16 (36%)	12 (38%)	0	33 (12%)
Size without treatment	0	2 (5%)	0	0	2 (<1%)
Sclerosis on baseline CT	N/A	N/A	N/A	65 (50%)	65 (24%)
Lesion on baseline MRI	N/A	N/A	N/A	28 (22%)	28 (10%)
Lesion on baseline bone scan	N/A	N/A	N/A	8 (6%)	8 (3%)
Sclerosis on follow up CT	N/A	N/A	N/A	12 (9%)	12 (4%)
Lesion on follow up MRI	N/A	N/A	N/A	2 (2%)	2 (<1%)
Lesion on follow up bone scan	N/A	N/A	N/A	10 (8%)	10 (4%)

Source: FDA clinical reviewer analysis.

Note that the total number of criteria in this table differs from the total number of regions in the prior table because more than one criterion could be selected for a single region.

Abbreviations: CT = computed tomography, MRI = magnetic resonance imaging, N = number of regions, N/A = Not Applicable

The most commonly used criteria for characterizing lesions under the composite reference standard were based on baseline imaging results available at study entry, totaling 37% when all imaging modalities were considered. These criteria were exclusively applied to bone, and they make up 78% of the bone evaluations. In contrast, the prostate/prostate bed was largely (79%) assessed by histopathology. These differences in region distribution and criteria used for assigning reference standard results to regions adequately explain the differences in PPV between the primary and secondary analyses. It is also noted that the use of baseline imaging

to determine the reference standard results is one possible mechanism for the introduction of bias based on the availability of conventional imaging, as discussed earlier.

Table 42. ⁶⁸Ga-PSMA-11 PET Positivity Rate Stratified by PSA Level

PSA Range (ng/mL)	Patients N	PET Positive Patients N	PET Positivity Rate % (95% CI)	PET Positive Patients With Composite Reference Data N	PPV % (95% CI)
[0-0.5)	136	49	36% (28%, 44%)	12	92% (62%, 100%)
[0.5-1)	79	44	56% (45%, 67%)	18	83% (59%, 96%)
[1-2)	89	74	83% (75%, 91%)	32	97% (84%, 100%)
[2-∞]	331	302	91% (88%, 94%)	153	92% (87%, 96%)
Any PSA	635	469	74% (70%, 77%)	215	92% (88%, 95%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, N = number of patients, PET = positron emission tomography, PPV = positive predictive value, PSA = prostate-specific antigen, PSMA = prostate-specific membrane antigen

Prostate cancer recurrence is often detected by rising PSA level before the tumor can be visualized by currently approved imaging tests. As shown in Table 42, ⁶⁸Ga-PSMA-11 PET also showed a direct correlation between PSA level and rate of positive PET result. The positive PET scan rate at low PSA values is not ideal, but suggests a meaningful advance over other imaging methods. Unfortunately, there was little reference standard data at lower PSA values to allow validation of the PET results, but what information was available fails to show degradation in PPV at low PSA values. When a similar analysis was performed on the subset of the Full Data Analysis group excluding the 313 patients with protocol deviations for time between PSA measurement and PET scan of greater than 30 days, similar trends were seen.

The secondary endpoints included the evaluation of inter-reader reproducibility. Per-reader results using the composite reference standard are listed in [Table 43](#) below.

Table 43. Per Reader Patient-Level Comparison of ⁶⁸Ga-PSMA-11 PET Versus Composite Reference Standard for Detection of Recurrent Prostate Cancer

Reader Number	True Positive	False Positive	PPV
1	73	2	97%
2	78	4	95%
3	83	5	94%
4	75	6	93%
5	77	5	94%
6	54	9	86%
7	54	9	86%
8	42	9	82%
9	46	5	90%

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen

As in the PSMA-PreRP study, the above performance data from the PSMA-BCR study could not be reliably compared among readers because the readers interpreted different subsets of the

PET scans. The number of cases interpreted by each reader was also relatively small. The range of per reader PPV results against the composite reference standard was 82 to 97%.

Although direct comparison of per-reader performance for the major endpoints of the PSMA-BCR study was not possible, reader concordance rate and Fleiss' kappa were calculated to provide some estimate of the degree of inter-reader agreement ([Table 44](#)).

Table 44. Measures of Inter-Reader Agreement for ⁶⁸Ga-PSMA-11 PET in the Inter-Reader Set

Region	Patients With All Readers		Kappa (N=635) Point Estimate (95% CI)
	Concordant (N=635) N (%)		
Prostate/prostate bed	500 (79%)		0.65 (0.60, 0.70)
Pelvic lymph node	512 (81%)		0.73 (0.69, 0.77)
Soft tissue	524 (83%)		0.70 (0.65, 0.75)
Bone	557 (88%)		0.78 (0.73, 0.82)
All regions	498 (78%)		0.58 (0.52, 0.63)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, N = number of patients, PET = positron emission tomography, PSMA = prostate-specific membrane antigen

The concordance rate was based on region-level (rather than subregion-level) data. Both of these measures indicated reasonable inter-reader agreement. The prostate/prostate bed region had slightly lower concordance rate and kappa compared to other regions, suggesting that this was a more difficult region to read. Given the frequent occurrence of post-treatment changes in the area, urinary excretion of radiotracer, and possible artifact from scatter or scatter correction from the bladder, this observation was not surprising.

For an additional secondary endpoint, referring clinicians were asked to complete surveys regarding the management of patients before ⁶⁸Ga-PSMA-11 PET, within 30 days after the scan, and at 6 months. Comparison of the pre-imaging and 30 day post-imaging surveys provided information regarding change in intended management, while the 6-month survey was used to determine whether the intended management was implemented. Intended management survey results are shown in Table 45.

Table 45. Results of the Survey of Intended Management in PSMA-BCR, Including Patients With and Without Reference Standard Data

Survey Result	N	%
N=382		
No change in intended management	107	28%
Any change in intended management	275	72%
Addition of surgery/radiation therapy	46	12%
Addition of systemic therapy	47	12%
Removal of surgery/radiation therapy	24	6%
Removal of systemic therapy	47	12%
Combination of addition/removal	96	25%
Dose modification/active surveillance	8	2%
Not categorized	7	2%

Source: Table 10 of the PSMA-BCR clinical study report.

Abbreviations: BCR = biochemical recurrence, N = number of patients, PSMA = prostate-specific membrane antigen

The result of the ⁶⁸Ga-PSMA-11 scan resulted in a change in intended management for 72% of patients for whom the management survey was completed. Addition and removal of therapies were reported with similar frequency, though the most common response was a combination of addition and removal which likely reflected a change from localized to systemic therapy, or vice versa. However, there were several limitations of these results. The most important was that the effect of any management change on patient outcome was not assessed. Thus, it was unclear if management decisions were changed appropriately. Additionally, survey data was missing for 40% of the patients, and it was possible that surveys were more likely to be completed if a change in management was intended. Furthermore, implementation of the intended management changes was surveyed in only a subset of 211 patients, and the intended management was not implemented in 23%.

Dose/Dose Response

The administered dose of radiotracer was not reported for 3 patients. A single dose range of 3 to 7 mCi was studied with injected activities averaging 5.1 ± 1.2 mCi in the patients with histopathology reference data, 5.1 ± 1.1 mCi in the patients with composite reference data, and 5.0 ± 1.1 mCi in the enrolled patients.

Durability of Response

Not applicable to this NDA.

Persistence of Effect

Not applicable to this NDA.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Not applicable to this NDA.

Additional Analyses Conducted on the Individual Trial

Because of the difficulties involved in collection of reliable reference standard data for regions without malignancy, there were practical study design limitations in determining the number of true negative, and often false negative, patients. Absence of this information precluded assessment of sensitivity and specificity. Correct detection rate (CDR), defined as the

proportion of reference standard validated true positive patients in the sample, was explored as an alternate test statistic of potential value in this situation ([Table 46](#)).

Table 46. Correct Detection Rate for ⁶⁸Ga-PSMA-11 PET by Histopathology and Composite Reference Standards

Reference	True Positive N	False Positive N	PET Negative N	Correct Detection Rate % (95% CI)
Histopathology	71	15	166	28% (23%, 34%)
Composite	192	18	166	51% (46%, 56%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, N = number of patients, PET = positron emission tomography, PSMA = prostate-specific membrane antigen

Note that for studies of patients with biochemically recurrent prostate cancer, CDR could be considered to approximate sensitivity because there should be few disease negative (i.e., false positive or true negative) patients in the sample. Patients categorized as false positive would thus be considered false negative by this logic, as the PET did not localize the correct site of disease. Similarly, PET negative patients could be considered false negative.

In the PSMA-BCR study, there were many PET positive patients without reference standard data, which complicates the CDR analysis. In [Table 46](#), these patients were excluded from analysis. The resulting CDR values suggested that ⁶⁸Ga-PSMA-11 PET should have clinical utility given the low detection rate of currently approved imaging alternatives. However, this analysis was limited by the potential for overestimation of performance due to possible biased inclusion in the reference standard set.

Due to the method of data encoding, only four lesions could be reported per patient, and this would only occur when lesions were present in all four regions. When multiple subregions were assessed per region, if there was a mixture of true positive and false positive subregions, the region was coded as true positive. This rule also applied at the patient-level when multiple regions were positive in the same patient. The net effect would raise the patient-level PPV relative to the subregion-level PPV. To evaluate the extent of elevation of the primary and secondary PPV endpoints by this effect, PPV was calculated for the sub-population where only a single subregion was evaluated for the reference standard ([Table 47](#)).

Table 47. PPV for ⁶⁸Ga-PSMA-11 PET by Histopathology and Composite Reference Standards in the Subset of Patients With a Single Subregion Assessed for the Reference Standard

Diagnostic Performance Measure	Histopathology	Composite
True positive (N)	59	134
False positive (N)	15	18
PPV (%; 95% CI)	80% (71%, 89%)	88% (83%, 93%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, N = number of patients, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen

The PPV point estimates in the sub-population where only a single subregion was evaluated for the reference standard was only mildly decreased relative to the full histopathology reference standard set and full composite reference standard set, 80% versus 83%, respectively, for the histopathology reference, and 88% versus 91%, respectively, for the composite reference. This observation suggests that the data encoding method did not substantially affect the PPV result.

To further investigate the possibility of biased enrollment or selection for follow up based on conventional imaging results at baseline, the reference standard set was stratified by the results of baseline conventional imaging ([Table 48](#)).

Table 48. PPV for ⁶⁸Ga-PSMA-11 PET by Composite Reference Standard, Stratified by Baseline Conventional Imaging Result

Baseline Conventional Imaging Result	True Positive (N=192) N (%)	False Positive (N=18) N (%)	PPV % (95% CI)
Positive	44 (23%)	0	100% (92%, 100%)
Negative	42 (22%)	4 (22%)	91% (79%, 98%)
Equivocal	15 (8%)	2 (11%)	88% (64%, 99%)
Absent	91 (47%)	12 (67%)	88% (82%, 95%)
Not positive	148 (77%)	18 (100%)	89% (84%, 94%)

Source: FDA clinical reviewer analysis.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, N = number of patients, PET = positron emission tomography, PPV = positive predictive value, PSMA = prostate-specific membrane antigen

In this exploratory analysis, PPV was highest in the conventional imaging positive group (100% [92-100%]), compared to PPV of 89% (84-94%) when results from patients with negative, equivocal, and absent conventional imaging were pooled (i.e., not positive). These results alone did not confirm that bias existed, as it was not surprising that patients with disease detectable by conventional imaging had a higher PPV for the PET scan. However, the results did suggest that use of baseline conventional imaging as a reference standard coupled with preferential follow up of patients with positive baseline imaging could have improved measured test performance. Importantly, exclusion of patients with positive baseline conventional imaging from analysis still resulted in a reasonable PPV of 89% (84-94%). Of additional note, patients with negative baseline conventional imaging, who presumably had less advanced disease and less potential bias for study inclusion and reference standard follow up, still demonstrated reasonable PPV of 91% (79-98%).

8.1.5. PSMA-PreRP-Meta and van Kalmthout, et al. 2019

The Applicant conducted a meta-analysis (PSMA-PreRP-Meta) of the literature published from January 2012 to April 2018 and identified five studies with a total of 266 patients that compared ⁶⁸Ga-PSMA-11 PET to histopathology for detection of pelvic nodal disease prior to radical prostatectomy. One small study of 30 patients was prospectively designed; the remaining four were retrospective. Most of the papers included only patients who were classified as intermediate to high risk by the D'Amico criteria. Across the five studies, the meta-

analysis of the study results by a simple random effects model with no fixed effect covariate reported that the sensitivity, specificity, PPV, NPV, and accuracy were 0.74 (95% CI, 0.51–0.89), 0.96 (95%CI, 0.85–0.99), 0.93 (95% CI, 0.86–0.99), 0.85 (95% CI, 0.75–0.93), and 0.86 (95% CI, 0.79–0.92), respectively.

Table 49. Overview of the Five Studies in PSMA-PreRP-Meta Reporting a Total of 266 Patients

Study	Patients	True Positive	False Positive	True Negative	False Negative
Budaus (2016)	30	4	0	18	8
Herlemann (2016)	34	20	4	8	2
Maurer (2016)	130	27	1	88	14
Van Leeuwen (2017)	30	7	1	18	4
Zhang (2017)	42	14	1	26	1

Source: (Hope et al. 2019).

Abbreviations: PSMA = prostate-specific membrane antigen

The Applicant noted that the studies of Herlemann, et al. (2016) and Zhang, et al. (2017) included patients with initial staging as well as patients with biochemical recurrence. These patients could not be distinguished based on the available published information. Therefore, the Applicant conducted an additional meta-analysis leaving out the studies of Herlemann, et al. (2016) and Zhang, et al. (2017), with the results shown below:

- Sensitivity: 0.57 (95% CI, 0.37–0.76)
- Specificity: 0.99 (95% CI, 0.96–1.00)
- PPV: 0.98 (95% CI, 0.88–1.00)
- NPV: 0.81 (95% CI, 0.70–0.91)
- Accuracy: 0.84 (95% CI, 0.74–0.9)

During the NDA review, the Applicant was requested to further review the literature for additional studies published since completion of their meta-analysis. On March 4, 2020, the Applicant responded with a list of six relevant articles. Most of these were small, retrospective, or did not directly compare PET results to histopathology. However, there was one prospective study (van Kalmthout et al. 2019) with a very similar design to the PSMA-PreRP trial, the results of which are listed separately from those of the original meta-analysis in Table 50.

Table 50. Comparison of ⁶⁸Ga-PSMA-11 Performance for Detection of Pelvic Lymph Nodes Between the PSMA-PreRP-Meta, (van Kalmthout et al. 2019), and PSMA-PreRP Studies

Diagnostic Performance Measure	PSMA-PreRP-Meta (N=190) Point Estimate (95% CI)	van Kalmthout, et al. (N=96) Point Estimate (95% CI)	PSMA-PreRP (N=123) Point Estimate (95% CI)
Sensitivity (95%CI)	57% (37%, 76%)	42% (27%, 58%)	47% (29%, 65%)
Specificity (95%CI)	99% (96%, 100%)	91% (79%, 97%)	90% (84%, 96%)
PPV (95%CI)	98% (88%, 100%)	77% (54%, 91%)	61% (41%, 81%)
NPV (95%CI)	81% (70%, 91%)	68% (56%, 78%)	84% (77%, 91%)

Diagnostic Performance Measure	PSMA-PreRP-Meta (N=190) Point Estimate (95% CI)	van Kalmthout, et al. (N=96) Point Estimate (95% CI)	PSMA-PreRP (N=123) Point Estimate (95% CI)
% reference positive (95%CI)	34% (27%, 40%)	43% (33%, 53%)	24% (17%, 32%)

Sources: Applicant response to IR of October 25, 2019, Table 14 in section 8.1.2 of this review.

Notes: For the % reference positive in PSMA-PreRP-Meta, the data from 3 studies were weighted by sample size.

Abbreviations: ⁶⁸Ga = gallium-68, CI = confidence interval, N = number of patients, NPV = negative predictive value, PPV = positive predictive value, PSMA = prostate-specific membrane antigen

Performance of ⁶⁸Ga-PSMA-11 PET for detection of pelvic nodal metastatic prostate cancer, as measured by sensitivity and specificity, trended higher for the meta-analysis than for PSMA-PreRP. However, the sensitivity and specificity of the van Kalmthout, et al. (2019) study were more similar to PSMA-PreRP, and the differences in PPV and NPV between the two studies are likely explained by the lower percentage of reference standard positive patients in PSMA-PreRP. Together, these observations suggest that the largely retrospective nature of the studies in PSMA-PreRP-Meta may have biased the results, and that the PSMA-PreRP performance results are more valid.

While the inherent weaknesses of these published reports limit use of their results as substantial evidence of effectiveness, they do provide some supportive evidence. In particular, as these results were drawn from experience in four countries, they indicate that the limited number of study sites and geographic coverage of the PSMA-PreRP trial should not restrict its applicability to the broader U.S. population.

8.1.6. PSMA-BCR-Meta

The Applicant conducted a meta-analysis (PSMA-BCR-Meta) of the literature published from January 2012 to April 2018 and identified 15 studies comparing ⁶⁸Ga-PSMA-11 PET to histopathology for detection of recurrent prostate cancer in the biochemically recurrent population. Of these, two were prospective and 13 were retrospective. The sample sizes ranged from 3 to 48 patients with a total of 256 patients included in the meta-analysis. Many patients in the included studies were not incorporated into the meta-analysis due to use of non-histopathology reference standard information. The range of PSA levels in PSMA-BCR-Meta was difficult to interpret because of the lack of information on prostatectomy rates. As for PSMA-BCR, sampling of PET negative lesions was also not consistent, and therefore PPV was the most relevant statistic for analysis. Also note that the method for choosing patients for tissue sampling to generate histopathology data was usually undefined in the literature reports, and there was related potential for selection bias.

Table 51. Summary of Literature-Based Studies Included for Meta-Analysis PSMA-BCR-Meta

Study	Total Study Patients	Patients Included in Meta-Analysis	True Positive Patients	False Positive Patients
Afaq	100	11	10	1
Afshar-Oromieh (2013)	37	6	6	0
Afshar-Oromieh (2014)	37	7	7	0

Study	Total Study Patients	Patients Included in Meta-Analysis	True Positive Patients	False Positive Patients
Afshar-Oromieh (2015)	319	42	37	0
Ceci	70	7	6	1
Demirkol	22	3	3	0
Einspieler	118	6	6	0
Morigi	38	10	9	0
Eiber	248	12	12	0
Grubmuller	117	16	16	0
Pfister	28	28	22	6
Rauscher (2016)	22	22	22	0
Rauscher (2016)	48	48	42	3
Siriwardana	35	35	32	0
Van Leeuwen	70	3	3	0

Source: (Hope et al. 2019).

Abbreviations: BCR = biochemical recurrence, PSMA = prostate-specific membrane antigen

The meta-analysis of the study results by a simple random effects model with no fixed effect covariate reported a patient-level PPV of 0.99 with a 95% confidence interval of (0.96, 1.00). Since no information was available regarding ITD patients and how those 256 patients were selected from ITD patients, any analysis to seek insight into whether the almost perfect PPV would only be maintained with the histopathology reference standard or could be extended to ITD patients was not feasible.

For comparison, as detailed in Section 8.1.4, PPV of 83% (75-91%) was determined for the primary histopathology-derived endpoint of the prospective PSMA-BCR trial. As in the pre-prostatectomy population, the decreased test performance in PSMA-BCR compared to the meta-analysis may be attributed to the more rigorous, prospective design of the PSMA-BCR trial. However, the meta-analysis again provides supportive evidence of effectiveness of ⁶⁸Ga-PSMA-11 PET in a broader population.

8.1.7. Integrated Assessment of Effectiveness

The Applicant's data support the effectiveness of ⁶⁸Ga-PSMA-11 for imaging of prostate cancer. However, there are important gaps in the resulting evidence that must be considered when evaluating whether standards for effectiveness have been met. These gaps can be divided broadly into issues of test performance and issues of experimental design and execution, discussed in turn below.

Test performance:

The PSMA-PreRP study failed to meet its primary endpoint goal for the lower bound of the 95% CI of sensitivity to be greater than 65%, with an observed point estimate of 47% and a 95% confidence interval of 29-65%. However, it is important to note that the sensitivity goal was chosen based on the performance of the agent in preliminary retrospective analyses, rather than on a clinically meaningful threshold. Therefore, failure to meet the sensitivity goal does not necessarily indicate lack of potential clinical utility. Because definitive therapies for prostate

cancer such as prostatectomy and radiotherapy are associated with significant morbidity, and pelvic nodal metastases may spare patients from receiving them, identification of pelvic nodal disease on PET could provide benefit by avoiding futile therapy. While low sensitivity will decrease the number of patients who benefit, each individual patient with true positive results will potentially benefit. Conversely, patients with pelvic nodal metastasis that is missed by the PET scan will likely proceed to definitive therapy just as they would have with no PET scan at all.

Given this clinical context, the most relevant statistic is PPV, which ideally would be high enough to avoid additional confirmatory testing of positive results. In PSMA-PreRP, PPV was initially estimated at 61% with a 95% confidence interval of 41-81%. A conservative modification of the Applicant's post hoc analysis estimated PPV at 74% with a 95% confidence interval of 54-93% (Table 22). As discussed further below, trial execution issues likely underestimated performance in PSMA-PreRP. Also, since PPV is dependent upon prevalence of metastasis in the intended patient population, performance would be expected to improve in patients with suspected metastasis (i.e., those of higher risk stratification). This point will be reflected in the labeled indications statement. The fraction of patients with positive pelvic lymph nodes in PSMA-PreRP, 24%, was within the typical range reported in the published literature, though estimates vary substantially based on numerous risk factors as well as the extent of pelvic lymph node dissection (Liss et al. 2013; Heck et al. 2014; Batra et al. 2015).

It is also noted that current treatment algorithms for prostate cancer prior to definitive therapy incorporate conventional imaging techniques with low sensitivity. For example, multiparametric MRI has sensitivity of up to 55 to 73% (Caglic et al. 2019) for metastasis in this setting. As such, clinicians are familiar with the limitations of low sensitivity imaging techniques. Along these lines, Section 5: Warnings and Precautions of the labeling will include information on the risk of misdiagnosis. Specifically, this section will state that a negative image does not rule out the presence of prostate cancer and a positive image does not confirm the presence of prostate cancer.

Subgroup analyses in the PSMA-PreRP study showed a trend for higher sensitivity and PPV in patients with summed Gleason score of 8 or higher. This observation may be explained in part by greater expression of PSMA in higher grade prostate cancers (Bravaccini et al. 2018), resulting in greater binding of radiotracer. While the sample sizes were not sufficient to demonstrate statistical significance, the trend in point estimate between the group with summed Gleason score of at least 8 versus the group with summed Gleason score of less than 8 was large enough to warrant mention in labeling (sensitivity: 55% versus 25%, PPV: 71% versus 33%, sample size: 65 versus 58).

Consultation with the FDA Division of Oncology yielded a similar assessment of the potential clinical utility for ⁶⁸Ga-PSMA-11 PET in the pre-definitive therapy setting. The consultant judged that the utility appears to be most apparent for men with higher grade tumors (Gleason score 8-10) which would place men into the NCCN high or very high risk category. On the other hand, the consultant judged the utility in men with intermediate risk tumors to be less evident.

While the PSMA-BCR study met its primary endpoint goal for PPV for detection of prostate cancer in biochemically recurrent patients and showed reasonable PET positivity at clinically relevant low PSA levels, subgroup analyses suggest that performance may be modestly decreased in the prostate and prostate bed compared to the remainder of the body. The cause cannot be determined from the study results, but it is most likely a combination of architectural distortion from prior therapies, uptake in residual prostate tissue, excreted radiotracer in the posterior urethra, and scatter or scatter correction artifact from the urinary bladder. This issue will also be mentioned in labeling. Of note, the prostate or prostate bed may be treated with radiotherapy in biochemically recurrent patients regardless of whether tumor is identified there because it is a common site of disease recurrence.

Experimental design and execution:

In the PSMA-PreRP trial, it was anticipated that 75% of patients would proceed to prostatectomy with pelvic lymph node dissection, and thus have reference standard data. However, only 39% of the enrolled patients received surgery. This observation raises the possibility of biased selection for entry into the primary analysis cohort. While the reasons for patients choosing other therapies could not be captured on an individual basis, the majority of the excluded patients (59%) proceeded to radiation therapy. It seems the most likely explanation for the low surgery rate is that the inclusion criterion for planned prostatectomy was not stringently enforced. The Applicant suggested that if there was bias related to this issue, it would typically involve patients with easier to diagnose disease, such as bulky pelvic lymph nodes, who opt to forgo surgery. The Applicant presents the reasonable argument that such bias would actually underestimate test performance by potentially restricting analysis to patients with relatively less advanced disease that is more difficult to detect.

The type of initial definitive therapy in the PSMA-PreRP study was limited to prostatectomy because this therapy is often accompanied by template pelvic lymph node dissection as standard of care, which allowed collection of histopathology data for the study. In clinical practice, other therapies, particularly external beam radiotherapy or brachytherapy, are often used. However, it is expected that the sensitivity and specificity of ⁶⁸Ga-PSMA-11 PET will be similar between patients who are candidates for radiotherapy and those who are candidates for surgery.

The PSMA-BCR trial was affected by missing data at multiple levels. The case report form did not allow capture of lesion-level PET data, though this was offset somewhat by the use of 20 subregions. Similarly, the case report form restricted reference standard determination to the region-level. Many patients also had reference standard data for only some of their PET positive regions. Finally, the majority of PET positive patients had no reference standard data for the primary PPV endpoint, and a large minority had no data for the secondary PPV endpoint. Because no study specific follow up was required, the decision of whether or not to obtain reference standard information was made by the treating clinicians who had access to the ⁶⁸Ga-PSMA-11 PET result in this open-label study. Accordingly, the likelihood of unintended selection

bias and the potential impact on study results are both assessed as high. This concern is supported by subgroup analyses based on PSA level and availability of baseline conventional imaging that showed differences between patients with and without reference standard data. Multiple exploratory analyses were performed to attempt to control for these factors, all of which showed only mild decreases in PPV. Thus, while it is considered probable that the PPV of the test was overestimated, the impact appears to have been minor.

An additional source of bias in the PSMA-BCR trial may have been the lack of blinding of the PET readers to PSA level. Because lesions could not be considered indeterminate in the trial, PSA data may have influenced categorization of lesions when readers were unsure. It also may have prompted a more thorough search for abnormalities in patients with higher PSA levels. Note there is some justification for making PSA level available to PET readers in routine clinical use, but it cannot be assumed to be always available, particularly outside academic settings, and therefore ⁶⁸Ga-PSMA-11 PET would ideally be able to perform adequately without it. The lack of PSA blinding may have potentially improved PSA stratified PET positivity results, but this was a secondary endpoint. While the study was not powered to detect an effect on PSA stratified PPV, no effect was seen in such analysis.

In both the PSMA-PreRP and PSMA-BCR trials, PET readers were selected from a pool (numbering six and nine, respectively), and each reader examined a different subset of PET scans. This practice was related to resource constraints, and it prevented formal evaluation of per reader results for the major endpoints. The necessary use of majority results for the PET scans is a weakness for both studies. However, analyses of multiple diagnostic performance metrics, including concordance rates, kappa values, and individual reader results, suggest acceptable reproducibility in reader performance such that the majority read data can be considered reasonably valid.

Summary:

After considering the above issues, the review team finds that the Applicant has submitted sufficient evidence of effectiveness to meet the regulatory standards for approval. The Applicant's initially proposed indication (b) (4)

is overly broad (b) (4)

The Applicant's initial proposal could also be interpreted (b) (4) The indications in the labeling now focus on the populations studied in the clinical trials.

While the populations studied in the PSMA-PreRP and PSMA-BCR trials were at different points in disease course, they shared the same type of cancer. Since the underlying mechanism of detecting metastasis is identical in these populations, the trials are considered mutually supportive. As an example, the ability of ⁶⁸Ga-PSMA-11 to detect extrapelvic metastatic disease prior to initial definitive therapy of prostate cancer was not assessed in the PSMA-PreRP study. However, the ability of ⁶⁸Ga-PSMA-11 to detect distant metastases in this population can be

reasonably extrapolated from the pelvic lymph node results given the performance of ^{68}Ga -PSMA-11 in detecting bone and extrapelvic soft tissue metastases in the PSMA-BCR study.

It is anticipated that ^{68}Ga -PSMA-11 will provide substantial clinical utility for patients with prostate cancer. ^{68}Ga -PSMA-11 is the first PET radiotracer to target PSMA, and the first approved imaging agent to target the extracellular domain of PSMA. Routine image interpretation of ^{68}Ga -PSMA-11 PET is anticipated to be straightforward due to good availability of the radiotracer to the binding site and favorable time of clearance of nonbound radiotracer from the blood pool. An exploratory comparison of ^{68}Ga -PSMA-11 to CT and MRI from PSMA-PreRP data, also suggests that ^{68}Ga -PSMA-11 will outperform conventional imaging (Table 25).

^{111}In -capromab (Prostascint), which binds the intracellular domain of PSMA, was approved for single-photon imaging of prostate cancer, but its marketing has been discontinued. In addition to ^{111}In -capromab, two other radiotracers have been approved for biochemically recurrent prostate cancer, ^{11}C -choline and ^{18}F -fluciclovine, and their use has been reported in the literature (Castellucci et al. 2009; Andriole et al. 2019). These radiotracers both identify the increased metabolism associated with prostate cancer, and thus are relatively nonspecific. No direct comparison of test performance is available in the application.

When stratified by PSA, ^{68}Ga -PSMA-11 PET appears to show favorable detection rates at low PSA levels in the biochemical recurrence setting. Conventional imaging methods such as CT and $^{99\text{m}}\text{Tc}$ -medronate bone scan are typically considered to have low detection rates, particularly at lower PSA levels (Kane et al. 2003; Okotie et al. 2004). It should be noted that reported detection rate data are not validated by a reference standard and when stratified by PSA may be confounded by varying proportions of patients with prostatectomy.

8.2. Review of Safety

8.2.1. Safety Review Approach

Safety data were collected in the PSMA-PreRP and PSMA-BCR studies listed in section 7.1. In addition, due to the extensive investigational use of ^{68}Ga -PSMA-11 prior to initiation of the Applicant's development plan, available safety results from the published literature were collected in the PSMA-PreRP-Meta and PSMA-BCR-Meta meta-analyses. All of these sources of safety data were reviewed.

No specific safety issues were encountered during development of the drug.

8.2.2. Review of the Safety Database

Overall Exposure

The pooling of safety data from the two clinical trials and two meta-analyses was discussed at the pre-NDA meeting and agreement between the Applicant and FDA was reached. However, the Applicant reported that only 3 of the 40 publications included in the meta-analyses mentioned adverse events. Each of the three articles reported that no adverse events (AEs) were identified but did not describe the procedure for AE monitoring. Therefore, the meta-analyses will be excluded from further safety discussion.

Safety data were available for 960 patients in the PSMA-PreRP and PSMA-BCR studies, with the safety population in each study defined as all enrolled patients who received a ⁶⁸Ga-PSMA-11 injection. The PSMA-PreRP and PSMA-BCR studies were pooled for safety analysis because they had identical dosing, administration, and follow up procedures, and apart from the difference in primary versus recurrent prostate cancer, the enrollment criteria were very similar.

Each patient received a single dose of ⁶⁸Ga-PSMA-11, which is appropriate for the population of intended use, where PSMA PET imaging will be performed once or at widely spaced intervals. The dose range in the draft prescribing information is 3 to 7 mCi, which matches the administered dose in the pooled safety population of 5.1 ± 1.1 mCi (mean ± SD).

Table 52. Demographic Characteristics of the Safety Analysis Population

Demographic Parameters	Pooled Safety Set (N=960) N (%)	PSMA-PreRP (N=325) N (%)	PSMA-BCR (N=635) N (%)
Age			
Mean years (SD)	68 (8.0)	68 (8.4)	69 (7.7)
Median (years)	69	69	69
Min, max (years)	40, 95	40, 93	44, 95
Age Group			
< 65 years	273 (28%)	101 (31%)	172 (27%)
≥ 65 years	687 (72%)	224 (69%)	463 (73%)
Race			
White	814 (85%)	269 (83%)	545 (86%)
Black or African American	17 (2%)	6 (2%)	11 (2%)
Asian	41 (4%)	18 (6%)	23 (4%)
American Indian or Alaska Native	2 (<1%)	1 (<1%)	1 (<1%)
Native Hawaiian or Other Pacific Islander	5 (<1%)	4 (1%)	1 (<1%)
Other	45 (5%)	20 (6%)	25 (4%)
Missing	36 (4%)	7 (2%)	29 (5%)
Ethnicity			
Hispanic or Latino	42 (4%)	12 (4%)	30 (5%)
Not Hispanic or Latino	743 (77%)	297 (91%)	446 (70%)
Missing	175 (18%)	16 (5%)	159 (25%)
Dose			
Dose (mCi) (SD)	5.1 (1.1)	5.3 (1.1)	5.0 (1.1)

Demographic Parameters	Pooled Safety Set (N=960) N (%)	PSMA-PreRP (N=325) N (%)	PSMA-BCR (N=635) N (%)
Diuretic			
Furosemide administered	864 (90%)	278 (86%)	586 (92%)
Missing	9 (<1%)	9 (3%)	0

Source: FDA clinical reviewer analysis.

Abbreviations: BCR = biochemical recurrence, N = number of patients, PSMA = prostate-specific membrane antigen, SD = standard deviation

The safety population was predominantly white patients with relatively few black patients. However, there are no available data to suggest that race will influence likelihood or severity of adverse events.

Adequacy of the safety database:

The size and demographic distribution of the safety database is acceptable.

8.2.3. Adequacy of Applicant’s Clinical Safety Assessments

Categorization of Adverse Events

Patients were monitored for adverse events for 2 hours after drug injection and by phone call at 1 to 3 days after injection. However, most of the patients at UCLA were called substantially later than 3 days after injection. This affected 362 patients (38% of the safety population, >99% of the UCLA safety population), and at least 49 of these patients were not reachable.

The Applicant stated that they coded adverse events using CTCAE version 4 terminology. Upon review of the safety database, it was found that the Applicant coded only one AE per patient, regardless of the number of complaints recorded in the investigator verbatim terms. Therefore, for the purpose of this review, investigator verbatim terms were recoded into the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 lowest level terms, allowing multiple terms per patient where applicable. Afterwards, the lowest level terms were translated into preferred terms for analysis.

The Applicant reported AEs in 26 patients, however the safety database shows AEs were coded for 28 patients. This discrepancy likely related to a data entry error in the variable that codes for whether or not an adverse event occurred. All 28 patients with coded events were considered in the analyses below.

Routine Clinical Tests

Blood pressure and heart rate were measured before and after injection of ⁶⁸Ga-PSMA-11.

Clinical laboratory testing was not performed. Neither the review team nor the Applicant (according to response to IR of October 7, 2019) are aware of published investigations of the effect of ⁶⁸Ga-PSMA-11 on laboratory results. However, it is reasonable to assume that the likelihood of a meaningful effect on laboratory values is low due to the intended microdose of the drug (on the order of 5 µg mass dose per injection) and the anticipated infrequent administration. In addition, the FDA guidance for industry *Developing Medical Imaging Drug and Biological Products Part 1: Conducting Safety Assessments* states that for lower risk (Group 1) agents like ⁶⁸Ga-PSMA-11, a less extensive clinical safety evaluation is appropriate. Therefore, the absence of clinical laboratory testing was considered acceptable.

8.2.4. Safety Results

Deaths

No deaths were reported during the observation period.

Serious Adverse Events

No serious adverse events were reported.

Dropouts and/or Discontinuations Due to Adverse Effects

No study dropouts or discontinuations due to adverse events were reported.

Significant Adverse Events

No significant adverse events were reported.

Treatment Emergent Adverse Events and Adverse Reactions

A total of 35 treatment emergent adverse events were reported in 28 (2.9%) patients among the 960 patients in the safety population. The AE rate was lower at UCLA than UCSF, 3/363 (0.8%) versus 25/597 (4.2%), respectively, likely related to the late AE survey performed at UCLA. Therefore, the rates for individual adverse events are calculated for the entire safety population and the UCSF safety population separately, since the rate at UCSF is likely more accurate. The most common adverse events reported were diarrhea, dizziness, and nausea/vomiting. All AEs were classified as grade 1 (mild) by CTCAE version 4.

Table 53. Treatment-Emergent Adverse Events in the Safety Population

MedDRA SOC or PT	Pooled Safety Set (N=960) N (%)	UCSF Safety Set (N=597) N (%)
Gastrointestinal disorders	11 (1.1%)	8 (1.3%)
Diarrhea**	4 (0.4%)	4 (0.7%)
Nausea**	4 (0.4%)	2 (0.3%)
Vomiting**	1 (0.1%)	1 (0.2%)
Dysphagia	1 (0.1%)	1 (0.2%)
Abdominal discomfort	1 (0.1%)	0
Nervous system disorders	8 (0.8%)	8 (1.3%)
Dizziness	4 (0.4%)	4 (0.7%)
Headache	2 (0.2%)	2 (0.3%)
Lethargy	1 (0.1%)	1 (0.2%)
Hypoesthesia**	1 (0.1%)	1 (0.2%)
General disorders and administration site conditions	5 (0.5%)	5 (0.8%)
Fatigue**	2 (0.2%)	2 (0.3%)
Injection site pruritus	1 (0.1%)	1 (0.2%)
Pain**	1 (0.1%)	1 (0.2%)
Asthenia	1 (0.1%)	1 (0.2%)
Renal and urinary disorders	4 (0.4%)	4 (0.7%)
Bladder pain	1 (0.1%)	1 (0.2%)
Bladder spasm	1 (0.1%)	1 (0.2%)
Urinary retention	1 (0.1%)	1 (0.2%)
Nephrolithiasis	1 (0.1%)	1 (0.2%)
Psychiatric disorders	2 (0.2%)	2 (0.3%)
Initial insomnia	1 (0.1%)	1 (0.2%)
Autoscopy	1 (0.1%)	1 (0.2%)
Vascular disorders	2 (0.2%)	2 (0.3%)
Hypotension	1 (0.1%)	1 (0.2%)
Hot flush**	1 (0.1%)	1 (0.2%)
Eye disorders	1 (0.1%)	1 (0.2%)
Vision blurred	1 (0.1%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	1 (0.1%)	1 (0.2%)
Muscular weakness**	1 (0.1%)	1 (0.2%)
Skin and subcutaneous tissue disorders	1 (0.1%)	1 (0.2%)
Rash	1 (0.1%)	1 (0.2%)
Patients with any adverse event	28 (2.9%)	25 (4.2%)

Source: FDA clinical reviewer analysis.

** indicates that the adverse event was considered possibly, probably, or definitely related to study drug administration in at least 1 patient

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients, PT = preferred term, SOC = system organ class, UCSF = University of California, San Francisco

Adverse events were considered not related to the study drug by the investigators in 12 patients (43%) and unlikely to be related in an additional eight patients (29%). Nine AEs considered possibly, probably, or definitely related to ⁶⁸Ga-PSMA-11 were reported in the remaining eight patients (29%, double asterisk in above table), and were considered to be ARs for review purposes and labeling. These events included two of the four diarrhea cases and two of the five nausea/vomiting cases. In addition, because of its relatively high frequency, dizziness was considered an AR. All other ARs were assessed by the investigators as possibly, probably, or definitely related in one patient each. All ARs were graded as mild in intensity.

An adverse event of nephrolithiasis, considered unrelated to the study drug by the investigators, had not resolved over the observation period. Two other patients had missing data for the AE outcome variable, one with nausea and the other with autoscopia. However, the investigator verbatim description for the autoscopia event indicated the symptom lasted until midnight on the day of injection. All other AEs were reported to resolve during the observation period.

Laboratory Findings

Clinical laboratory data were not available. See Section [8.2.3](#) for additional information.

Vital Signs

Assessment of vital sign data was by shift table, by correlation of changes in vital signs to ⁶⁸Ga-PSMA-11 dose, and by examination of patients with the largest changes. No findings were identified to suggest a meaningful effect of ⁶⁸Ga-PSMA-11 on heart rate or blood pressure.

Electrocardiograms

Electrocardiograms (ECGs) were not obtained in either of the trials that enrolled the safety population. One published report states that there was no change in ECG after administration of 3.2 to 4.3 mCi ⁶⁸Ga-PSMA-11 in five patients with known or suspected prostate cancer (Pfoeb et al. 2016).

QT

No formal QT study was performed for this single administration microdose drug and no study was needed.

Immunogenicity

Immunogenicity evaluation was not needed and was not performed for this single administration microdose drug.

8.2.5. Analysis of Submission-Specific Safety Issues

No submission-specific safety issues were identified.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

COA data were not collected and are not needed.

8.2.7. Safety Analyses by Demographic Subgroups

Table 54. Adverse Event Rates by Patient Age

Reported Events	Age < 65	Age ≥ 65
Patients (N, % of total)	273 (28%)	687 (72%)
Adverse events (N, % of total)	8 (23%)	27 (77%)
Patients with adverse events (N, % of total)	7 (25%)	21 (75%)

Source: FDA clinical reviewer analysis.

Abbreviations: N = number

A trend was suggested towards more adverse events in the patients who were 65 years or older, but this more likely reflects general health status and is of doubtful relationship to the study drug.

The relatively small number of AE reports and the predominantly white study population prevent meaningful subgroup analyses for race or ethnicity.

Table 55. Adverse Event Rates by Administered Dose of ⁶⁸Ga-PSMA-11

Reported Events	Dose < 0.0611 mCi/kg	Dose ≥ 0.0611 mCi/kg
Patients (N, % of total)	472 (50%)	480 (50%)
Adverse events (N, % of total)	21 (60%)	14 (40%)
Patients with adverse events (N, % of total)	16 (57%)	12 (43%)

Source: FDA clinical reviewer analysis.

Abbreviations: N = number

Eight patients were excluded from this analysis due to missing dose or weight information. The median dose of ⁶⁸Ga-PSMA-11 was 0.0611 mCi/kg. Grouping of patients by administered dose greater than or less than the median value did not reveal any evidence of dose-related adverse effect.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No studies of carcinogenicity were performed and none are needed. As with all radioactive drugs, there is believed to be a low, dose-dependent risk for induction of malignancy. Refer to Section [6](#) for radiation dosimetry information.

Human Reproduction and Pregnancy

⁶⁸Ga-PSMA-11 is not intended for use in females.

Pediatrics and Assessment of Effects on Growth

⁶⁸Ga-PSMA-11 is not intended for use in the pediatric population. A pediatric study waiver was granted, per agreed iPSP letters of February 14, 2019, filed to IND 130649 (UCLA) and IND 127621 (UCSF).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

While there were a small number of protocol deviations for administered doses greater than intended, the maximum dose administered was 7.6 mCi (intended range 3 to 7 mCi), and no large overdose occurred during the studies. No literature report of overdose was found in PubMed at the time of this review. In the absence of clinical experience to guide management of overdose, it is reasonable to recommend increasing drug clearance by hydration and, if clinically feasible, by administration of a diuretic. The main goal of such measures is to reduce patient radiation exposure. As for any overdose involving radioactive materials, the effective dose to the patient should be estimated if possible. These recommendations are included in drug labeling.

No controlled substance staff consult review was performed.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

⁶⁸Ga-PSMA-11 is first-in-class and no relevant postmarket experience is available. Upon review of the published literature, no safety signal was identified from investigational use or foreign use programs for ⁶⁸Ga-PSMA-11 or related compounds.

Expectations on Safety in the Postmarket Setting

In terms of adverse events, no significant new issues are anticipated in the postmarket setting. However, the translation of ⁶⁸Ga-PSMA-11 PET results into clinically actionable information is one area where safety issues could arise. As with all tests, false positive and false negative results may occur, and if they are acted upon, patient management could be adversely affected. Additionally, despite PSMA being termed “prostate-specific,” it is expressed in other tumor types. These issues have been addressed in the drug labeling to better inform clinicians of the limitations of the test and to reduce associated risk of misdiagnosis.

8.2.10. Integrated Assessment of Safety

Adverse reactions in the 960 patients dosed in two prospectively conducted clinical trials were rare and non-serious. No safety signal was noted. Risk from radiation exposure is typical of PET oncology imaging and estimated to be minimal. As mentioned above, the potential risk of misdiagnosis from ⁶⁸Ga-PSMA-11 PET will be managed through appropriate labeling.

8.2.11. Specific Safety Studies/Clinical Trials

None.

8.3. Statistical Evaluation

8.3.1. PSMA-PreRP Study

In the PSMA-PreRP study, a total of 325 patients were enrolled, but 198 patients did not undergo prostatectomy after imaging. As discussed previously, the decision to forego surgery was in most cases almost certainly related to incorporating results of the ⁶⁸Ga-PSMA-11 PET into patient management. Thus, it seems patients with more advanced disease, and presumably more easily detectable disease, comprised many of those who did not receive surgery, thereby potentially underestimating ⁶⁸Ga-PSMA-11 PET performance in the trial.

These assumptions aside, a tipping point analysis was conducted by imputing the 202 patients who did not have histopathology results from pelvic lymph nodes with probability ‘p’ being histopathology-positive and probability ‘1-p’ being histopathology-negative, where p ranged from 0% to 100% with an increment of 10%. The results are shown in [Table 56](#).

Table 56. Tipping Point Analysis – PSMA-PreRP Study*

Tipping Point Analysis	Sensitivity With 95% CI	Specificity With 95% CI
Applicant's Analysis (N=123)	47% (14/30) (29%, 65%)	90% (84/93) (84%, 96%)
Histopathology results of pelvic lymph nodes (positive: negative)		
0:100	47.0% (28%, 66%)	66.0% (61%, 72%)
10:90	46.0% (37.7%, 54.4%)	67.3% (65.7%, 68.9%)
20:80	45.7% (37.7%, 53.7%)	68.2% (66.0%, 70.5%)
30:70	45.5% (38.8%, 52.2%)	69.4% (66.7%, 72.1%)
40:60	45.4% (39.3%, 51.4%)	70.7% (67.4%, 73.9%)
50:50	45.2% (40.1%, 50.4%)	72.2% (68.6%, 75.9%)
40:60	45.1% (40.7%, 49.6%)	74.2% (70%, 78.4%)
70:30	45.1% (41.3%, 48.9%)	76.7% (72.1%, 81.2%)
80:20	45.0% (42.1%, 48.0%)	79.8% (75.2%, 84.5%)
90:10	45.0% (43.0%, 47.0%)	84.1% (80%, 88.3%)
100:0	45.0% (38.0%, 52.0%)	90.0% (82%, 95%)

Source: FDA statistics reviewer analysis.

*Imputations were performed for patients who did not have histopathology results

Abbreviations: CI = confidence interval, N = number of patients, PSMA = prostate-specific membrane antigen

As the probability ratio went from 0:100 to 100:0, the imputed sensitivity estimates appeared

to be stable with point estimates ranging from 45% to 47%. In contrast, the range of imputed specificity estimates appeared to be wider with the lower bounds of the 95% confidence interval estimates ranging from 61% to 82%. By random imputation (i.e., imputation ratio of 50:50), the lower bounds of the 95% confidence interval estimates for sensitivity and specificity were 40.1% and 68.6%, respectively.

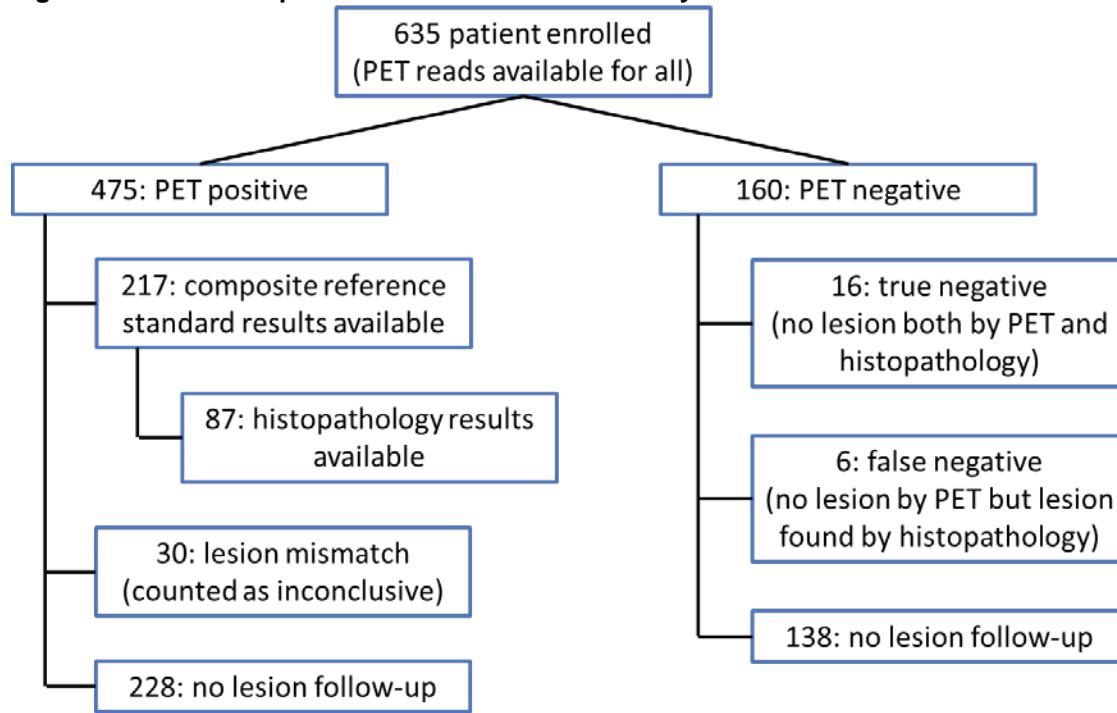
Ultimately, the PSMA-PreRP trial failed to meet its pre-specified sensitivity and specificity endpoints with the point estimate and the lower bound of the 95% CI for sensitivity below 50% with or without imputation. However, the fraction of patients with pelvic lymph node metastasis in the study was similar to that reported in the literature, accounting for distribution of risk factors (Liss et al. 2013; Heck et al. 2014; Batra et al. 2015). In the PSMA-PreRP study, the percentage of patients with confirmed disease among those patients who had pathology results was 24% (17%, 32%) and the estimated PPV based on the majority PET read was 61% (41%, 81%) (or 74% [54-93%] by modified post hoc analysis of Table 22). Given that the lower bound of the estimated PPV was considerably higher than the rate of disease both observed in the trial and estimated in the population of intended use, it appears that ⁶⁸Ga-PSMA-11 PET will likely have sufficient utility to allow approval in this clinical setting.

8.3.2. PSMA-BCR Study

As detailed in Section [8.1.4](#), patient- and region-level PPVs measured against either histopathology or composite reference standard exceeded the pre-specified performance threshold of 0.70 (70%) when evaluated at the 5% significance level using the Wilson score method. However, a major statistical concern is that the use of a subset of the intend-to-diagnose (ITD) patients (i.e., use of only patients with histopathology or composite reference standard) for efficacy analysis might introduce patient-selection bias that could lead to successful PPV evaluation. Therefore, sensitivity analyses with various imputations were conducted to gather a reasonable level of confidence that the PPV performance would be maintained in the ITD patients.

Reference standard results were only available for 46% of PET-positive patients (217/475): 87 by histopathology and 130 by conventional imaging or serum PSA level follow-up. Thus, the proportion of PET-positive patients without standard reference results was 54% (258/475). A summary of patient disposition is provided in [Figure 11](#).

Figure 11. Patient Disposition in the PSMA-BCR Study



Source: FDA statistical reviewer figure.

Abbreviations: BCR = biochemical recurrence, PET = positron emission tomography, PSMA = prostate-specific membrane antigen

A tipping point analysis was conducted by imputing the unavailable reference standard values using varying reference standard positive to reference standard negative ratios from 100:0 (best case) to 0:100 (worst case) at the patient-level. The purpose of this analysis was to find the tipping point that turned the study PPV results from win to fail, and vice versa. Of note, unlike the analyses in Section 8.1.4 that excluded seven patients without prior prostatectomy or definitive radiotherapy, the analyses in this section included all patients as they focused on the potential effects of unavailable reference standard data and the estimated performance in ITD patients based on a variety of statistical imputations.

As shown in Table 57, assuming 50% reference standard positive and 50% reference standard negative among 258 patients without reference standard information, the lower bound of the 95% confidence interval of patient-level PPV did not exceed the pre-specified threshold of 0.70.

Table 57. Patient-Level Tipping Point Analysis – PSMA-BCR Study

Reference Standard- Positive to Reference Standard-Negative Ratio*	Patient-Level PPV	95% CI	Study Win/Fail
100:0	458/475 = 0.96	(0.94, 0.98)	Win
90:10	432/475 = 0.91	(0.88, 0.93)	Win
80:20	406/475 = 0.85	(0.82, 0.88)	Win
70:30	381/475 = 0.80	(0.76, 0.84)	Win
60:40	355/475 = 0.75	(0.71, 0.78)	Borderline win

Reference Standard- Positive to Reference Standard-Negative Ratio*	Patient-Level PPV	95% CI	Study Win/Fail
50:50	329/475 = 0.69	(0.65, 0.73)	Fail
40:60	303/475 = 0.64	(0.59, 0.68)	Fail
30:70	277/475 = 0.58	(0.54, 0.63)	Fail
20:80	252/475 = 0.53	(0.49, 0.58)	Fail
10:90	226/475 = 0.48	(0.43, 0.52)	Fail
0:100	200/475 = 0.42	(0.38, 0.47)	Fail

Source: FDA statistical reviewer analysis.

* Among 258 patients with no reference standard results

Abbreviations: BCR = biochemical recurrence, CI = confidence interval, PPV = positive predictive value, PSMA = prostate-specific membrane antigen

The percentage of patients without reference standard data of 54% could be deemed high enough that a sensitivity analysis would provide limited insight into the impact of unavailable reference standard data on PPV in ITD patients. However, the reviewer opined that a 60%:40% ratio of reference standard positive to reference standard negative might be a conservative scenario considering the observed patient-level PPVs of 0.83 (lower bound of 95% confidence interval: 0.75) and 0.91 (lower bound of 95% confidence interval: 0.88) relative to histopathology and composite reference standard, respectively. Of important note, these estimates would not be valid if investigators intentionally referred patients whose PET-positive lesions were much more likely to be true positive to histopathology or conventional imaging follow-up.

A similar tipping point analysis was conducted on a region-level basis. There were 711 PET-positive regions from the ITD patients. Most patients had one or two PET-positive regions. Reference standard results were only available for 35% of ITD PET-positive regions (249/711): 90 by histopathology and 159 by conventional imaging follow-up. Therefore, the proportion of ITD PET-positive regions without standard reference results was 65% (462/711).

As shown in [Table 58](#), assuming 65% as reference standard positive and 35% as reference standard negative among 462 regions without reference standard data, the results produced a borderline study win, i.e., the lower bound of the 95% confidence interval of region-level PPV exceeded the pre-specified threshold of 0.70.

Table 58. Region-Level Tipping Point Analysis – PSMA-BCR

Reference Standard- Positive to Reference Standard-Negative Ratio*	Region-Level PPV	95% CI	Study Win/Fail
100:0	691/711 = 0.97	(0.96, 0.98)	Win
90:10	645/711 = 0.91	(0.88, 0.93)	Win
80:20	599/711 = 0.84	(0.81, 0.87)	Win
70:30	552/711 = 0.78	(0.74, 0.81)	Win
65:35	429/711 = 0.74	(0.71, 0.77)	Borderline win
60:40	506/711 = 0.71	(0.68, 0.74)	Fail
50:50	460/711 = 0.65	(0.61, 0.68)	Fail
40:60	414/711 = 0.58	(0.55, 0.62)	Fail

Reference Standard- Positive to Reference Standard-Negative Ratio*	Region-Level PPV	95% CI	Study Win/Fail
30:70	368/711 = 0.52	(0.48, 0.55)	Fail
20:80	321/711 = 0.45	(0.42, 0.49)	Fail
10:90	275/711 = 0.37	(0.35, 0.42)	Fail
0:100	229/711 = 0.32	(0.29, 0.36)	Fail

Source: FDA statistical reviewer analysis.

* Among 462 regions with no reference standard results

Abbreviations: BCR = biochemical recurrence, CI = confidence interval, PPV = positive predictive value, PSMA = prostate specific membrane antigen

In the reviewer's opinion, the proportion of ITD PET-positive regions without standard reference values of 65% was too high for this analysis to reliably provide insight into the impact of unavailable reference standard data on PPV in ITD patients, even considering the patient-level PPVs of 0.83 and 0.91 in patients with histopathology and composite reference standard data, respectively. A finer exploratory analysis is needed for region-level PPV.

Serum PSA level is a patient-level clinical factor that may be thought of as at least partially correlated with reference standard results, as higher PSA levels suggest more disease burden. Therefore, if BCR patients with higher PSA levels tended to be preferentially referred to histopathology or composite reference standard determination, PPV in the reported study results might overestimate the value that would have been obtained for ITD patients. [Table 59](#) shows the distribution of patients with respect to a range of PSA levels in histopathology versus composite reference standard versus no follow-up (patients with no reference standard results available). Patients with no follow-up included a relatively higher proportion of patients with PSA level ≤ 2 .

Table 59. Reference Standard Distribution in Patients With Respect to PSA Level

PSA Level (ng/mL)	Patients With Histology (% of Total)	Patients With Composite Reference Standard	
		Patients With Composite Reference Standard (% of Total)	Patients With No Follow-Up (% of Total)
≤ 0.5	6 (7%)	15 (7%)	37 (14%)
0.5 to ≤ 1	3 (3%)	17 (8%)	28 (11%)
1 to ≤ 2	11 (13%)	31 (14%)	44 (17%)
2 to ≤ 5	36 (41%)	72 (33%)	64 (25%)
> 5	31 (36%)	82 (38%)	85 (33%)
Total	87	217	258

Source: FDA statistical reviewer analysis.

Abbreviations: PSA = prostate-specific antigen

An exploratory analysis was conducted by imputing unavailable reference standard values with the lower bound of the 95% confidence interval of PPV among patients with composite reference standard results available in each PSA level category (the lowest possible PPV value based on available data in the group of interest) as shown in [Table 60](#). The PPV in ITD patients with imputation was evaluated successfully to be 0.86 (lower bound of 95% confidence interval: 0.82).

Table 60. Analysis by PSA Level Using PPV in Composite Reference Standard Patients

PSA Level (ng/mL)	PPV in Histology Patients (95% CI)	PPV in Composite Reference Standard Patients (95% CI)	Patients With No Follow-Up	Imputation Ratio	PPV (95% CI)
≤ 0.5	6/6 = 1.00 (0.61, 1)	15/15 = 1.00 (0.80, 1)	37	0.80	
0.5 to ≤ 1	1/3 = 0.67 (0.06, 0.79)	14/17 = 0.82 (0.59, 0.94)	28	0.59	
1 to ≤ 2	10/11 = 0.91 (0.62, 0.98)	30/31 = 0.97 (0.84, 0.99)	44	0.84	407/475 = 0.86 (0.82, 0.88)
2 to ≤ 5	28/36 = 0.78 (0.62, 0.88)	64/72 = 0.89 (0.80, 0.94)	64	0.80	
> 5	27/31 = 0.87 (0.71, 0.95)	77/82 = 0.94 (0.86, 0.97)	85	0.86	

Source: FDA statistical reviewer analysis.

Abbreviations: CI = confidence interval, PPV = positive predictive value, PSA = prostate-specific antigen

A similar exploratory analysis was conducted by imputing unavailable reference standard values with the lower bound of the 95% confidence interval of PPV among patients with histopathology results available in each PSA level category, as shown in [Table 61](#).

Table 61. Analysis by PSA Level Using PPV in Histopathology Patients

PSA Level (ng/mL)	PPV in Histology Patients (95% CI)	PPV in Composite Reference Standard Patients (95% CI)	Patients With No Follow-Up	Imputation Ratio	PPV (95% CI)
≤ 0.5	6/6 = 1.00 (0.61, 1)	15/15 = 1.00 (0.80, 1)	37	0.61	
0.5 to ≤ 1	1/3 = 0.67 (0.06, 0.79)	14/17 = 0.82 (0.59, 0.94)	28	0.06	
1 to ≤ 2	10/11 = 0.91 (0.62, 0.98)	30/31 = 0.97 (0.84, 0.99)	44	0.62	352/475 = 0.74 (0.70, 0.78)
2 to ≤ 5	28/36 = 0.78 (0.62, 0.88)	64/72 = 0.89 (0.80, 0.94)	64	0.62	
> 5	27/31 = 0.87 (0.71, 0.95)	77/82 = 0.94 (0.86, 0.97)	85	0.71	

Source: FDA statistical reviewer analysis.

Abbreviations: CI = confidence interval, PPV = positive predictive value, PSA = prostate-specific antigen

Note that use of PPV based on histopathology results as an imputation ratio might be a conservative approach that would have an unfavorable impact on the study results. Some sample sizes are less than 15 and, as such, confidence intervals are wide in 3 of the PSA level categories. The lower bound of PPV in the 0.5 - 1 PSA level category is 0.06, which may be unrealistic. Even under this imputation, the PPV in ITD patients with imputation was borderline with a lower bound of 95% confidence interval of 0.70.

Region location may also be thought of as a source of patient selection bias, as a patient whose

PET-positive lesion is located in a region that is easier to biopsy or image may be more likely to be referred for follow-up. [Table 62](#) shows the distribution of patients with respect to region locations in histopathology, composite reference standard, and no follow-up groups.

Table 62. Reference Standard Distribution in Patients With Respect to Region

Region	Regions in Histology Patients (% of Total)	Regions in Composite Reference Standard Patients (% of Total)	Regions in No Follow-Up Patients (% of Total)
Prostate bed	51 (57%)	62 (25%)	105 (23%)
Pelvis	19 (21%)	45 (18%)	196 (42%)
Extra-pelvis	19 (21%)	31 (12%)	121 (26%)
Bone	1 (1%)	110 (44%)	41 (9%)
Total	90	249	462

Source: FDA statistical reviewer analysis.

It is known that bone lesions are often difficult to biopsy. Accordingly, most PET-positive bone lesions were followed-up with conventional imaging rather than biopsied for histopathology. Conversely, prostate bed is more easily biopsied as reflected in the preponderance of histopathology in this region. Pelvic lymph nodes, however, can be difficult to biopsy or to document size change on imaging. As such, patients with no follow-up included a much higher proportion of pelvis regions than those in the histopathology and composite reference standard groups.

An exploratory analysis was conducted by imputing unavailable reference standard values with the lower bound of the 95% confidence interval of PPV among regions with reference standard results available in each region, as shown in [Table 63](#). The PPV in ITD patients with imputation was evaluated successfully to be 0.83 (lower bound of 95% confidence interval: 0.80).

Table 63. Analysis by Region Using PPV in Composite Reference Standard Patients

Region	PPV in Histology Patients (95% CI)	PPV in Composite Reference Standard Patients (95% CI)	Regions in No Follow-Up Patients	Imputation Ratio	PPV of (95%CI)
Prostate bed	39/51 = 0.76 (0.63, 0.86)	49/62 = 0.79 (0.67, 0.87)	105	0.67	590/711 = 0.83 (0.80, 0.86)
Pelvis	19/19 = 1.00 (0.83, 1)	43/45 = 0.96 (0.85, 0.99)	196	0.85	
Extra-pelvis	17/19 = 0.89 (0.69, 0.97)	27/31 = 0.87 (0.71, 0.95)	121	0.71	
Bone	1/1 = 1.00 (0.2, 1)	109/110 = 0.99 (0.95, 0.99)	41	0.95	

Source: FDA statistical reviewer analysis.

Abbreviations: CI = confidence interval, PPV = positive predictive value

A similar exploratory analysis was conducted by imputing unavailable reference standard values with the lower bound of the 95% confidence interval of PPV among patients with histopathology results available in each region, as shown in [Table 64](#). The PPV in ITD patients with imputation was evaluated successfully to be 0.77 (lower bound of 95% confidence interval:

0.74).

Table 64. Analysis by Region Using PPV in Histopathology Patients

Region	PPV in Histology	PPV in Composite	Regions in No Follow-Up Patients	Imputation Ratio	PPV (95% CI)
	Patients (95% CI)	Standard Patients (95% CI)			
Prostate bed	39/51 = 0.76 (0.63, 0.86)	49/62 = 0.79 (0.67, 0.87)	105	0.63	
Pelvis	19/19 = 1.00 (0.83, 1)	43/45 = 0.96 (0.85, 0.99)	196	0.83	549/711 = 0.77 (0.74, 0.80)
Extra- pelvis	17/19 = 0.89 (0.69, 0.97)	27/31 = 0.87 (0.71, 0.95)	121	0.69	
Bone	1/1 = 1.00 (0.20, 1)	109/110 = 0.99 (0.95, 0.99)	41	0.20	

Source: FDA statistical reviewer analysis.
Abbreviations: CI = confidence interval, PPV = positive predictive value

The Applicant’s response dated January 24, 2020, to the FDA’s Day-74 letter included an important statement regarding potential sources of patient selection bias. The Applicant stated that patients with low PSA frequently had PET-positive lesions that were sub-centimeter in size. In such cases, the Applicant further stated that the biopsies were often not performed due to procedural infeasibility.

This statement implies the possibility of systematic bias in selection of patients for reference standard follow-up. Specifically, patients with PET-positive lesions greater than a centimeter in size presumably were more often referred to biopsy than patients with subcentimeter lesions. A similar systematic bias can also be hypothesized for imaging follow-up, where correlative conventional imaging findings may be more difficult to demonstrate in tiny lesions.

The Applicant’s statement also invokes the related factor of PSA and its potential contribution to systematic bias in the selection of patients for reference standard follow-up. It is reasonable to hypothesize that PET-positive lesions in patients with higher PSA would be more likely to be true positive, thereby encouraging reference standard collection in these patients. The following tables examine these potential sources of systematic bias by focusing on sensitivity analysis of PPV in subcentimeter lesions at both relatively high PSA (> 2) and low PSA (≤ 2).

[Table 65](#) summarizes region-level PPV for subcentimeter lesions, assessed separately in patients with PSA level ≤ 2 ng/mL and PSA level > 2 ng/mL. PET-positive lesion size was defined to be the average of sizes calculated by three readers. There were only 96 regions where reference standard results and size data were available.

Table 65. Region-Level PPV for Subcentimeter Lesions by PSA Level

Condition	Regions With Reference Standard Result and Size Data Available	PPV (95% CI)
PSA ≤ 2 ng/mL PET-positive lesion size < 1 cm	34	32/34 = 0.94 (0.81, 0.98)
PSA > 2 ng/mL PET-positive lesion size < 1 cm	62	54/62 = 0.87 (0.77, 0.93)

Source: FDA statistical reviewer analysis.

Abbreviations: CI = confidence interval, PET = positron emission tomography, PPV = positive predictive value, PSA = prostate-specific antigen

Conservatively assuming that regions in no follow-up patients, regardless of their PSA levels, all had PET-positive lesions of subcentimeter size, an exploratory analysis was conducted by imputing unavailable reference standard values with the lower bound of the 95% confidence interval of region-level PPV in each corresponding condition category in Table 65. The PPV in ITD patients with imputation was evaluated successfully to be 0.83 (lower bound of 95% confidence interval: 0.80), as shown in [Table 66](#).

Table 66. Region-Level Analysis With Imputation Derived From Table 65

PSA Level	Regions With Reference Standard Results Available (True Positives)	Regions in No Follow-Up Population	Imputation Ratio	PPV of ITD Patients (95% CI)
PSA ≤ 2 ng/mL (assume maximum PET-positive lesion size < 1 cm)	70 (66)	156	0.81	591/711 = 0.83 (0.80, 0.86)
PSA > 2 ng/mL (assume maximum PET-positive lesion size < 1 cm)	179 (163)	306	0.77	

Source: FDA statistical reviewer analysis.

Abbreviations: CI = confidence interval, ITD = intent-to-diagnose, PET = positron emission tomography, PSA = prostate-specific antigen

Moving to patient-level evaluation of a similar exploratory analysis, [Table 67](#) summarizes PPV for patients with maximum lesion size of less than a centimeter, assessed separately in patients with PSA level ≤ 2 ng/mL and PSA level > 2 ng/mL. PET-positive lesion size was defined to be the average of sizes calculated by three readers. Only 93 patients had reference standard results and size data.

Table 67. Patient-Level PPV for Subcentimeter Lesions by PSA Level

Condition	Patients With Reference Standard Result and Size Data Available	PPV (95% CI)
PSA ≤ 2 ng/mL Maximum PET-positive lesion size < 1 cm	33	31/33 = 0.94 (0.80, 0.98)

Condition	Patients With Reference Standard Result and Size Data Available	PPV (95% CI)
PSA > 2 ng/mL Maximum PET-positive lesion size < 1 cm	60	52/60 = 0.87 (0.76, 0.93)

Source: FDA statistical reviewer analysis.

Abbreviations: CI = confidence interval, PET = positron emission tomography, PPV = positive predictive value, PSA = prostate-specific antigen

Conservatively assuming that patients with no follow-up, regardless of their PSA levels, all have PET-positive lesions of a maximum size of less than a centimeter, an exploratory analysis was conducted by imputing unavailable standard reference values with the lower bound of the 95% confidence interval of patient-level PPV in each corresponding condition category in Table 67. The PPV in ITD patients with imputation was evaluated successfully to be 0.84 (lower bound of 95% confidence interval: 0.81), as shown in [Table 68](#).

Table 68. Patient-Level Sensitivity Analysis With Imputation Derived From Table 67

PSA Level	Patients With Reference Standard Results Available (True Positives)	Patients With No Follow-Up	Imputation Ratio	PPV (95% CI)
PSA ≤ 2 ng/mL (assume maximum PET-positive lesion size < 1 cm)	63 (59)	109	0.80	400/475 = 0.84 (0.81, 0.87)
PSA > 2 ng/mL (assume maximum PET-positive lesion size < 1 cm)	154 (141)	149	0.76	

Source: FDA statistical reviewer analysis.

Abbreviations: CI = confidence interval, PET = positron emission tomography, PPV = positive predictive value, PSA = prostate-specific antigen

Since subcentimeter PET-positive lesions are difficult to biopsy and thus were not likely to be followed up for histopathology, it is useful to focus further on PPV in subcentimeter PET-positive lesions confirmed only by histopathology. [Table 69](#) summarizes region-level PPV using histopathology for subcentimeter lesions, assessed separately in patients with PSA level ≤ 2 ng/mL and PSA level > 2 ng/mL. Only 61 regions had histopathology results and size data.

Table 69. Region-Level PPV Using Histopathology for Subcentimeter Lesions by PSA Level

Condition	Regions With Histopathology Result and Size Data Available	PPV (95% CI)
PSA ≤ 2 ng/mL PET-positive lesion size < 1 cm	13	13/13 = 1.00 (0.72, 1.00)
PSA > 2 ng/mL PET-positive lesion size < 1 cm	48	42/48 = 0.86 (0.75, 0.94)

Source: FDA statistical reviewer analysis.

Abbreviations: CI = confidence interval, PET = positron emission tomography, PPV = positive predictive value, PSA = prostate-specific antigen

Conservatively assuming that regions in no follow-up patients, regardless of their PSA levels, all have PET-positive lesions of subcentimeter size, an exploratory analysis was conducted by imputing unavailable reference standard values with the lower bound of the 95% confidence interval of region-level PPV in each corresponding condition category in [Table 69](#). The PPV in ITD patients with imputation was evaluated successfully to be 0.81 (lower bound of 95% confidence interval: 0.78), as shown in [Table 70](#).

Table 70. Region-Level Sensitivity Analysis With Imputation Derived From Table 69

PSA Level	Regions With Reference Standard Results Available (True Positives)	Regions in No Follow-Up Patients	Imputation Ratio	PPV of ITD Patients (95% CI)
PSA ≤ 2 ng/mL (assume PET-positive lesion size < 1 cm)	70 (66)	156	0.72	571/711 = 0.80 (0.77, 0.83)
PSA > 2 ng/mL (assume PET-positive lesion size < 1 cm)	179 (163)	306	0.75	

Source: FDA statistical reviewer analysis.

Abbreviations: CI = confidence interval, ITD = intent-to-diagnose, PET = positron emission tomography, PSA = prostate-specific antigen

Moving to patient-level evaluation of a similar sensitivity analysis, [Table 71](#) summarizes PPV using histopathology for patients with maximum lesion size of less than a centimeter, assessed separately in patients with PSA level ≤ 2 ng/mL and PSA level > 2 ng/mL. Only 42 patients had histopathology results and size data.

Table 71. Patient-Level PPV Using Histopathology for Subcentimeter Lesions by PSA Level

Condition	Patients With Histopathology Result and Size Data Available	PPV (95% CI)
PSA ≤ 2 ng/mL Maximum PET-positive lesion size < 1 cm	13	13/13 = 1.00 (0.72, 1.00)
PSA > 2 ng/mL Maximum PET-positive lesion size < 1 cm	29	23/29 = 0.79 (0.62, 0.90)

Source: FDA statistical reviewer analysis.

Abbreviations: CI = confidence interval, PET = positron emission tomography, PPV = positive predictive value, PSA = prostate-specific antigen

Conservatively assuming that patients with no follow-up, regardless of their PSA levels, all have PET-positive lesions of a maximum size of less than a centimeter, an exploratory analysis was conducted by imputing unavailable reference standard values with the lower bound of 95% confidence interval of patient-level PPV in each corresponding condition category in [Table 71](#). The estimated PPV in the ITD patients based on the above imputation was 0.78 (lower bound of

95% confidence interval: 0.74), as shown in [Table 72](#).

Table 72. Patient-Level Sensitivity Analysis With Imputation Derived From Table 71

PSA Level	Patients With Reference Standard Results Available (True Positives)	Patients With No Follow-Up	Imputation Ratio	PPV (95% CI)
PSA ≤ 2 ng/mL (assume maximum PET-positive lesion size < 1 cm)	63 (59)	109	0.72	371/475 = 0.78 (0.74, 0.82)
PSA > 2 ng/mL (assume maximum PET-positive lesion size < 1 cm)	154 (141)	149	0.62	

Source: FDA statistical reviewer analysis.

Abbreviations: CI = confidence interval, PET = positron emission tomography, PPV = positive predictive value, PSA = prostate-specific antigen

In summary, based on data submitted in this NDA, it is recommended that ⁶⁸Ga-PSMA-11 be approved for PET of patients with biochemical recurrence. The primary efficacy endpoints of patient- and region-level PPVs confirmed by histopathology have been carefully evaluated. Even though the proportion of patients whose reference standard results were unavailable was high at 54% on a patient-level and 65% on a region-level, extensive analyses by imputation or with available subgroup data that explored potential factors that may have biased collection of reference standard information, such as PSA level, region location, and lesion size, consistently suggest a similar positive conclusion regarding patient- and region-level PPV in most of the imputed analyses. These supportive analyses appear to provide a reasonable level of confidence that the satisfactory PPV performance measured in the trial would be maintained in ITD patients with imputation.

Statistically, PPV alone without any counter measure such as NPV does not fully establish diagnostic performance. Therefore, the win criterion of a clinical study that focuses solely on PPV has to be carefully chosen. PPV and NPV are affected by the prevalence of disease, which is difficult to define in the biochemical recurrence setting since each patient can be considered inherently positive for disease. The prevalence of disease by region is even more challenging to define for assessment of PPV and NPV at region-level, as well as at lesion-level.

In the biochemical recurrence setting, the more important consideration is the prevalence of disease that can be successfully imaged, which will in turn be dependent on the imaging techniques that are used. In the PSMA-BCR study, of the 271 patients with baseline conventional imaging results available, 30% (24-35%) had their baseline conventional imaging interpreted as positive, and 44% (38-49%) had their baseline conventional imaging interpreted as either positive or equivocal. Of note, not all of these positive or equivocal interpretations were confirmed to be truly positive, so these rates overestimate actual disease that could be imaged by conventional techniques. These estimated rates of imaged disease are also similar to

those generally reported in the literature for conventional imaging in the setting of biochemical recurrence. While dependent on PSA level among other risk factors, the detection rate in the general BCR population has been estimated as <15% for both CT and bone scan (Kane et al. 2003; Okotie et al. 2004). Thus, the PPV goal of 0.70 for ⁶⁸Ga-PSMA-11 PET that was met in the PSMA-BCR trial appears to be clinically relevant as it is considerably higher than estimates of imaged disease using conventional techniques.

8.4. Conclusions and Recommendations

The review team finds the benefit of ⁶⁸Ga-PSMA-11 outweighs its risks. The Applicant has presented sufficient evidence to warrant the approval of ⁶⁸Ga-PSMA-11 for PET imaging of prostate cancer in patients with suspected metastasis who are candidates for initial definitive therapy or in whom recurrence is suspected based on elevated PSA levels.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting or other external consultation was needed for this NDA.

10 Pediatrics

Prostate cancer incidence is essentially zero in the pediatric population. Thus, it is not possible to conduct pediatric studies for the proposed indication. On January 16, 2019, the FDA Pediatric Review Committee agreed to grant a full waiver of pediatric studies.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Agreement between the Applicant and FDA was reached for the Prescribing Information. Highlights are summarized below, with particular emphasis on changes from the Applicant's initially submitted version.

Section 1. INDICATIONS AND USAGE

- Claims [REDACTED] (b) (4) were removed to more closely align with the submitted data.

- The indicated patient populations were defined as men with prostate cancer:
 - with suspected metastasis who are candidates for initial definitive therapy.
 - with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.

Section 2. DOSAGE AND ADMINISTRATION

- To improve clarity, the radioactivity dose was defined as a range of 3 mCi to 7 mCi (b) (4) An analogous change to a specified range of 50 to 100 minutes was made for the recommended time between drug injection and PET scan initiation.
- Consistent with the labeling of other PET drugs, instructions were added to handle ⁶⁸Ga PSMA-11 with appropriate safety measures to minimize radiation exposure. Use of the word “minimize” was deemed appropriate given the context and precedent in the labeling of other PET drugs.
- Use of a diuretic administered with the radiotracer to potentially reduce artifact from excreted material in the urinary tract was added as an option. This information was based on the use of a diuretic in the large majority of patients in the adequate and well-controlled trials.
- Criteria for determining whether radiotracer uptake could be considered suspicious for malignancy, based on criteria used in the adequate and well-controlled trials, were added to the Image Interpretation subsection.

Section 5. WARNINGS AND PRECAUTIONS

- Consistent with the labeling of other PET drugs approved for prostate cancer imaging, information about image interpretation error was added to convey that negative images do not rule out prostate cancer, and positive images do not confirm the presence of prostate cancer. Clinical correlation, which may include histopathological evaluation of the suspected prostate cancer site, was recommended.
- Consistent with the labeling of other PET drugs approved for prostate cancer imaging, language was added regarding the non-specificity of ⁶⁸Ga PSMA-11 for prostate cancer. Given the context, other information in the labeling, and precedent in the labeling of other PET drugs, it was not deemed necessary to qualify this language with a statement (b) (4)
- The potential for serum PSA level and location of disease to affect test performance in the biochemical recurrence population was added.
- The potential for Gleason score to affect test performance in patients imaged prior to initial definitive therapy was added.

Section 6. ADVERSE REACTIONS

- The most common ARs reported in the adequate and well-controlled trials were added (nausea, diarrhea, and dizziness).

Section 7. DRUG INTERACTIONS

- A statement was added to convey that androgen deprivation therapy as well as other therapies targeting the androgen pathway, such as androgen receptor antagonists, could affect the uptake of ⁶⁸Ga PSMA-11 in prostate cancer. It was also stated that the effect of these treatments on test performance has not been established.

Section 14. CLINICAL STUDIES

- Additional detail was provided for the study design and results of the PSMA-PreRP and PSMA-BCR studies.
- Description [REDACTED] (b) (4) was removed. While these provided supportive evidence, the numerical estimates of test performance provided by the adequate and well-controlled trials were considered more reliable and were included in the labeling.

12 Risk Evaluation and Mitigation Strategies

A risk evaluation and mitigation strategy is not needed for ⁶⁸Ga-PSMA-11.

13 Postmarketing Requirements and Commitment

No postmarketing requirement or commitment is recommended for this application.

14 Office Director (or Designated Signatory Authority) Comments

I concur with the review team's recommendation to approve Ga68-PSMA-11 for use in patients with prostate cancer as indicated in the approved labeling.

15 Appendices

15.1. References

Afshar-Oromieh, A, N Debus, M Uhrig, TA Hope, MJ Evans, T Holland-Letz, FL Giesel, K Kopka, B Hadaschik, C Kratochwil, and U Haberkorn, 2018, Impact of long-term androgen deprivation therapy on PSMA ligand PET/CT in patients with castration-sensitive prostate cancer, *Eur J Nucl Med Mol Imaging*, 45(12):2045-2054.

Afshar-Oromieh, A, H Hetzheim, W Kubler, C Kratochwil, FL Giesel, TA Hope, M Eder, M Eisenhut, K Kopka, and U Haberkorn, 2016, Radiation dosimetry of (68)Ga-PSMA-11 (HBED-CC) and preliminary evaluation of optimal imaging timing, *Eur J Nucl Med Mol Imaging*, 43(9):1611-1620.

Afshar-Oromieh, A, A Malcher, M Eder, M Eisenhut, HG Linhart, BA Hadaschik, T Holland-Letz, FL Giesel, C Kratochwil, S Haufe, U Haberkorn, and CM Zechmann, 2013, PET imaging with a [68Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions, *Eur J Nucl Med Mol Imaging*, 40(4):486-495.

Andriole, GL, L Kostakoglu, A Chau, F Duan, U Mahmood, DA Mankoff, DM Schuster, BA Siegel, and LS Group, 2019, The impact of Positron Emission Tomography with 18F-Fluciclovine on the treatment of biochemical recurrence of prostate cancer: Results from the LOCATE trial, *J Urol*, 201(2):322-331.

Batra, V, G Gautam, J Jaipuria, M Suryavanshi, R Khera, and R Ahlawat, 2015, Predictive factors for lymph node positivity in patients undergoing extended pelvic lymphadenectomy during robot assisted radical prostatectomy, *Indian J Urol*, 31(3):217-222.

Bergeron, RJ, J Wiegand, and GM Brittenham, 2002, HBED ligand: preclinical studies of a potential alternative to deferoxamine for treatment of chronic iron overload and acute iron poisoning, *Blood*, 99(8):3019-3026.

Bostwick, DG, A Pacelli, M Blute, P Roche, and GP Murphy, 1998, Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases, *Cancer*, 82(11):2256-2261.

Bravaccini, S, M Puccetti, M Bocchini, S Ravaioli, M Celli, E Scarpi, U De Giorgi, MM Tumedei, G Raulli, L Cardinale, and G Paganelli, 2018, PSMA expression: a potential ally for the pathologist in prostate cancer diagnosis, *Sci Rep*, 8(1):4254.

Caglic, I, V Kovac, and T Barrett, 2019, Multiparametric MRI - local staging of prostate cancer and beyond, *Radiol Oncol*, 53(2):159-170.

Castellucci, P, C Fuccio, C Nanni, I Santi, A Rizzello, F Lodi, A Franceschelli, G Martorana, F Manferrari, and S Fanti, 2009, Influence of trigger PSA and PSA kinetics on ¹¹C-Choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy, *J Nucl Med*, 50(9):1394-1400.

Chang, SS, VE Reuter, WD Heston, NH Bander, LS Grauer, and PB Gaudin, 1999, Five different anti-prostate-specific membrane antigen (PSMA) antibodies confirm PSMA expression in tumor-associated neovasculature, *Cancer Res*, 59(13):3192-3198.

Cookson, MS, G Aus, AL Burnett, ED Canby-Hagino, AV D'Amico, RR Dmochowski, DT Eton, JD Forman, SL Goldenberg, J Hernandez, CS Higano, SR Kraus, JW Moul, C Tangen, JB Thrasher, and I Thompson, 2007, Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes, *J Urol*, 177(2):540-545.

D'Amico, AV, R Whittington, SB Malkowicz, D Schultz, K Blank, GA Broderick, JE Tomaszewski, AA Renshaw, I Kaplan, CJ Beard, and A Wein, 1998, Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer, *JAMA*, 280(11):969-974.

Eder, M, O Neels, M Muller, U Bauder-Wust, Y Remde, M Schafer, U Henrich, M Eisenhut, A Afshar-Oromieh, U Haberkorn, and K Kopka, 2014, Novel preclinical and radiopharmaceutical aspects of [⁶⁸Ga]Ga-PSMA-HBED-CC: A new PET tracer for imaging of prostate cancer, *Pharmaceuticals (Basel)*, 7(7):779-796.

Eder, M, M Schafer, U Bauder-Wust, WE Hull, C Wangler, W Mier, U Haberkorn, and M Eisenhut, 2012, ⁶⁸Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging, *Bioconjug Chem*, 23(4):688-697.

Emmett, L, C Yin, M Crumbaker, G Hruby, A Kneebone, R Epstein, Q Nguyen, A Hickey, N Ihsheish, G O'Neill, L Horvath, V Chalasani, P Stricker, and AM Joshua, 2019, Rapid modulation of PSMA expression by androgen deprivation: Serial (⁶⁸Ga)-PSMA-11 PET in men with hormone-sensitive and castrate-resistant prostate cancer commencing androgen blockade, *J Nucl Med*, 60(7):950-954.

Heck, MM, M Souvatzoglou, M Retz, R Nawroth, H Kubler, T Maurer, M Thalgott, BM Gramer, G Weirich, IC Rondak, EJ Rummeny, M Schwaiger, JE Gschwend, B Krause, and M Eiber, 2014, Prospective comparison of computed tomography, diffusion-weighted magnetic resonance imaging and [¹¹C]choline positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer patients, *Eur J Nucl Med Mol Imaging*, 41(4):694-701.

Hofman, MS, RJ Hicks, T Maurer, and M Eiber, 2018, Prostate-specific membrane antigen PET: Clinical utility in prostate cancer, normal patterns, pearls, and pitfalls, *Radiographics*, 38(1):200-217.

Hope, TA, JZ Goodman, IE Allen, J Calais, WP Fendler, and PR Carroll, 2019, Metaanalysis of (68)Ga-PSMA-11 PET accuracy for the detection of prostate cancer validated by histopathology, *J Nucl Med*, 60(6):786-793.

Humphrey, PA, 2017, Histopathology of prostate cancer, *Cold Spring Harb Perspect Med*, 7(10).

Kane, CJ, CL Amling, PA Johnstone, N Pak, RS Lance, JB Thrasher, JP Foley, RH Riffenburgh, and JW Moul, 2003, Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy, *Urology*, 61(3):607-611.

Kratochwil, C, A Afshar-Oromieh, K Kopka, U Haberkorn, and FL Giesel, 2016, Current status of prostate-specific membrane antigen targeting in Nuclear Medicine: Clinical translation of chelator containing prostate-specific membrane antigen ligands into diagnostics and therapy for prostate cancer, *Semin Nucl Med*, 46(5):405-418.

Lenzo, NP, D Meyrick, and JH Turner, 2018, Review of gallium-68 PSMA PET/CT imaging in the management of prostate cancer, *Diagnostics (Basel)*, 8(1).

Leventis, AK, SF Shariat, and KM Slawin, 2001, Local recurrence after radical prostatectomy: correlation of US features with prostatic fossa biopsy findings, *Radiology*, 219(2):432-439.

Liss, MA, K Palazzi, SP Stroup, R Jabaji, OA Raheem, and CJ Kane, 2013, Outcomes and complications of pelvic lymph node dissection during robotic-assisted radical prostatectomy, *World J Urol*, 31(3):481-488.

Mohler, JL, ES Antonarakis, AJ Armstrong, AV D'Amico, BJ Davis, T Dorff, JA Eastham, CA Enke, TA Farrington, CS Higano, EM Horwitz, M Hurwitz, JE Ippolito, CJ Kane, MR Kuettel, JM Lang, J McKenney, G Netto, DF Penson, ER Plimack, JM Pow-Sang, TJ Pugh, S Richey, M Roach, S Rosenfeld, E Schaeffer, A Shabsigh, EJ Small, DE Spratt, S Srinivas, J Tward, DA Sheehy, and DA Freedman-Cass, 2019, Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology, *J Natl Compr Canc Netw*, 17(5):479-505.

Okotie, OT, WJ Aronson, JA Wieder, Y Liao, F Dorey, KJ De, and SJ Freedland, 2004, Predictors of metastatic disease in men with biochemical failure following radical prostatectomy, *J Urol*, 171(6 Pt 1):2260-2264.

Pfob, CH, S Ziegler, FP Graner, M Kohner, S Schachoff, B Blechert, HJ Wester, K Scheidhauer, M Schwaiger, T Maurer, and M Eiber, 2016, Biodistribution and radiation dosimetry of (68)Ga-PSMA HBED CC-a PSMA specific probe for PET imaging of prostate cancer, *Eur J Nucl Med Mol Imaging*, 43(11):1962-1970.

Poulsen, MH, H Petersen, PF Hoiland-Carlsen, JS Jakobsen, O Gerke, J Karstoft, SI Steffansen, and S Walter, 2014, Spine metastases in prostate cancer: Comparison of technetium-99m-MDP whole-body bone scintigraphy, [(18) F]choline positron emission tomography(PET)/computed tomography (CT) and [(18) F]NaF PET/CT, *BJU Int*, 114(6):818-823.

Prasad, V, IG Steffen, G Diederichs, MR Makowski, P Wust, and W Brenner, 2016, Biodistribution of [(68)Ga]PSMA-HBED-CC in patients with prostate cancer: Characterization of uptake in normal organs and tumour lesions, *Mol Imaging Biol*, 18(3):428-436.

Ray Banerjee, S, Z Chen, M Pullambhatla, A Lisok, J Chen, RC Mease, and MG Pomper, 2016, Preclinical comparative study of (68)Ga-labeled DOTA, NOTA, and HBED-CC chelated radiotracers for targeting PSMA, *Bioconjug Chem*, 27(6):1447-1455.

Roach, M, 3rd, G Hanks, H Thames, Jr., P Schellhammer, WU Shipley, GH Sokol, and H Sandler, 2006, Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference, *Int J Radiat Oncol Biol Phys*, 65(4):965-974.

Salas Fragomeni, RA, T Amir, S Sheikhabahaei, SC Harvey, MS Javadi, LB Solnes, AP Kiess, ME Allaf, MG Pomper, MA Gorin, and SP Rowe, 2018, Imaging of nonprostate cancers using PSMA-targeted radiotracers: Rationale, current state of the field, and a call to arms, *J Nucl Med*, 59(6):871-877.

Sandgren, K, L Johansson, J Axelsson, J Jonsson, M Ogren, M Ogren, M Andersson, S Strandberg, T Nyholm, K Riklund, and A Widmark, 2019, Radiation dosimetry of [(68)Ga]PSMA-11 in low-risk prostate cancer patients, *EJNMMI Phys*, 6(1):2.

Sathekge, M, T Lengana, A Maes, M Vorster, J Zeevaart, I Lawal, T Ebenhan, and C Van de Wiele, 2018, (68)Ga-PSMA-11 PET/CT in primary staging of prostate carcinoma: preliminary results on differences between black and white South-Africans, *Eur J Nucl Med Mol Imaging*, 45(2):226-234.

Schafer, M, U Bauder-Wust, K Leotta, F Zoller, W Mier, U Haberkorn, M Eisenhut, and M Eder, 2012, A dimerized urea-based inhibitor of the prostate-specific membrane antigen for ⁶⁸Ga-PET imaging of prostate cancer, *EJNMMI Res*, 2(1):23.

Siegel, RL, KD Miller, and A Jemal, 2019, Cancer statistics, 2019, *CA Cancer J Clin*, 69(1):7-34.

Silver, DA, I Pellicer, WR Fair, WD Heston, and C Cordon-Cardo, 1997, Prostate-specific membrane antigen expression in normal and malignant human tissues, *Clin Cancer Res*, 3(1):81-85.

van Kalmthout, LWM, HE van Melick, J Lavalaye, RP Meijer, A Kooistra, JMH de Klerk, A Braat, HP Kaldewey, PC de Bruin, B de Keizer, and M Lam, 2019, Prospective validation of gallium-68

prostate specific membrane antigen-positron emission tomography/computerized tomography for primary staging of patients with prostate cancer, J Urol, 203(3):537-545.

von Eyben, FE, M Picchio, R von Eyben, H Rhee, and G Bauman, 2018, (68)Ga-labeled prostate-specific membrane antigen ligand positron emission tomography/computed tomography for prostate cancer: A systematic review and meta-analysis, Eur Urol Focus, 4(5):686-693.

Wang, Y, G Shao, J Wu, C Cui, S Zang, F Qiu, R Jia, Z Wang, and F Wang, 2018, Preparation of (68)Ga-PSMA-11 with a synthesis module for micro PET-CT imaging of PSMA expression during prostate cancer progression, Contrast Media Mol Imaging, 2018:8046541.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): PSMA-PreRP

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>31</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>18</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): PSMA-BCR

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>20</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>7</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DIANE C HANNER
11/23/2020 03:01:58 PM

SUNNY O AWE
11/23/2020 03:05:30 PM

ADEBAYO A LANIYONU
11/23/2020 03:10:56 PM

CHRISTY S JOHN
11/23/2020 03:18:30 PM

NAM ATIQR RAHMAN
11/23/2020 03:38:08 PM

SHANE C MASTERS
11/23/2020 03:40:40 PM

AUGUST A HOFLING
11/23/2020 03:43:57 PM

YANG YANG
11/23/2020 03:45:09 PM

SUNGWON N LEE
11/23/2020 03:56:26 PM

JYOTI ZALKIKAR
11/23/2020 04:12:18 PM

SUE JANE WANG
11/23/2020 04:17:13 PM

LIBERO L MARZELLA
11/23/2020 04:43:53 PM

ALEXANDER GOROVETS
11/23/2020 05:14:14 PM