CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215833Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	133661
Request Receipt Date	04/19/2021
Product	177Lu-PSMA-617
Indication	for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy (ARDT) and taxane-based chemotherapy
Drug Class/Mechanism of Action	Beta-emitting radiopharmaceutical bound to an anti-PSMA small molecule
Sponsor	Advanced Acclelerator Applications, a Novartis company
ODE/Division	OOD/DO1
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and*** *will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR)****.*** *Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

The proposed indication is for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy (ARDT) and taxane-based chemotherapy.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES **X**NO

3. **Was the BTDR submitted to a PIND?** ☐YES **X**NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? **X**YES ☐NO

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

X YES, the BTDR is adequate and sufficiently complete to permit a substantive review

☐ Undetermined

☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐

ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐

v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Drug

177Lu-PSMA-617 is a small molecule PSMA-targeted radioligand therapy. The non-radioactive precursor molecule has a PSMA binding motif and a DOTA-chelator connected by a linker. The drug has a high PSMA-specific binding. Once bound, it is internalized, with a high degree of tumor retension. The radioligand, Lutetium 177 (177Lu), is a beta emitter with a half life of 6.7 days and a mean range of the beta particles of 0.7 mm in soft tissue (maximum range is 2.1 mm).

Disease and intended population

Prostate cancer is the most common solid tumor in US men and is the second leading cause of cancer death among US men. In 2019, an estimated 174,650 new cases of prostate cancer will be diagnosed and 31,620 deaths will occur in the US [1]. Typically, men dying of prostate cancer have metastatic castrate-resistent disease (mCRPC). Multiple mechanisms have been implicated in the development of castrate resistence. However, the androgen receptor (AR) pathway frequently remains activated in mCRPC, and AR signaling remains a therapeutic target early in the development of castrate resistence. Both of the AR-directed agents abiraterone and enzalutamide have demonstrated an overall survival benefit vs placebo in men with mCRPC and are approved for treatment in this setting either following docetaxel chemotherapy [2 3] or in the chemotherapy-naïve setting[4 5]. Ultimately, resistance develops to these second generation AR-targeted therapies. Both docetaxel[6] and cabazitaxel [7] have demonstrated a statistically significant OS improvement of approximately 3 months vs mitoxantrone plus prednisone/prednisolone in the second or third-line setting in men with mCRPC. Both taxanes can be toxic, and in this elderly patient population, many patients are not candidates for these therapies. In men with asymptomatic or minimally symptomatic mCRPC, Sipuleucil-T, a therapeutic cancer vaccine, produced a 4 month overall survival advantage vs placebo and was approved for use in this population by FDA. Finally, in men with mCRPC involving bone without visceral metastases, the calcium mimetic alpha particle emitter Radium-223 demonstrated a 3 month OS benefit vs placebo, and was approved for use by FDA in this patient population. However, for many patients with mCRPC who have progressed after AR-directed therapy and a taxane, there is no good therapy available.

Prostate specific membrane antigen (PSMA) is a transmembrane protein expressed on prostate cancer cells. PSMA is overexpressed in prostate cancer, but it is also expressed at much lower levels in some normal tissues, e.g., small bowel, kidney, salivary and lacrimal glands. Expression in the tumor tends to increase as prostate cancer becomes more advanced, with the highest expression tending to occur in advanced, high-grade metastatic castrate resistant disease. Thus, PSMA provides a potential target for both imaging and therapy of advanced prostate cancers.

Regulatory history

A previous preliminary request for BTD was made by Endocyte, Inc., another Novartis company who has assumed responsibility for IND 133661, and a telephone conference was held 12/11/2017. At that time the request was denied by FDA, due to insufficient clinical data. A second formal BTD request was made on 08/12/2020 but was denied again for insufficient clinical data to determine whether 177Lu-PSMA-617 demonstrated substantial benefit over existing therapies on one or more clinically significant endpoints.

After commencement of the VISION trial, a discussion was held with FDA on 8/16/2018 resulting in the addition of rPFS as an alternative primary endpoint. Following the initiation of enrollment, a high early drop-out rate in the BSC arm became evident, mostly due to withdrawal of consent to follow-up. Thus, rPFS data could not be collected on these patients, which could bias the rPFS analysis. Remedial measures were instituted and made effective 3/5/2019. The primary endpoint of rPFS was altered to focus only on patients prospectively

randomized after 3/5/2019. The OS analysis was planned on an intent to treat basis and includes all randomized patients, including those randomized before 3/5/2019. FDA agreed to this plan on 5/2/2019.

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The alternate primary endpoints were radiographic progression-free survival (rPFS) or overall survival (OS). The study was to be considered positive if either primary endpoint was achieved. Key secondary endpoints included overall response rate (ORR) based on independent central review per RECIST v1.1, duration of response (DOR), disease control rate (DCR) based on independent central review per RECIST v1.1, and time to first skeletal event (SSE).

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

Overall survival is the preferred clinically significant accepted by the division for patients with this disease. rPFS by blinded independent radiologic review per RECIST v1.1 and PCWG3 criteria is a clinically significant endpoint accepted by the division for patients with this disease.

Overall response rate is an intermediate endpoint that usually correlates with drug activity and is often used to support accelerated approval, with careful consideration given to a demonstrated adequate duration of response and reasonable toxicity profile for the clinical setting. Confirmatory trials to verify the clinical benefit usually are randomized trials with overall survival as the endpoint representing clinical benefit.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

The following is a summary of phase 3 randomized trials for the 2nd and 3rd-line agents currently approved for the treatment of men with metastatic castrate resistant prostate cancer.The docetaxel study as first line therapy is 4

included for point of reference. Data are presented in Table 1 for the primary efficacy endpoints of the respective trials. Although these agents have been demonstrated to produce a statistically significant overall survival advantage versus standard of care or placebo, the actual duration of survival prolongation vs. the control arm is short, i.e., in the range of 3-4 months. In addition, the likelihood and duration of response decreases through later lines of therapy. Finally, many patients in this population are too infirm to tolerate taxane-based chemotherapy due to the associated toxicity. Thus, additional effective therapies are needed for men with mCRPC who have progressed through 2nd line therapies.

Table 1: Summary of 2nd and 3rd Line Therapies for Metastatic Castrate-Resistent Prostate Cancer

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
cabazitaxel	mCRPC after doectaxel	25 mg/m^{2}IV every 3 weeks with prednisone 10 mg po daily	Median overall survival 15.1 months vs 12.7 months vs mitoxantrone + prednisone; ORR 14.4% vs 4.4% (HR & CI not given, P0.0005)	Significantly higher incidence of TEAEs grade 3-4 with cabazitaxel (both hematologic and non-hematologic; requires growth factor support)	OS HR: 0.70; 95% CI 0.59-0.83; P<0.0001; PFS 2.8 vs 1.4 months (HR: 0.74, 95% CI 0.64-0.86; P<0.0001) [7]
docetaxel	mCRPC	75 mg/m^2 IV every 3 weeks with prednisone 5mg BID	Median overall survival 19.2 months vs 16.3 months for mitoxantrone + prednisone	Significantly more Grade 3-4 AEs with docetaxel	HR, 0.79; 95% CI 0.67-0.93; P=0.004; [6]
Radium-223	CRPC with symptomatic bone metastases and no known visceral disease	55 kBq/kg every 4 weeks for up to 6 injections	Median OS 14.9 months vs 11.3 months for placebo	Bone marrow suppression, increased fracture risk with Abiraterone, embryo fetal toxicity, nausea, vomiting, diarrhea and peripheral edema	HR, 0.70; 95% CI 0.58-0.83, P<0.001. [8]
Sipuleucel-T	Asymptomatic or minimally symptomatic mCRPC	At least 50 million autologous CD54+ cells activated with PAP-GM-CSF, suspended in	Median OS 25.8 months vs 21.7 months for placebo	Chills, fatigue, fever, back pain, nausea, joint ache, headache	HR, 0.775; 95% CI 0.61-0.98, P=0.032 [9]

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
		250 mL of Lactated Ringer's Injection; 3 doses given at approximately 2 week intervals			

For third line therapies, i.e., for those patients who have progressed after prior docetaxel and a novel antiandrogen (e.g., abiraterone or enzalutamide), the preferred regimens per NCCN 2021 guidelines are cabazitaxel (see table above) or docetaxel rechallenge if the patient did not demonstrate definitive evidence of progression on prior docetaxel therapy in the castrate-sensitive setting.

In addition, 2 PARP inhibitors, rucaparib and olaparib are approved for men with mCRPC, but only for those with germline and/or somatic BRCA mutations (rucaparib) or other homologous recombination repair mutations in addition to BRCA in the case of olaparib. Men with these genetic alterations represent only a small subset of the mCRPC population, on the order of 20%. Olaparib may be used even in patients who have not received a taxane. Mitoxantrone/prednisone may be used for palliation in symptomatic patients who cannot tolerate other therapies. Radium-223 may be used for patients with symptomatic bone metastases. Pembrolizumab may be used for patients with microsatellite instability-high or DNA mismatch repair deficient tumors, but few patients with mCRPC meet these criteria.

Other hormonal therapy options may be considered for patients who do not meet specific qualifications for treatment with a PARP inhibitor, immune checkpoint inhibitor or other treatments listed in the table above (Radium and Sipuleucel-T). These options include abiraterone for those who have received enzalutamide, and enzalutamide for those who have received abiraterone, ketoconazole (usually with hydrocortisone), first generation anti-androgens (nilutamide, flutamide, or bicalutamide), corticosteroids (hydrocortisone, prednisone or methylprednisolone), estrogens including diethylstilbestrol and antiandrogen withdrawal. Response rates would be expected to be low (<5%) and of short duration.

In patients unable or unwilling to receive a taxane, and not qualified for one of the PARP inhibitors or Pembrolizumab, the sequencing of these agents is a matter of debate, with no clear evidence supporting the use of one over another.

Currently, it is possible that the newer androgen receptor antagonists daralutamide and apalutamide might be used off-label for third line therapy for mCRPC, the proposed indication for 177Lu-PSMA-617. Both are approved for CRPC without metastases detected on conventional imaging (i.e., bone scans, CT scans, MRIs, but not solely by PSMA targeted scans), but not for patients with CRPC and detectable metastases. Additionally, Radium-223 might be used off-label for men with symptomatic bone metastases and other known sites of disease and Sipuleucil-T might be used for men with non-minimally symptomatic mCRPC. The use of ketoconazole, estrogens, and/or steroids in this setting is considered off-label, although recommended as an alternative by national guidelines (NCCN 2021).

The response rates for these agents in the third line setting would be expected to be lower than that noted in the table above for second line treatments (<5%), and of shorter duration. The exception to that statement may be the PARP inhibitors and Pembrolizumab, but only for the narrow patient populations with the mutations for which these drugs were approved noted above.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that

requested breakthrough therapy designation[3].

At present there are no other drugs being studied for the same indication or similar indications that requested breakthrough therapy designation.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The VISION study supports the BTDR. It is an Endocyte-sponsored phase 3, open-label, international, randomized study to evaluate the safety and efficacy of 177Lu-PSMA-617 in patients with progressive PSMA-positive mCPRC who had progressed on a next generation androgen signaling inhibitor (abiraterone or enzalutamide) and 1-2 taxane regimens, when administered with best supportive care/best standard of care (BSC) vs best supportive care/best standard of care (BSC) alone. BSC was investigator-determined, but excluded cytotoxic chemotherapy, investigational agents, immunotherapy and systemic radioisotopes. BSC had to be determined before randomization. A wide range of options were permitted, including ketoconazole, estrogens, LHRH analogues, corticosteroids, 5-alpha reductase inhibitors, 1st and 2nd generations anti-androgens, targeted radiation therapy (external beams, brachytherapy and Y90 selective internal radiation therapy to the liver) and bone targeted agents such as bisphosphonates. PSMA positivity was determined by central review of 68Ga-PSMA-11 scans.

The study diagram is presented below:

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

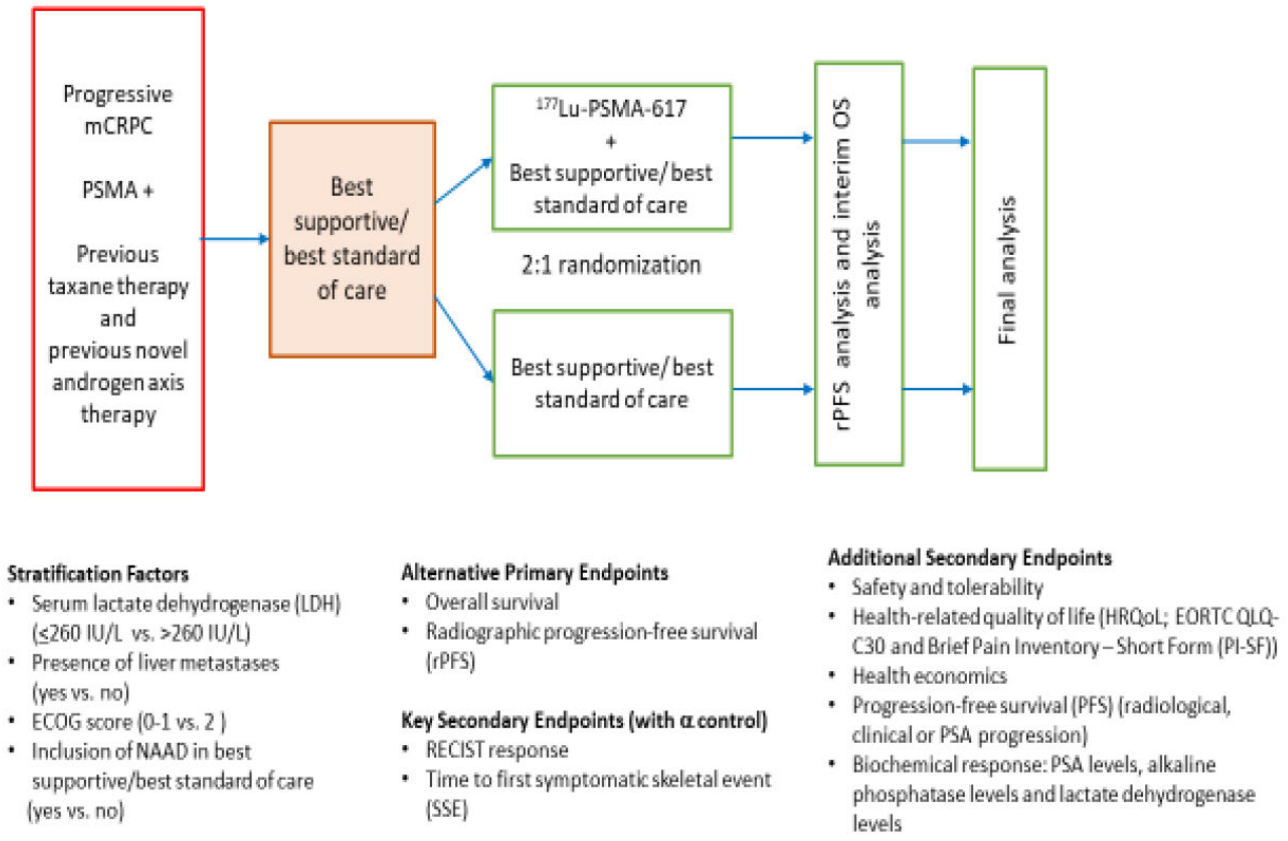


Figure 1 Diagram of trial design

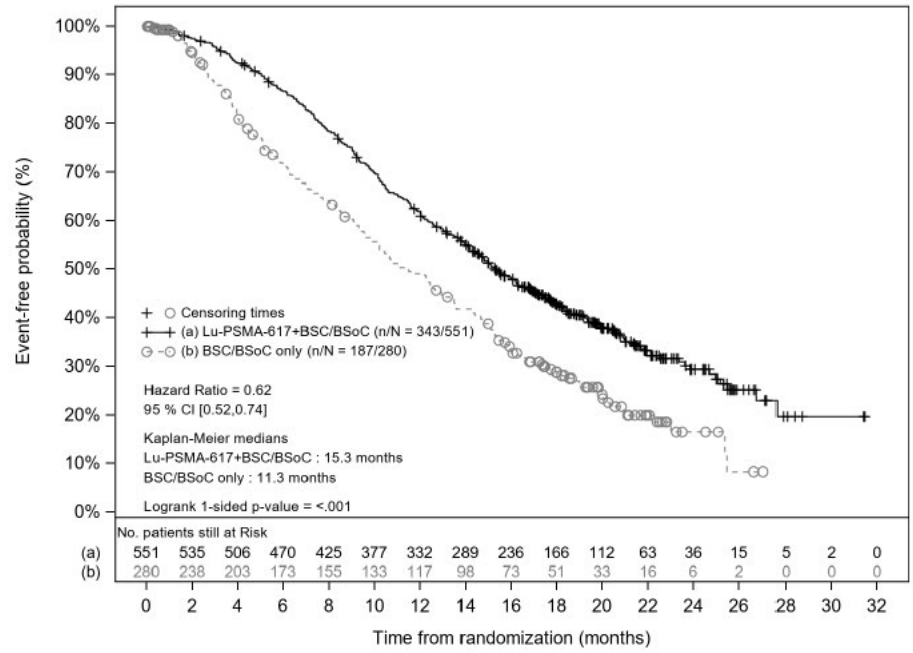
ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

Source: Sponsor's protocol version 2.0; 01/16/2019

Between 6/4/2018 and 10/23/2019, 1003 patients underwent 68Ga-PSMA-11PET/CT screening and 869 (87%) met the criteria for enrollment (at least 1 PSMA-positive lesion and no PSMA-negative lesions). 831 patients were randomized 2:1 to receive 177Lu-PSMA-617 plus BSC vs BSC alone. 177Lu-PSMA-617 was given at a dose of 7.4 GBq every 6 weeks for up to 6 cycles. Patients were assessed after 4 cycles to determine if they qualified for 2 additional cycles (showed evidence of response and had signs of residual disease on conventional imaging and has shown good tolerance of 177Lu-PSMA-617). The cutoff date for efficacy analysis was 1/27/2021, corresponding to a median follow-up of 20.9 months.

Although the study was designed to be positive if it met either of the primary endpoints of rPFS or OS, the study met both of its primary efficacy endpoints. The median OS (95% CI) was 15.3 months (14.2,16.9) vs 11.3 months (9.8, 13.5) for 177Lu-PSMA-617+BSC vs BSC only, HR 0.62, 95% CI 0.52, 0.74; p<0.001.

Figure 5-1 Kaplan-Meier plot of overall survival (Full analysis set)

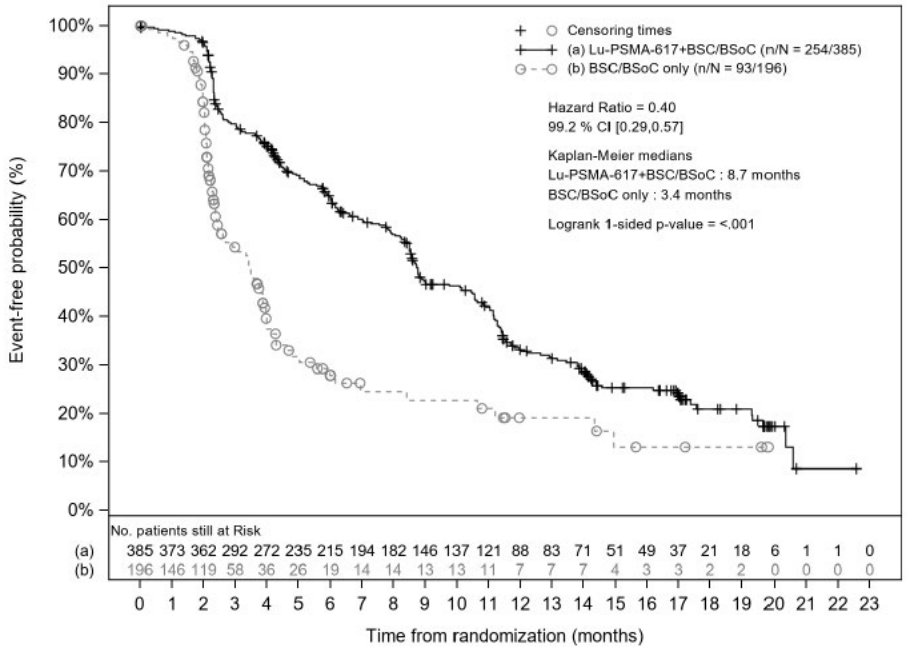


Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.

n/N: Number of events/number of patients in treatment arm.

The median rPFS (99.2% CI) by independent central review (PCWG3 criteria) was 8.7 months (7.9, 10.8) vs 3.4 months (2.4, 4.0), for the 177Lu-PSMA-617+BSC vs BSC arm (HR 0.40, 99.2% CI 0.29, 0.57; p<0.001).

Figure 5-2 Kaplan-Meier plot of radiographic progression-free survival based on independent central review (PFS-Full analysis set)



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.

n/N: Number of events/number of patients in treatment arm.

The study also met its secondary endpoints.

ORR in the 177Lu-PSMA-617+BSC arm was 29.8% vs 1.7% in the BSC arm (odds ratio 24.99; 95% CI 6.05, 103.24. The median DOR was 9.8 months (95% CI 9.1, 11.7) in the 177Lu-PSMA-617+BSC vs 10.6 months in the BSC arm (95% CI NE since there were only 2 responders in this arm). The median time to SSE was 11.5 months (95% CI 10.3, 13.2) in the 177Lu-PSMA-617+BSC arm vs 6.8 months (5.2, 8.5) in the BSC arm, HR 0.50, 95% CI 0.40, 0.62; p<0.001).

Considering pre-specified subgroup, efficacy in patients receiving a next generation anti-androgen as part of BSC/BSoC was analyzed. This treatment was received by 57% in the 177Lu-PSMA-617+BSC/BSoC arm and 66% in the BSC/BSoC arm. The results are as follows: OS (median, 95% CI): 177Lu+BSC 17.8 months (15.7, 20.6) vs BSC 13.3 monthss (10.7, 15.1); HR 0.55 (95% CI 0.43, 0.70); rPFS (median, 95% CI) :177Lu+BSC 10.2 months (8.5, 11.2) vs BSC 3.9 months (3.1, 5.6); HR (95% CI) 0.46 (0.33, 0.65); ORR 177Lu+BSC 28.3% vs BSC 2.3%; DoR 177Lu+BSC 10.3 months (8.3, 18.0) vs BSC 2.3 months.

Efficacy was also compared by the number of lines of taxanes received (1 vs 2 or more). The results are as follows: 1 taxane was received by 66% in 177Lu+BSC arm vs 59% in BSC arm and ≥2 taxanes were received by 33% in 177Lu+BSC arm vs 41% in BSC arm. OS (median, 95% CI) for those receiving 1 taxane was: 177Lu+BSC 16.2 months (14.7, 18.1) vs BSC 11.8 months (9.8, 14.4); HR (95% CI) 0.59 (0.46, 0.75) and for those receiving ≥2 taxanes was: 177Lu+BSC 13.6 months (11.5, 15.4) vs BSC 10.6 months (8.3, 13.5); HR (95% CI) 0.73 (0.53, 0.99). rPFS for those receiving 1 taxane was 177Lu+BSC 8.9 months (8.5, 11.0) vs BSC 3.4 months (2.4, 4.0); HR (95% CI) 0.39 (0.27, 0.54) and for those receiving ≥2 taxanes was 177Lu+BSC 8.3 months (6.2, 10.4) vs BSC 3.5 months (2.2, 4.0); HR (95% CI) 0.44 (0.30, 0.66). The ORR for those receiving 1 taxane was 177Lu+BSC 25.1% vs BSC 1.6% and the DoR for 177Lu+BSC was 9.8 months (8.2, 18.0). The ORR for those receiving ≥2 taxanes was 177Lu+BSC 34.6% vs BSC 1.6% and the DOR for 177Lu+BSC was 9.8 months (7.2, 11.0).

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

The data provided should be considered preliminary evidence of a substantial improvement over available therapies. The control arm included active treatment comparators, which lends support to the conclusion of benefit in the study arm. Although some patients in this trial might have been eligible for a PARP inhibitor or pembrolizumab if MSI-H, these represent only a small minority of this patient population. Also, neither PARP inhibitor was approved for this indication at the time of patient enrollment in the VISION trial. The expression of PSMA was detected in 87% of patients, which would make most patients with mCRPC who have progressed after next generation anti-androgens and a taxane potentially eligible for this treatment. The number of patients was adequate. The primary endpoints included overall survival, rather than surrogate endpoints for benefit.

The response rate in the control arm unsurprisingly was very poor, consistent with a heavily pretreated patient population that had received both a prior taxane and a next generation androgen receptor targeted agent therapy.

The safety profile of 177Lu-PSMA-617 was generally favorable and predictable from other studies. The most common AEs with 177Lu-PSMA-617+BSC were fatigue, dry mouth, nausea, anemia, back pain, arthralgias, decreased appetite and constipation (all >20%). The most common ≥Grade 3 AEs were hematologic. Serious acute kidney injury occurred in 1.7%. In the BSC arm, the most frequent AEs (>20%) was fatigue. Dry mouth occurred in only 1 patient. Of note is that higher grade AEs were less frequent in this trial compared to what would be expected to occur with taxanes. Key safety points are summarized in the table below.

Table 2: Safety in the VISION study

	177Lu-PSMA-617+BSC **N=529**	**BSC** **N=205**
TEAEs	98.1%	82.9%
Serious TEAEs	36.3%	27.8%
TEAE ≥Grade 3	52.7%	38.0%
Fatal TEAEs	3.6%	2.9%
TEAEs leading to discontinueation	11.9%	Not stated

The TheraP trial also supports breakthrough designation [10] primarily through its safety analysis. Its primary efficacy endpoint would not be accepted for registration as it does not correlate with measures of clinical benefit.

This trial was an unblinded randomized phase 2 trial conducted at 11 centers in Australia by the ANZUP cooperative group. Men with mCRPC progressing on docetaxel, were eligible for cabazitaxel and had PSMA-positive metastatic disease were randomized 1:1 to cabazitaxel or 177Lu-PSMA-617. Patients were stratified by disease burden (≤20 vs > 20 sites of metastases) and whether they had received prior newer anti-androgen (abiraterone or enzalutamide). The dosing regimen for 177Lu-PSMA-617 was slightly different vs the VISION trial. In TheraP, men initially received 8.5 GBq and this dose was decreased by 0.5 GBq/cycle. Dosing interval was Q6 weeks for up to 6 cycles. Treatment with 177Lu-PSMA-617 was stopped if PSMA positivity disappeared on subsequent scans, presumably due to a metabolic complete response.

The primary efficacy endpoint of TheraP differed from VISION, being the proportion of patients with at least a 50% reduction in PSA from baseline (PSA50). Other endpoints included PFS, ORR, pain reduction and QoL. Central radiographic review was not performed. AEs were assessed by CTCAE v4.03.

There were 99 patients in the 177Lu-PSMA-617 arm and 101 in the Cabazitaxel arm. By intention to treat, PSA50 occurred more frequently in the 177Lu-PSMA-617 arm vs cabazitaxel (66%, 95% CI 56-75 vs 37%, 95% CI 27-46; p<0.0001). PFS was also superior in the 177Lu-PSMA-617 arm vs cabazitaxel (HR 0.63, 95% CI 0.46-0.86; p=0.0028). This difference was more evident with longer follow-up. Althought the median PFS in both arms was 5.1 months, PFS at 12 months was 19% (95% CI 12-27%) vs 3% (95% CI 1-9%), respectively, for 177Lu-PSMA-617 vs cabazitaxel. ORR in patients with measurable disease was greater with 177Lu-PSMA-617 vs cabazitaxel (49%, 95% CI 33-65% vs 24%, 95% CI 11-38%; RR 2.12, 95% CI 1.10-4.08; p=0.019). Pain scores and QoL were both more frequently improved with 177Lu-PSMA-617 vs cabazitaxel.

The safety of 177Lu-PSMA, importantly for consideration of this BTDR, was superior to cabazitaxel. 183 patients who received at least 1 dose of either agent were included in the safety analysis. Grade 3-4 AEs occurred in 33% of patients receiving 177Lu-PSMA-617 vs 53% in the cabazitaxel arm. Grade 3-4 thrombocytopenia was more common with 177Lu-

PSMA-617 (11% vs 0%). Grade 3-4 neutropenia was less common with 177Lu-PSMA-617 (4% vs 13%) as was febrile neutropenia (0% vs 8%). Discontinuations due to AEs was less common with 177Lu-PSMA-617 (1% vs 4%). Dose reductions due to AEs were less frequent with 177Lu-PSMA-617 (n=12 vs n=21).

12. Division's recommendation and rationale (pre-MPC review):

X GRANT:

Provide brief summary of rationale for granting:

The VISION trial met its primary endpoints OS and rPFS, and demonstrated an OS for a 3rd line therapy similar to what would be anticipated for a second line therapy following a taxane. The study regimen, 177Lu-PSMA-617+BSC, was well-tolerated, with fewer high-grade AEs than would be expected from chemotherapy. The combination of an overall survival comparable to an earlier line of therapy plus a favorable toxicity profile provides substantial evidence of improvement over existing therapies.

The safety analysis of the TheraP trial, which compared 177Lu-PSMA-617 directly to cabazitaxel, supports the recommendation to grant breakthrough as it demonstrated a superior safety profile for 177Lu-PSMA-617 over the currently recommended first choice third line therapy for mCRPC.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

   The Division plans to meet with the sponsor in June 2021 in a pre-NDA meeting to discuss the sponsor's plans for submission of an NDA during the third quarter of 2021.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2019. CA Cancer J Clin 69:7-34, 2019
2. Fizazi K, Scher HI, Molina A, et al: Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 13:983-92, 2012
3. Scher HI, Fizazi K, Saad F, et al: Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 367:1187-97, 2012
4. Ryan CJ, Smith MR, Fizazi K, et al: Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302):

final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 16:152-60, 2015

5. Beer TM, Armstrong AJ, Rathkopf DE, et al: Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 371:424-33, 2014

6. Berthold DR, Pond GR, Soban F, et al: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 26:242-5, 2008

7. de Bono JS, Oudard S, Ozguroglu M, et al: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 376:1147-54, 2010

8. Parker C, Nilsson S, Heinrich D, et al: Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 369:213-23, 2013

9. Kantoff PW, Higano CS, Shore ND, et al: Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 363:411-22, 2010

10. Hofman MS, Emmett L, Sandhu S, et al: [(177)Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet 397:797-804, 2021

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☐ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 10/13/20 /M. Raggio

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/

MITCHELL S ANSCHER
06/08/2021 12:34:52 PM

CHANA WEINSTOCK
06/08/2021 12:59:18 PM

AMNA IBRAHIM
06/11/2021 10:53:22 AM

IND 133661

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Lisa Daniel, PhD
Global Program Regulatory Manager
3000 Kent Avenue, Suite 1950
West Lafayette, IN 47906

Dear Dr. Daniel:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ^{177}Lu-PSMA-617.

We also refer to the telecon between representatives of your firm and the FDA on June 2, 2021. The purpose of the meeting was to discuss and obtain agreement that the data package including results from the pivotal study, VISION, along with supportive data and publications are sufficient to support filing of NDA.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

[1]We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, contact Kelly Chiang, Regulatory Project Manager, at Kelly.Chiang@fda.hhs.gov or 301-796-5822.

Sincerely,

{See appended electronic signature page}

Kelly Chiang, PharmD
Regulatory Project Manager
Oncology 1 Group
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

{See appended electronic signature page}

Chana Weinstock, MD
Clinical Team Lead
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 2, 2021 from 12:00 – 1:00 PM EST
Meeting Location: Via Teleconference

Application Number: IND 133661
Product Name: ^{177}Lu-PSMA-617

Indication: Treatment of PSMA-expressing metastatic, castration-resistant, prostate cancer (mCRPC)

Sponsor Name: Novartis Pharmaceuticals Corporation
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Chana Weinstock, MD
Meeting Recorder: Kelly Chiang, PharmD

FDA ATTENDEES

Laleh Amiri-Kordestani, MD, Division Director, DO1
Amna Ibrahim, MD, Deputy Director, DO1
Daniel Suzman, MD, Acting Supervisory Associate Director, DO1
Chana Weinstock, MD, Clinical Team Leader, DO1
Sundeep Agrawal, MD, Acting Clinical Team Leader, DO1
Mitchell Anscher, MD, Clinical Reviewer, DO1
Elaine Chang, MD, Clinical Reviewer, DO1
Tiffany Ricks, PhD, Supervisory Pharmacologist/Toxicologist Reviewer, DHOT
Mallorie Fiero, PhD, Biometrics Team Leader (Acting), DBV
Haley Gittleman, PhD, Biostatistics Reviewer, DBV
Salaheldin Hamed, PhD, Clinical Pharmacology Team Leader, DCPV
Christy John, PhD, Clinical Pharmacology Reviewer, DCPV
William Pierce, PharmD, Captain, USPHS Commissioned Corps, Associate Director of Labeling, DO1
Anthony Fotenos, MD, PhD, Clinical Team Leader, (DIRM)
Gang Niu, MD, Clinical Reviewer (DIRM)
CAPT Diane Hanner, MPH, MSW, LSW, Senior Program Management Officer, (DIRM)
John Amartey, PhD, CMC-quality reviewer/OPQ/ONDP
Kelly Chiang, PharmD, Regulatory Project Manager, DRO-OD

SPONSOR ATTENDEES

Andrew Cavey, Global Program Head

Christopher Jordan, Sr. Global Program Regulatory Director
Catherine Guiard, Global Program Regulatory Director
Lisa Daniel, Global Program Regulatory Manager
Paula Rinaldi, US Head Regulatory Affairs
Giuseppe Randazzo, Director Regulatory Policy and Intelligence
Amrita Sawhney, IDMT Lead
Bijoyesh Mookerjee, Sr. Global Program Clinical Head
Richard Messmann, Sr. Clinical Development Medical Director
Patrick Klein, Director, RLT Safety and DMPK
Lars Blumenstein, Associate Director PKS Oncology
Euloge Kpamegan, Sr. Director Biostatistics
Michelle DeSilvio, Associate Director Biostatistics
Geoffrey Holder, Sr. Global Program Safety Team Lead
Rodica Ababii, Senior Medical Safety Lead
Lorenza Fugazza, Head of Technical R&D
Wendy Perez, Global Trial Director
Renee Verrone, Senior Global Labeling Manager

1.0 BACKGROUND

The purpose of this pre-NDA meeting is to provide an overview of key data from the VISION study evaluating ^{177}Lu-PSMA-617 (Pluvitco) in advanced prostate cancer and to gain agreement on the data needed to support a regulatory submission for the proposed indication, to confirm adequacy of the statistical analysis methods for the primary and secondary endpoints, and to discuss the content and format of the NDA.

Pluvitco/^{177}Lu-PSMA-617 is a radiopharmaceutical; its mechanism of action is via targeted beta radiation therapy delivered via binding to PSMA and subsequent internalization into the cell. ^{177}Lu-PSMA-617 has not received marketing authorization in any country.

Based primarily on the results of VISION, the Sponsor is planning to submit a 505(b)(1) NDA for ^{177}Lu-PSMA-617 in July/August 2021. The proposed indication statement is:

"Tradename", is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy (ARDT) and taxane-based chemotherapy"

Originally, the Sponsor was going to rely on the published literature to support label information for dosimetry, ECG and PK. However, they now have their own data on these issues, so will submit via the 505(b)(1) rather than the 505(b)(2) pathway.

The Sponsor will also submit a 505(b)(2) NDA for the imaging agent ^{68}Ga-PSMA-11, which was used during clinical development to determine patient eligibility for treatment

with ^{177}Lu-PSMA-617. A separate pre-NDA meeting has been requested through Division of Imaging and Radiation Medicine (DIRM).

Prostate cancer remains the 2nd leading cause of cancer deaths among US men, with ~191,000 new cases and ~33,000 deaths estimated in 2020. Although most patients present with localized disease, ~12% present with metastatic disease. Most patients with metastatic disease are treated with androgen deprivation therapy (ADT), but resistance develops inevitably, leading to the castrate resistant state (mCRPC) which is responsible for most deaths from prostate cancer. The median survival for mCRPC is ~15-18 months.

Numerous 1st and 2nd line therapies are available for mCRPC, but resistance to these therapies inevitably develop. For men who have progressed on both newer androgen receptor directed agents and a taxane, the intended population for ^{177}Lu-PSMA-617, effective options are limited and include a second taxane (i.e. cabazitaxel) and radium-223 for those with bone-only metastases. A small subset of men with HRR mutations or MSI-H are also eligible for PARP inhibitors or pembrolizumab, respectively.

PSMA is a protein expressed on the surface of prostate cancer cells, and its overexpression is correlated with more advanced, mCRPC. It is also expressed to a lesser extent in kidney, small bowel, salivary and lacrimal gland. Thus, PSMA presents a potential target for both imaging and therapy of advanced prostate cancer.

VISION is a phase 3 multi-center, open-label, randomized study to evaluate the efficacy, safety and tolerability of ^{177}Lu-PSMA-617 in patients with PSMA-positive mCRPC. The study met both of its alternate primary endpoints, OS and rPFS. The key secondary endpoints, ORR, DCR and time to first skeletal events, significantly favored ^{177}Lu-PSMA-617+best standard of care/best supportive care (BSC) vs BSC alone. The data collection cut-off date was 1/27/2021.

Abbreviated regulatory history:

January 30, 2018, FDA Type B EOP2: focused on the phase 3 study and the overall clinical and non-clinical plan, and development of imaging agent ^{68}Ga-PSMA-11, with intention to support registration.

August 16, 2018, FDA Type B EOP2: to request feedback on potential for expedited path based on data from VISION and to seek feedback on rPFS to support NDA. The FDA stated that rPFS is an appropriate endpoint for regulatory approval, but it should be assessed by BICR and will depend on the magnitude of effect and risk-benefit vs available therapies. The FDA recommended that the Sponsor conduct a formal interim analysis of OS with alpha allocation at the time of rPFS analysis to demonstrate no detrimental effect on OS at the time of this analysis.

May 2, 2019, FDA Type A meeting: to obtain guidance on mitigating the challenges caused by the high withdrawal of consent in the control arm. The FDA considered

Sponsor's plan to increase enrollment and adjust allocation of alpha between rPFS and OS to allow for analysis of fewer rPFS events to be acceptable.

March 24, 2020, FDA Type C meeting WRO: Discussed the organization and layout of NDA content, including use of literature to support the application and the analytical approach to bridge the clinical trial formulation of ^{177}Lu-PSMA-617 and the commercial formulation.

This product is also currently under review for breakthrough therapy designation. A study diagram for VISION is presented below:

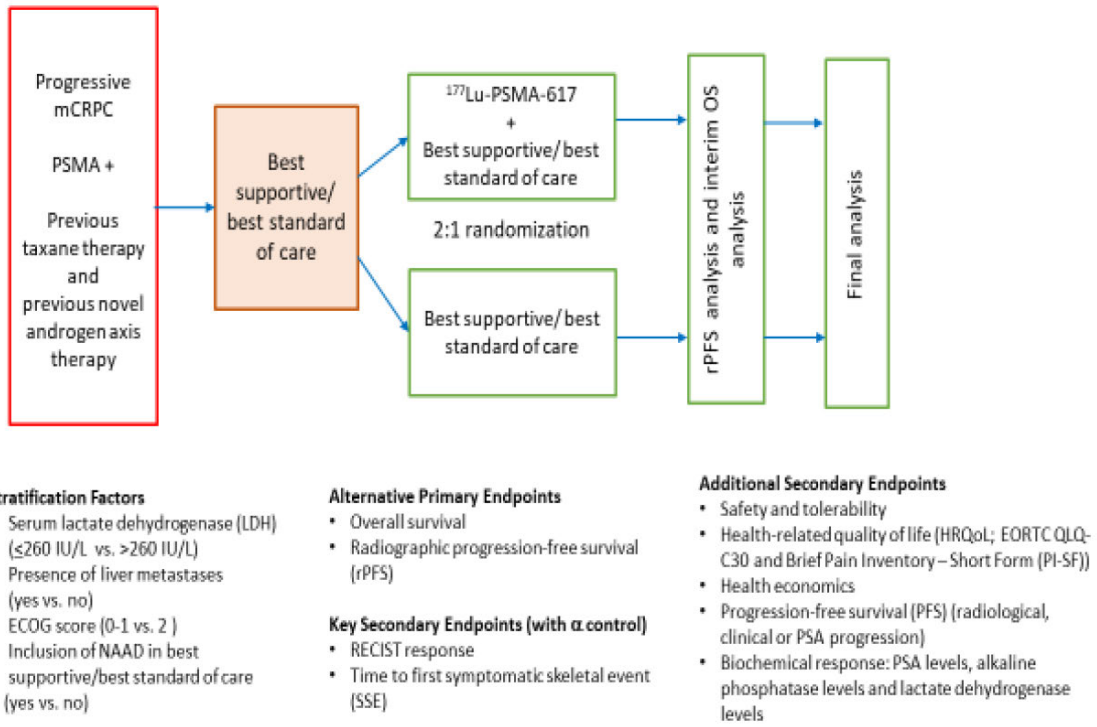


Figure 1 Diagram of trial design

ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

The Sponsor plans to submit the following data in support of the NDA: results of VISION for safety and efficacy; VISION sub-study for dosimetry (although not discussed at the March 2020 meeting), PK and ECG; RESIST-PC for safety only; and publications from non-sponsored studies for safety and efficacy.

Table 1: Summary of key data to be submitted

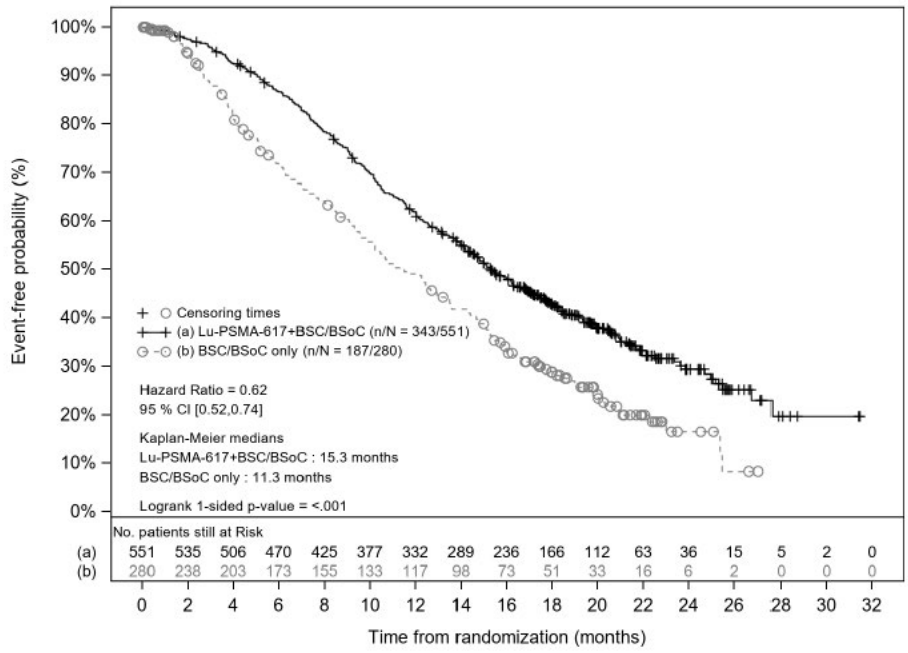
Study (#pts)	Design	Endpoints		177Lu-PSMA-617 dose	comments
VISION (831)	Phase 3, openlabel, randomized (2:1), multi-center PSMA+mCRPC; prior novel anti-androgen and 1-2 taxanes; 177Lu-PSMA-617+BSC vs BSC	Primary: OS and rPFS (BICR; RECIST1.1 and PCWG3) (alternate primary endpoints) Key secondary: ORR, DOR, DCR; time to SSE Other secondary: safety, tolerability, QOL, PFS, PSA		7.4 GBq Q6 weeks up to 6 cycles; BSC per MD choice	Enrollment dates 6/4/2018 to 10/23/2019; cut-off date for OS and rPFS 1/27/2021 (median f/u=20.9 months); Patients were assessed after 4 cycles to determine if they qualified for 2 additional cycles (showed evidence of response and had signs of residual disease on conventional imaging and has shown good tolerance of 177Lu-PSMA-617).
VISION sub-study (30)	Non-randomized cohort of ~30 patients from Germany	Primary: whole body and organ dosimetry up to C1D8 Secondary: PK, ECG, safety,		Same as VISION	

		tolerability, metabolic stability			
RESIST-PC (23)	Phase 2 non-randomized, investigator-initiated trial; PSMA+mCRPC progressed on ≥1 novel anti-androgen; taxane naïve or treated	Primary: 12-week PSA response; safety Secondary: max PSA response, bPFS, rPFS, DCR, QOL, pain scores, ECOG		Arm 1: 6.0 GBq Q8 weeks x4 or to renal dose of 23 Gy Arm 2: 7.4 GBq Q8 weeks x4 or renal dose of 23 Gy	Terminated early by new Sponsor after acquiring global rights to drug (planned for 200 pts); will include only safety data; enrollment closed 6/22/2018

Efficacy

The median OS (95% CI) was 15.3 months (14.2,16.9) vs 11.3 months (9.8, 13.5) for ^{177}Lu-PSMA-617+BSC vs BSC only, HR 0.62, 95% CI 0.52, 0.74; p<0.001.

Figure 5-1 Kaplan-Meier plot of overall survival (Full analysis set)

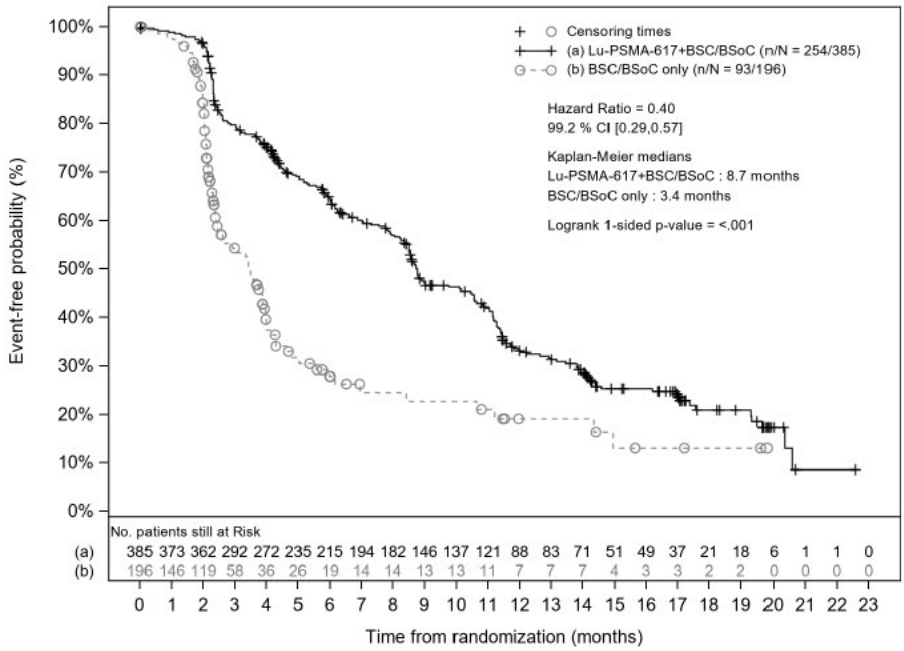


Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.

n/N: Number of events/number of patients in treatment arm.

The median rPFS (99.2% CI) by independent central review (PCWG3 criteria) was 8.7 months (7.9, 10.8) vs 3.4 months (2.4, 4.0), for the ^{177}Lu-PSMA-617+BSC vs BSC arm (HR 0.40, 99.2% CI 0.29, 0.57; p<0.001).

Figure 5-2 **Kaplan-Meier plot of radiographic progression-free survival based on independent central review (PFS-Full analysis set)**



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.

n/N: Number of events/number of patients in treatment arm.

The study also met its secondary endpoints: ORR per RECIST v1.1 in the ^{177}Lu-PSMA-617+BSC arm was 29.8% vs 1.7% in the BSC arm (odds ratio 24.99; 95% CI 6.05, 103.24. The median DOR was 9.8 months (95% CI 9.1, 11.7) in the ^{177}Lu-PSMA-617+BSC vs 10.6 months in the BSC arm (95% CI NE since there were only 2 responders in this arm). The median time to SSE was 11.5 months (95% CI 10.3, 13.2) in the 177Lu-PSMA-617+BSC arm vs 6.8 months (5.2, 8.5) in the BSC arm, HR 0.50, 95% CI 0.40, 0.62; p<0.001).

Per the Sponsor, the most common AEs with ^{177}Lu-PSMA-617+BSC were fatigue, dry mouth, nausea, anemia, back pain, arthralgias, decreased appetite and constipation (all >20%). The most common ≥Grade 3 AEs were hematologic. Serious acute kidney injury occurred in 1.7%. In the BSC arm, the most frequent AEs (>20%) was fatigue. Dry mouth occurred in only 1 patient. Of note is that higher grade AEs were less frequent in this trial compared to what would be expected to occur with taxanes. Key safety points are summarized in the table below.

Table 2: Safety in the VISION study

	177Lu-PSMA-617+BSC N=529	**BSC N=205**

TEAEs	98.1%	82.9%
Serious TEAEs	36.3%	27.8%
TEAE ≥Grade 3	52.7%	38.0%
Fatal TEAEs	3.6%	2.9%
TEAEs leading to discontinueation	11.9%	Not stated

The VISION sub-study results were not ready at the time the meeting package was submitted.

The RESIST-PC study was closed early by the Sponsor. The data will not be pooled with the VISION trial. The Sponsor states that the safety population consists of 64 patients, 41 of whom received 7.4 GBq of ^{177}Lu-PSMA-617 and 23 received 6.0 GBq Q8 weeks for up to 4 cycles. The safety data are summarized in the table below:

Table 3: safety data from RESIST-PC trial

	7.4 GBq 177-Lu-PSMA-617 (n=41)	6.0 GBq 177-Lu-PSMA-617 (n=23)
TEAEs	95.1%	95.7%
Severe TEAEs	17.1%	8.7%
Fatal TEAEs	2.4%	8.7%
TEAEs leading to discontinuation	1	0

The most frequently occurring TEAEs were dry mouth (57.8%), fatigue (53.1%) and nausea (46.9%). Only 1 event of nausea was severe. AEs occurring more frequently in the higher dose group were dry mouth (63.4% vs 47.8%), diarrhea (31.7% vs 13.0%), dyspnea (7.3% vs 0).

The FDA sent Preliminary Comments to Novartis on May 27, 2021.

2.0 DISCUSSION

Question 1: Does the Agency agree that the results from the proposed efficacy and safety package, which include the pivotal, randomized, Phase 3 VISION trial, and the VISION sub-study, combined with safety data from RESIST-PC and publications, are adequate to substantiate the safety and efficacy of 177Lu-PSMA-617 and support a full approval for the treatment of adult patients with mCRPC who have been previously treated with androgen receptor-directed therapy (ARDT, e.g., abiraterone, enzalutamide, etc.) and taxane-based chemotherapy?

FDA Response to Question 1: Although the VISION results presented appear sufficient to support review of an NDA, the acceptability of the efficacy and safety data from the VISION trial to support approval will be a review issue.

You should include in your safety analysis details about the reversibility of AEs at least possibly related to ^{177}Lu-PSMA-617+BSC/BSoC vs BSC/BSoC. You should include in these data the frequency, severity, and duration of xerophthalmia which is not mentioned in the meeting packet. You should fully characterize the chronic sequelae of xerostomia in terms of the use of artificial saliva, dental caries, and quality of life, etc. You should correlate AEs at least possibly related to ^{177}Lu-PSMA+SBC/BSoC with total radiation dose to the affected organ(s) and correlate this cumulative dose with reversibility, duration and severity of the AEs.

The VISION sub-study has not been previously reviewed by us, so we cannot comment on the acceptability of these data to support approval until the methodology and results have been reviewed. If these data are found to be unacceptable, this may change the regulatory pathway unless you will not be relying on published literature to support label information for dosimetry, ECG and PK. We recommend that you submit methodology and top-line results from your sub-study as soon as possible so that it does not impact your NDA submission timeline and request a Written Response Only (WRO) meeting to confirm the appropriateness of your regulatory pathway. You should clarify whether the sub-study patients were enrolled in the main VISION trial.

The safety data from the RESIST-PC should be submitted with the NDA, although these results can likely not be fully extrapolated to the VISION population. As some patients in the RESIST-PC trial were enrolled at an earlier phase in their disease, received a lower dose at a more prolonged interval vs the VISION patients, received fewer total cycles of ^{177}Lu-PSMA-617 than most patients in the VISION trial and the treatment also did not include the addition of BSC/BSoC, these data may not be comparable to that from the VISION trial. If available, and subject to the FDA review of the methodology employed, data from this study from the 7.4 GBq arm might be used to support overall safety information on dosimetry, ECG and PK. To the extent that safety follow-up in RESIST-PC exceeds that of VISION, your presentation of safety data from RESIST-PC should focus on long-term outcomes.

Retrospective data from the literature may be submitted although it will likely not be used to support either safety or efficacy claims, due to the assessment biases associated with these studies.

Whether the prospective data from the literature may be used to support claims of safety or efficacy for a regulatory decision will depend on the methodology of the studies, particularly inclusion criteria, doses and schedules and primary endpoints, and will be a review issue. None of the prospective studies had primary efficacy endpoints that correlate with clinical benefit, as they all used PSA response as the primary endpoint, so it is unlikely that any of these trials will support a claim of efficacy. The TheraP trial, which was a randomized phase 2 trial comparing ^{177}Lu-PSMA-617 vs cabazitaxel in men with mCRPC who had progressed after docetaxel may be submitted if available to support a safety

analysis, although the ^{177}Lu-PSMA-617 dosing regimen differed from the VISION trial, as did the eligibility criteria, so the 2 studies may not be completely comparable. The other prospective studies are small single arm trials with no comparators but may support a safety analysis although again inclusion criteria and dosing schedules differed from VISION.

Sponsor's Response dated June 1, 2021: We acknowledge the comments on safety analysis details and the analysis will be part of the Summary of Clinical Safety.

We anticipate that the sub-study data will be used for dosimetry, ECG and PK. The sub-study is modeled after a similar sub-study conducted for Lutathera and submitted as part of the NDA package for that product. As such, we believe the sub-study will be sufficient to support label information for dosimetry/ECG/PK and that a 505(b)(1) application is appropriate. A brief description of the sub-study is included below.

An efficacy and safety Phase 3 study (Study PSMA-617-01) was conducted in patients with progressive PSMA positive mCRPC. The sub-study was conducted in a non-randomized cohort (177Lu PSMA 617+BSC/BSoC) of 30 patients.

The purpose of this sub-study was to calculate whole body and organ radiation dosimetry of 177Lu-PSMA-617 to evaluate the dose to critical organs (e.g., kidney and bone marrow). This sub-study also evaluated the PK profile, ECGs, safety and tolerability, and urinary metabolic stability of 177Lu-PSMA-617.

The collection of dosimetry, pharmacokinetic, ECG, and urinary data occurred following the first dose of 7.4 GBq (±10%) 177Lu-PSMA-617, although enrolled patients continued in the sub-study as per the PSMA-617-01 protocol (177Lu-PSMA- 617 dose every 6 (±1) weeks for a maximum of 6 cycles). Patients in the sub-study were not part of the randomized portion of the study and were not included in the primary/secondary endpoint analyses.

Patients underwent full body (planar) and 3D SPECT/CT imaging, blood PK sampling and ECGs, during Cycle 1 of treatment. Urine was collected for HPLC (High performance liquid chromatography) analysis with in-line radiodetection (radio-HPLC). Baseline images were used to determine volumes in regions of interest (ROI) in selected major source organs such as the liver, spleen and kidneys. 3D SPECT/CT scans were also performed in the upper abdomen (comprising kidneys, liver and spleen). Dosimetry, PK, urine metabolite ID and PK/QT analysis will be presented in the Module 2.7.2.

In addition to the above mentioned analyses, a population PK analysis was carried out and exploratory analyses were conducted to explore the relationship between PK or organ radiation absorbed dose and acute toxicities related to the organ at risk using either popPK derived PK metrics or absorbed radiation dose. Since the sub-study is still ongoing, only acute safety after the first dose of 177Lu-PSMA-617 was assessed. The

results of these additional analyses are summarized in Module 2.7.2 and described in detail in a dedicated report.

Our current anticipated NDA submission timing is late July or early August, which does not allow time for a WRO meeting request cycle, unless we can consider the Meeting as a Type A meeting. We will submit the sub-study protocol to the IND as soon as possible and will include the final data in the NDA.

Please also note that the nonclinical data package to support submission will be based on sponsor-generated data, with the exception of primary pharmacology and supplemental biodistribution, which is not expected to be described in labeling. The nonclinical data also supports the intent to submit a 505(b)(1) application.

The RESIST-PC CSR, including safety analysis, will be included in the NDA package.

Retrospective and prospective data from the literature is intended to provide supporting and contextual information on the clinical use and development conducted prior to the assumption of formal drug development by Endocyte. It also provides additional information on safety of the product in these settings. The pivotal data, and associated label claims, will be supported by the VISION study and other sponsor-generated data.

Meeting Discussion: The FDA reiterated that a meeting request to discuss the protocol and topline results of the sub-study should be submitted, either as a Type A or in a timely manner to allow the FDA to provide responses prior to the date of NDA submission.

From overview of information provided, the sub-study may suffice for single dose dosimetry. Since the Sponsor has not stated how patients were followed or treated relative to the guidelines in the VISION study, it is difficult to determine whether these results should be included in any other type of analysis.

Question 2: A safety update will be submitted within 90 days after the date of the original submission in the event that priority review is granted. Does FDA agree with the content and timing of the proposed safety update?

FDA Response to Question 2: The 90-day safety update from the overall VISION patients and safety results should be submitted as proposed. However, in your meeting document you indicate that you will include safety data from the VISION sub-study. Patients in the sub-study who are not enrolled in the main VISION trial should be presented separately.

You state in the meeting document that you intend to submit safety data from 2 additional phase 3 studies that are expected to initiate enrollment in April and May 2021. No information is presented on the patient population, inclusion/exclusion criteria or dosing schedule. As a major concern pertaining to radiation-related AEs is the occurrence of irreversible late toxicity, the addition of

immature safety data from these 2 new studies will not contribute meaningfully to a safety analysis and should not be included in the summary of clinical safety for this NDA. Your 90-day safety update should include only updated safety data from patients in the VISION study. See also FDA response to Question 1 pertaining to the importance of providing data specific for radiation-related AEs. Also, you will need to provide follow up on all patients in the VISION trial until death or until loss to follow-up in order to ensure capture of all possible long-term safety data.

Sponsor's Response dated June 1, 2021: We acknowledge the feedback, and will focus the safety update on patients in VISION, including the sub-study.

Meeting Discussion: No meeting discussion was held.

Question 3: Does the Agency agree that the statistical analysis methods for the primary, key secondary, and other secondary endpoints for the pivotal, Phase 3 Study VISION, as described in the statistical analysis plan are adequate to support the approval of 177Lu-PSMA-617 in the indication specified?

FDA Response to Question 3: Yes, the analysis methods for the primary, key secondary, and other secondary endpoints for VISION appear acceptable.

Please clarify whether the OS results were based on your planned interim or final OS analysis and the alpha allocated to the OS results presented.

You should also discuss the impact of the operational, statistical, and design-related actions to mitigate the challenges caused by a high number of subjects withdrawing consent from the control arm discussed at the May 2019 meeting.

Your protocol required a 2nd PSMA scan for patients after 4 doses to assess response and residual disease and subsequent eligibility for the final 2 doses. In your NDA submission, you should present an analysis of how many patients were eligible for subsequent therapy, the outcomes in those who received 4 vs. 6 doses, and your plans for requiring further scanning for all patients after their 4th dose after approval. You should provide a justification for the additional two doses based on data from VISION. This will ultimately be a review issue.

Sponsor's Response dated June 1, 2021: The OS results were based on the final OS analysis.

The interim OS analysis planned per protocol had become redundant due to the speed at which OS events happened to accumulate. The required 508 OS events that were intended for the final analysis were reached before the required 364 rPFS events, at which an interim OS analysis would have occurred, resulting in the timing of the planned interim analysis to coincide with the final analysis for OS.

Consequently, the alpha level applicable to the one and final OS analysis depended on the rPFS results as follows:

- if p<0.004 1-sided is achieved for rPFS, then the one and final analysis of OS will be performed at a 1-sided α=0.025.
- if p<0.004 1-sided is not achieved for rPFS, then the one and final analysis of OS will be performed at a 1-sided α=0.021.

A discussion of the impact of the changes is being incorporated into the VISION CSR and the SCE. We have also included a brief discussion of the impact of the COVID-19 pandemic on the study, which was minimal.

We wish to clarify that a second PSMA scan was not required for patients to receive more than 4 doses. The protocol required an assessment of patient benefit per standard PCWG3 criteria and tolerability, and agreement between the investigator and patient to receive the planned additional 2 cycles.

As such, we have no plans to require further PSMA-targeted PET scanning for patients receiving 177Lu-PSMA-617 therapy. Draft labeling will propose patients should receive a full 6 cycles of treatment, assuming patient safety and tolerability.

The CSR will describe the number of patients who received ≤4 and >4 cycles.

Meeting Discussion: The FDA acknowledged the Sponsor's response. The safety profile of 4 vs 6 doses will be assessed during the review.

Question 4: The Applicant intends to apply for priority review for 177Lu-PSMA-617. Does FDA agree that the proposed application could qualify for priority review?

FDA Response to Question 4: Based on the information presented in the briefing package, the proposed application would appear likely to qualify for priority review. However, final determination will be made after the application is submitted.

Sponsor's Response dated June 1, 2021: The Sponsor acknowledges the FDA response. No further discussion is needed.

Meeting Discussion: No meeting discussion was held.

Question 5: Does the Agency agree with the overall eCTD core structure and content for the 177Lu-PSMA- 617 NDA dossier?

FDA Response to Question 5: It is unclear from your briefing package how you intend to use published literature to support your nonclinical package and labeling for ^{177}Lu-PSMA-617. If you intend to rely on literature or other studies, for

which you have no right of reference but that are necessary for approval, your application will be considered a 505(b)(2).

We recommend the use of an assessment aid (AAid) for this NDA application. For more information regarding the AAid, refer to Section 4 Additional Information. An AAid should include statistical sections(s) describing sample size calculations, interim analyses, control of Type-I error rate, pre-specified statistical analysis methods, and other statistical aspects. Results of subgroup analyses for the primary endpoint(s) should be included in the AAid. In general, results from exploratory endpoint analyses should be kept to a minimum in the AAid.

Please include in your NDA submission:

a) **SAS programs that produced all efficacy results reported in the CSR Section Efficacy Evaluation**

b) **All raw as well as derived variables in .xpt format**

c) **SAS programs by which the derived variables were produced from the raw variables.**

Sponsor's Response dated June 1, 2021: As noted in discussion of Question 1, we do not foresee relying on literature for the nonclinical labeling. This is a change in our expectations relative to previous FDA meetings based on completion of the substudy and our own nonclinical studies. Therefore, we believe that a 505(b)(1) is now appropriate.

We are planning to complete the Assessment Aid for the submission and will include the SAS programs and datasets as described.

Meeting Discussion: No meeting discussion was held.

Question 6: Does FDA agree that patient labeling is not applicable and thus not required for 177Lu-PSMA- 617?

FDA Response to Question 6: No. This will be a review issue, but we anticipate that patient labeling will be required for ^{177}Lu-PSMA-617. This is based on the requirements to provide written instructions summarizing precautions to minimize exposure and important safety-related precautions that a patient must adhere to after the administration of ^{177}Lu-PSMA-617. You should comment on whether you anticipate patient isolation following dosing will be necessary. We recommend submitting patient labeling with the labeling in your application.

The information on the patient label serves as a resource for both patients and other providers, which is especially important for providers charged with

following the patient for AEs. Thus, patient labeling is necessary for the safe use of this product.

Sponsor's Response dated June 1, 2021: By way of background, we note that the radiotherapeutic agents in the oncology space approved by FDA within the last 8 years US, namely Xofigo (radium Ra 223 dichloride) with initial US approval in 2013, Lutathera (lutetium Lu 177 dotatate) and Azedra (iobenguane I 131) with initial US approvals in 2018, do not provide patient labeling. Information that is specifically applicable to patients is conveyed in section 17 Patient Counseling Information for these radiotherapeutic agents.

Specifically, in the Xofigo Summary Review (Section 12. Labeling), FDA noted that "Patient labeling/Medication guide: Patient labeling or a medication guide are not required." Similarly, in the Lutathera Multi-Disciplinary Review and Evaluation (Section 10.2 Patient Labeling), FDA noted that patient labeling is "Not applicable". Finally, in the Azedra Multi-Disclipine Review (Section 13 Labeling Recommendations), there is no specific FDA commentary on the need for patient labeling. Due to the highly controlled, regulated use and administration of 177Lu-PSMA-617 in nuclear medicine facilities, AAA agrees with FDA's previous commentary for these 3 radiotherapeutic agents with regard to patient labeling not being applicable and not required. Thus, AAA had requested FDA agreement with our proposal that is consistent and in alignment with these precedents.

It is noted that we plan to provide information specifically applicable to patients in section 17 Patient Counseling Information of the proposed USPI as appropriate, including instructions for the healthcare provider to advise patients to report signs or symptoms related to specific labeled toxicities as well as to advise patients to minimize radiation exposure to others (including specific guidance on limiting close contact and sleeping arrangements). In addition, we plan to communicate in the proposed USPI the following: the need to minimize radiation exposure (consistent with institutional and good radiation safety practices, patient management procedures, NRC guidance, and instructions to the patient for follow-up radiation protection at home), as well as the need for the nuclear medicine physician to explain the necessary radioprotection precautions that the patient should follow to minimize radiation exposure before the patient is released from the facility.

With the aforementioned plans for labeling that are consistent with the radiotherapeutic precedent, AAA is of the opinion that communication of minimizing radiation exposure and AE toxicity management can be adequately addressed in the prescribing information. Furthermore, patients receive discharge instructions from the nuclear medicine facility administering the 177Lu-PSMA-617 treatment which provide more detailed instructions regarding safety-related precautions to minimize exposure after 177Lu-PSMA-617.

Therefore, we would like to understand FDA's current thinking on the necessity of patient labeling for radiotherapeutics such as 177Lu-PSMA-617 in light of the precedent

described above as well as the plans for 177Lu-PSMA-617 prescribing information noted above. AAA welcomes the agency's feedback on the above and guidance on provision of patient labeling in the context of the review process.

Meeting Discussion: The FDA acknowledges the rationale and past precedent for not submitting a PPI at filing, which is optional. However, requiring a Medication Guide under the requirements in 21 CRF 208.1 will be a review issue based on the overall safety profile and safety precautions required by patients for ^{177}Lu-PSMA-617 after this NDA is submitted. Patient labeling determinations for other products with potentially related hazards and the rationale the Sponsor provided will be considered closely during the NDA review. During the NDA review, the FDA will determine if ^{177}Lu-PSMA-617 poses a serious and significant public health concern that requires distribution of the FDA-approved patient information.

3.0 ADDITIONAL COMMENTS

CMC

Adoption of USAN name: In the NDA, provide the status of the USAN name for ^{177}Lu-PSMA-617 with supporting documentation and updates to the CMC review team if the USAN name has not been finalized by the time of NDA submission.

Sponsor's Response dated June 1, 2021: An INN has been accepted, and a USAN application using the same name has been submitted and is under review. A status update will be provided in the submission.

Meeting Discussion: No meeting discussion was held.

CLINICAL PHARMACOLOGY

1. **The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with the FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available at: https://www.fda.gov/media/74346/download). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.**

2. **Address the following questions in the Summary of Clinical Pharmacology:**

    a. **What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application?**

b. What are the exposure-response relationships for efficacy, safety and biomarkers?

c. What is the effect of ^{177}Lu-PSMA-617 on the QT/QTc interval, if any?

d. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?

e. Are ^{177}Lu-PSMA-617 or any of its metabolite substrates and inhibitors of CYP enzymes and transporters?

f. How do extrinsic (such as drug-drug interactions for androgen deprivation therapy and diuretics) and intrinsic factors (such as sex, race, disease, and renal impairment) influence exposure, efficacy, or safety? What dose modifications are recommended, if any?

3. Apply the following advice in preparing the clinical pharmacology sections of the original submission:

a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

b. Provide the final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.

c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.

- **Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**
- **Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.**

Sponsor's Response dated June 1, 2021: We acknowledge the comments, no further discussion needed.

Meeting Discussion: No meeting discussion was held.

REGULATORY

We recommend the use of an assessment aid (AAid) for this NDA application. More information can be found at https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project**. When submitting your AAid, it should not be longer than a total of 100 pages.**

Sponsor's Response dated June 1, 2021: As noted above, we acknowledge the recommendation and will provide an AAaid in the submission.

Meeting Discussion: No meeting discussion was held.

4.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 20, 2021, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with the FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and the FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in the FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with the FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[2]

PREA REQUIREMENTS

[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that the FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with the FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[3]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020, or Sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the Sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the FDA's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review Division with the cover letter clearly stating, "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The FDA strongly advises the complete meeting package to be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[5] and Pregnancy and Lactation Labeling Final Rule[6] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

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[3] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- The FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[7]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[8]

Office of Scientific Investigations (OSI) Requests

[7] http://www.fda.gov/ectd
[8] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[9]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate the FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review Division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[10]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[11]

[9] https://www.fda.gov/media/85061/download
[10] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[11] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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CHANA WEINSTOCK
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IND 133661

MEETING PRELIMINARY COMMENTS

Endocyte, Inc.
Attention: Christopher L. Jordan, MSHS, RAC
Vice President, Regulatory Affairs
3000 Kent Avenue, Suite A1-100
West Lafayette, IN 47906

Dear Mr. Jordan,

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ^{177}Lu-PSMA-617 solution for injection.

We also refer to your August 17, 2020, correspondence requesting a meeting to discuss and obtain FDA guidance on the proposed development of ^{177}Lu-PSMA-617 (b) (4)

(b) (4)

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call David Nartey, Regulatory Project Manager, at 301-796-4079.

Sincerely,

{See appended electronic signature page}

David Nartey, PharmD, MPH
Regulatory Project Manager
Oncology 1 Group
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

{See appended electronic signature page}

Daniel Suzman, MD
Clinical Team Leader
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: End of Phase 2

Application Number: IND 133661
Product Name: ^{177}Lu-PSMA-617

Indication: (b) (4)

Sponsor Name: Endocyte, Inc.

Regulatory Pathway: 505(b)(1) of the Food, Drug, and Cosmetics Act

INTRODUCTION:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for October 26, 2020, from 1:00 – 2:00 PM EST between Endocyte Inc., and the Division of Oncology 1. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

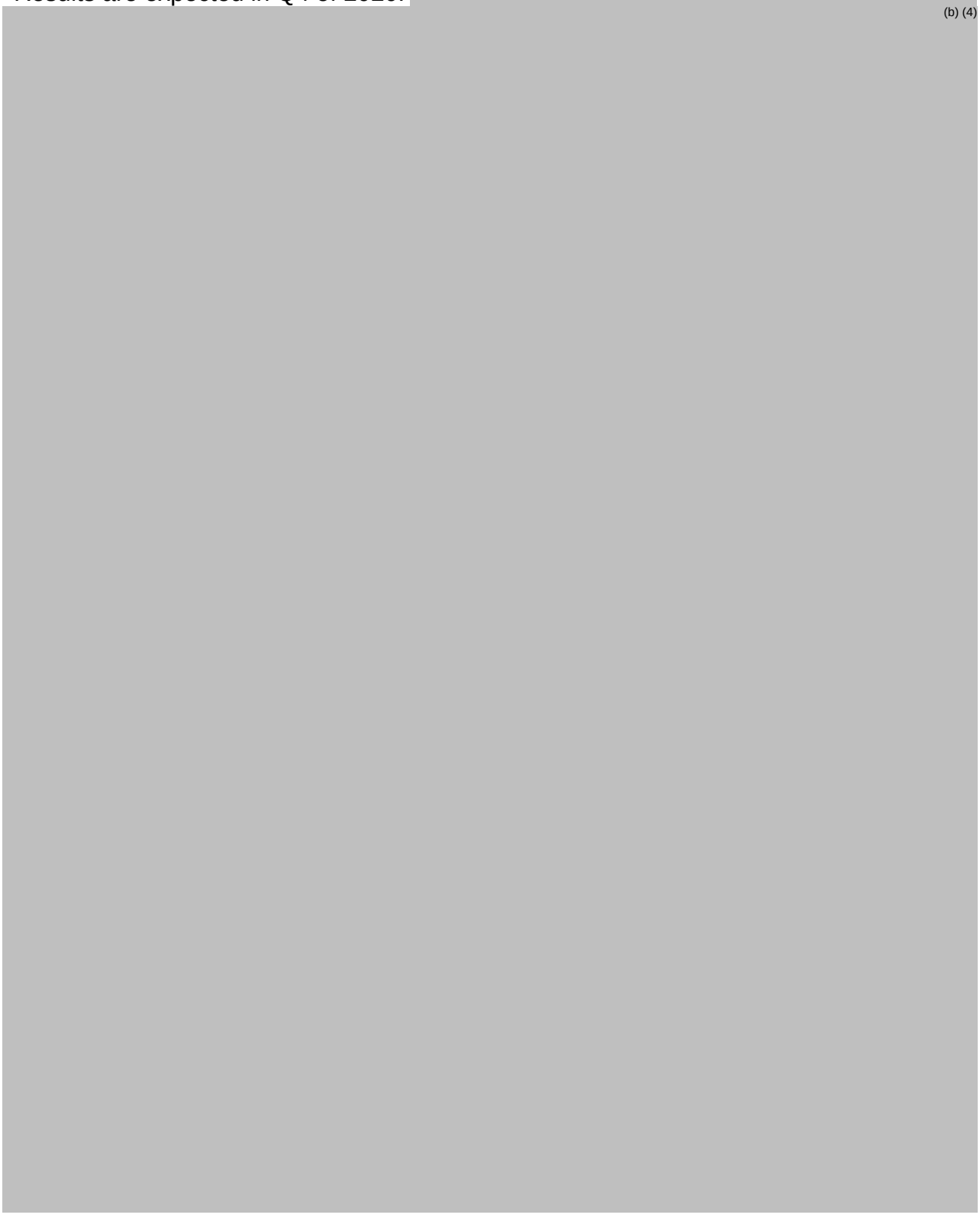
(b) (4)

(b) (4). ^{177}Lu-PSMA-617 is a radiopharmaceutical beta emitter currently being evaluated in the VISION trial, an

international, prospective, open label, multicenter randomized phase 3 study in patients with metastatic castration resistant prostate cancer (mCRPC) who have received abiraterone and/or enzalutamide and at least one prior taxane-containing regimen. Results are expected in Q4 of 2020.

(b) (4)

(b) (4)



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U.S. FOOD & DRUG ADMINISTRATION

IND 133661

MEETING PRELIMINARY COMMENTS

Endocyte, Inc.
Attention: Christopher L. Jordan, MSHS, RAC
Vice President, Regulatory Affairs
3000 Kent Avenue, Suite A1-100
West Lafayette, IN 47906

Dear Mr. Jordan:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ^{177}Lu-PSMA-617 solution for injection.

We also refer to your June 16, 2020, correspondence, received June 16, 2020, requesting a meeting to obtain FDA guidance regarding the proposed development of ^{177}Lu-PSMA-617 as a potential new therapy for mCRPC patients (b) (4)

(b) (4)

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, contact Kelly Chiang, Regulatory Project Manager, at Duyen.Mach@fda.hhs.gov or 301-796-5822.

Sincerely,

{See appended electronic signature page}

Kelly Chiang, PharmD
Regulatory Project Manager
Oncology 1 Group
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Daniel Suzman, MD
Clinical Team Lead
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comment

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type:	B
Meeting Category:	End of Phase 2
Application Number:	IND 133661
Product Name:	^{177}Lu-PSMA-617 solution for injection
Indication:	Treatment of PSMA-expressing, metastatic, castration-resistant prostate cancer (mCRPC)
Sponsor Name:	Endocyte, Inc.
Regulatory Pathway:	505(b)(1) of the Food, Drug, and Cosmetics Act

INTRODUCTION:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for August 25, 2020, from 12:00 – 1:00 PM EST, between Endocyte and the Division of Oncology 1. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

^{177}Lu-PSMA-617 is a radiopharmaceutical beta emitter produced by chelation of ^{177}-Lu with the precursor molecule PSMA-617 that targets PSMA expressing sites. It is currently being evaluated in the VISION trial, an international, prospective, open label, multicenter randomized phase 3 study in patients with mCRPC who have received abiraterone and/or enzalutamide and at least one prior taxane-containing regimen. Results are expected in the 4th quarter of 2020.

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/s/

DUYEN M MACH
08/18/2020 02:24:08 PM

DANIEL L SUZMAN
08/18/2020 02:48:16 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 133661

MEETING MINUTES

Endocyte, Inc.
Attention: Christopher Jordan
Senior Director, Regulatory Affairs
3000 Kent Avenue, Suite A1-100
West Lafayette, IN 47906

Dear Mr. Jordan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ^{177}Lu-PSMA-617.

We also refer to the telecon between representatives of your firm and the FDA on August 16, 2018. The purpose of the meeting was to discuss additional guidance regarding your potential accelerated path to submission based on interim data from Protocol PSMA-617-01. A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Janice Kim, Regulatory Project Manager, at (301) 796-9628.
Sincerely,

{See appended electronic signature page}

Janice Kim, PharmD, MS
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

{See appended electronic signature page}

V. Ellen Maher, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	EOP2
Meeting Date and Time:	August 16, 2018; 1:00 PM – 2:00 PM
Meeting Location:	Teleconference
Application Number:	IND 133661
Product Name:	177Lu-PSMA-617
Indication:	metastatic castration resistant prostate cancer
Sponsor/Applicant Name:	Endocyte, Inc.
Meeting Chair:	V. Ellen Maher, MD
Meeting Recorder:	Janice Kim, PharmD, MS

FDA ATTENDEES
Julia Beaver, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
V. Ellen Maher, MD, Clinical Team Leader, DOP1
Sundeep Agrawal, MD, Clinical Reviewer, DOP1
Lijun Zhang, PhD, Biostatistics Team Leader, DBV
Joyce Cheng, PhD, Biostatistics Reviewer, DBV
Janice Kim, PharmD, MS, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES
Alison Armour, MD, Chief Medical Officer
Caryn Barnett, Senior Director, Clinical Operations
Christopher Jordan, Senior Director, Regulatory Affairs
Mike Sherman, President, CEO
(b) (4) PhD, Consultant, Statistics

1.0 BACKGROUND

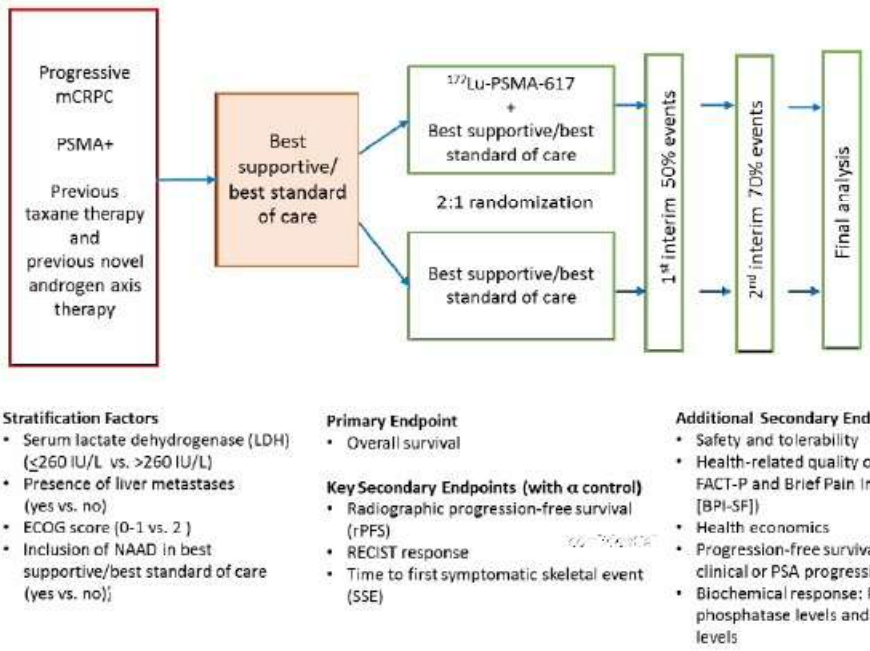
The purpose of this meeting is to obtain additional FDA guidance following the End-of-Phase 2 meeting held in January 2018. The sponsor requests feedback regarding the potential for an expedited path to submission based on data from Protocol PSMA-617-01, which is a Phase 3 study. The sponsor also seeks feedback on using radiographic progression free survival to support a New Drug Application, assuming positive data from their ongoing trial, and the use of overall response rate as an endpoint in metastatic castration-resistant prostate cancer.

Drug Background

The therapeutic agent that the sponsor is developing is ^{177}Lu-PSMA-617. ^{177}Lu-PSMA-617 is a beta particle-emitting radioactive therapeutic agent that the sponsor plans to administer intravenously. It is composed of 3 components: a pharmacophore ligand, (b) (4) that enables the radioisotope to bind to PSMA; a chelator DOTA; and a linker connecting these two. PSMA is a trans-membrane protein that is noted by the sponsor to be expressed in prostate cancer. The proposed mechanism of action of this drug is that binding of the ligand to PSMA can lead to internalization and sustained retention of ^{177}Lu-PSMA-617, which then causes DNA strand damage in prostate cancer cells. This therapy has been evaluated in Phase 1 dosimetry trials and compassionate use patients.
A prospective Phase 2 study by Hofman has also been reported in patients with metastatic castration resistant prostate cancer, and the therapeutic agent has demonstrated PSA declines in both this prospective study and in the compassionate use setting.

Study Design and Proposed Changes to Design

The sponsor has started enrolling patients onto its Phase 3 clinical trial, VISION. The design is summarized below.



Currently, the primary endpoint of the current trial design is overall survival (OS) and the planned sample size is 750 patients. Radiographic PFS is a secondary endpoint. The sponsor proposes to alter the design by making radiographic PFS and overall survival alternative primary endpoints. The sponsor states that this is distinct from co-primary endpoints where both have to be formally met to declare a positive trial. The sponsor states that with alternative primaries, it is postulated that a clinically convincing and formally statistically significant improvement on either endpoint, without detriment on the other, would represent a clinical benefit to the patient. The sponsor plans to maintain the enrollment size of 750 patients, and handle multiplicity through specified alpha allocation and recycling. The sponsor plans to maintain the other aspects of the trial, including trial size, overall duration, and follow-up. The sponsor states that the revised design would have 84% power for radiographic PFS and would continue to carry 90% power for overall survival. A comparison of the current and proposed design were provided by the sponsor and are listed below.

	Current Design	Proposed Design
Primary Endpoint	OS	rPFS and OS Alternate Primaries
Secondary Endpoints	rPFS, ORR, DCR, Time to SSE	ORR, DCR, Time to SSE
Assumptions regarding median survival, active vs control	13.7 vs 10 mo	Unchanged
Patient accural and follow-up times	13 mo and 15 mo	Unchanged
Target number of OS events	489	Unchanged
Expected Timing of final OS analysis	15 mo minimum follow-up	Unchanged
Target number of rPFS events	--	457
Expected Timing of rPFS analysis	--	3-4 mo minimum follow-up
Assumptions regarding median rPFS, active vs control	--	6 mo vs 4 mo
Interim Analyses	At 50% and 70% OS events	None
Alpha Control relating to OS and rPFS	Across OS analyses using an O'Brien and Fleming allocation	Allocation of 0.001 alpha to the analysis of rPFS and 0.024 to the analysis of OS

Sponsor's Rationale for Using Radiographic PFS as an Endpoint to Support NDA Submission

As mentioned above, the sponsor would like to change radiographic PFS from a secondary endpoint to an alternative co-primary endpoint. The sponsor cites multiple publications, including the Prostate Cancer Working Group 2 and 3 Recommendations, that find radiographic PFS to be an endpoint that demonstrates clinical benefit. It is also noted that radiographic PFS has correlated with an OS benefit in the COUGAR-302 and PREVAIL studies. The sponsor plans to conduct their radiographic PFS analysis based on investigator-assessed events. If the results of this analysis are positive, Endocyte plans to share the results with the agency and discuss the need for additional supportive information for other endpoints (safety and overall survival, etc.) If the agency were to agree that submission is appropriate, the sponsor would then plan for a pre-NDA meeting to discuss and confirm the submission plan.

Sponsor's Rationale for Inquiring about the use of ORR as an Endpoint in Metastatic CRPC

The sponsor notes that it has become aware of public reports from other sponsors that the use of RECIST Overall Response Rate (ORR) as an endpoint could support an FDA submission in metastatic CRPC. They cite the TRITON2 study sponsored by Clovis Oncology as an example. The sponsor does not intend to implement ORR as a potential endpoint to support submission without presenting a plan for FDA review first, but would like to request agency feedback in general, on the use of ORR to support either a first approval or supplemental approval.

FDA sent Preliminary Comments to Endocyte on August 9, 2018.

2. DISCUSSION

Question 1: Endocyte proposes to submit a New Drug Application for ^{177}Lu-PSMA-617 approval based on an analysis of rPFS during the recently started PSMA-617-01 Phase 3 clinical trial. The expected timing of the analysis would be 3-4 months after full enrollment. The decision to submit would be based on an IDMC recommendation, and Endocyte would request a Pre-NDA meeting with the Agency prior to submission to gain FDA input once the data are available. Regardless of the outcome of the rPFS analysis, the trial would continue patient follow-up as originally planned to provide longer term, mature overall survival data. Assuming positive data, does FDA agree with the plan to support an earlier submission of ^{177}Lu-PSMA-617 based upon an analysis of rPFS?

FDA Response to Question 1:

Radiographic PFS is an appropriate efficacy endpoint for regular approval, but

- **it should be assessed by independent central review and**
- **will depend on the magnitude of the effect and the risk-benefit of your therapy compared to available therapies.**

Sponsor Response [8/15/2018]: We agree with assessment by independent review. However, we intend to allow investigators to assess rPFS at the site for purposes of patient management. We are collecting all patient scans centrally, and will use the independent central review to support the rPFS analysis as described in the briefing document. To ensure appropriate assessment of rPFS events, the IDMC will be asked to compare (blinded to Endocyte) the results of investigator and central rPFS assessments early in the study and review any discrepancies in the results. The IDMC will then provide feedback to the sponsor for additional training of the investigators, as needed. Feedback will relate only to the process of assessing rPFS events, and will not include any information regarding interim study data. Only the independent central review will be used to determine when the required 457 rPFS events have occurred, and whether the predefined outcome has been achieved to support submission.

The sponsor will describe the independent central review process as part of the Imaging Charter, and submit it to the IND prior to conducting the rPFS analysis.

Discussion: **This approach is acceptable.**

FDA Response to Question 1 Continued: **You should conduct a formal interim analysis of OS with alpha allocated at the time of the rPFS analysis. It will be important to demonstrate no detriment in OS at the time of this analysis.**

Sponsor Response [8/15/2018]: We agree with conducting a formal OS analysis with alpha allocated at the time of the rPFS analysis. Final details will be included in the submission of the protocol amendment to implement the rPFS analysis, but we will assign an alpha of 0.001 to the interim OS analysis in order to preserve as much alpha as possible for the final, appropriately powered OS analysis.

Discussion: **This approach is acceptable.**

FDA Response to Question 1 Continued: **Given that there will be few treatment options available to patients who have progressed on study drug, we are concerned that you do not anticipate an improvement in OS. Please comment.**

Sponsor Response [8/15/2018]: We continue to have confidence that treatment with ^{177}Lu-PSMA-617 will result in an increase in both rPFS, and OS, relative to control. As noted in the briefing document, we will continue follow-up of patients post the analysis of rPFS to collect mature OS data regardless of the result attained on rPFS. Our goal in implementing the rPFS endpoint is to potentially accelerate the availability of what we strongly believe is an important, active therapy to patients as quickly as possible, while still demonstrating a robust statistical and clinical benefit.

Discussion: **No discussion needed.**

FDA Response to Question 1 Continued: **We reiterate that the primary analysis should be conducted using a stratified log-rank test.**

Sponsor Response [8/15/2018]: We understand FDA′s advice that the analysis of rPFS and OS should utilize a stratified log rank test. We also reiterate our concern regarding the potential for loss of statistical power based on a stratified log rank test that can occur as the number of strata increases, increasing the possibility of some strata having an empty cell for drug and a non- empty cell for control (or vice versa) that will then result in the exclusion of rPFS and/or OS events from that strata. This is not a desirable property of any test to compare randomized treatments for rPFS and/or OS. An identically structured Cox analysis with the exact same strata as covariates along with randomized treatment does not suffer from this power loss. However, we agree to conduct as the primary analysis a stratified log-rank test, and we will conduct the identically structured Cox analysis as well.

Discussion: **We recommend you use the Cox model as a sensitivity analysis.**

FDA Response to Question 1 Continued: Please comment on bone scan findings that might impact rPFS following treatment with ^{177}Lu-PSMA-617 in earlier studies.

Sponsor Response [8/15/2018]: We requested additional information regarding this request to ensure our understanding of the question being asked. Janice Kim, RPM, provided the following additional clarification from the reviewer:

> **We suspect that the assessment of rPFS with radiolabeled PSMA will be similar to the assessment following treatment with hormonal agents. However, we could envision a scenario in which less bone healing takes place following treatment with a radiolabeled product (due to increased death of normal osteoblasts). Therefore, distinguishing between bone healing and sites of tumor on bone scan would be less of a concern. We were interested in whether you had qualitative information on bone scans following treatment with radiolabeled PSMA.**

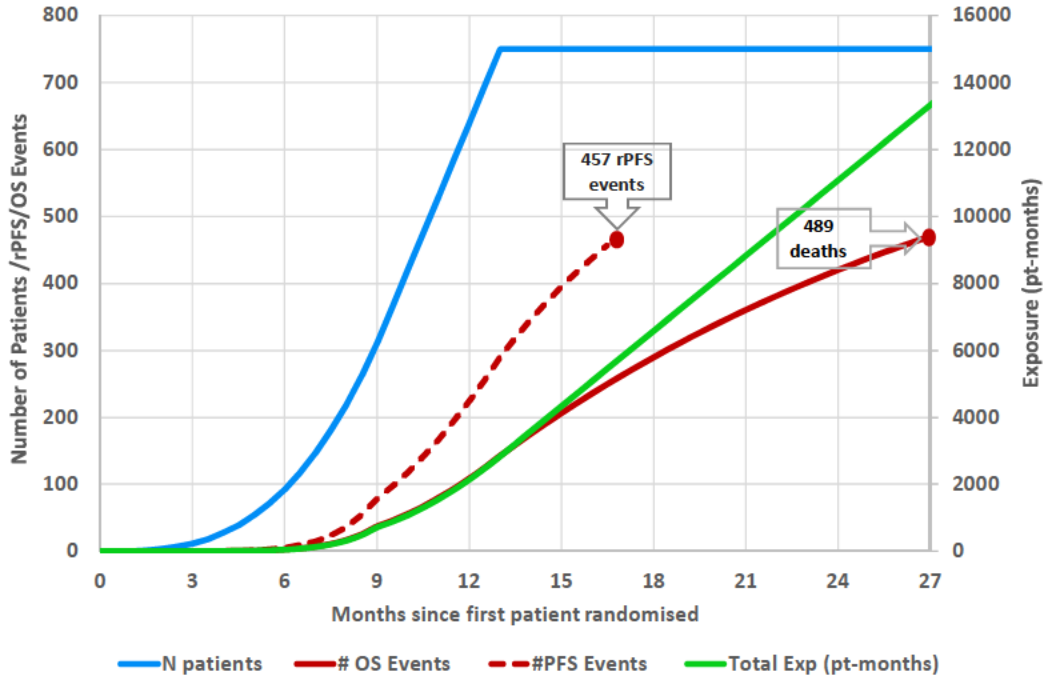
Sponsor Response [8/15/2018]: We do not have sufficient bone scan data from previous studies to address this question at this time. However, we expect the assessment of rPFS will be similar to hormonal agents as osteoblasts do not express PSMA and will not be targeted by ^{177}Lu-PSMA-617. ^{177}Lu-PSMA-617 emits beta irradiation which is low LET and low dose rate and provides optimal conditions for normal tissue repair.

Discussion: The sponsor states that study drug is unlikely to effect the bone micro environment. The sponsor has no data on the effect of study drug on bone scan readings.

FDA Response to Question 1 Continued: Your anticipated 15 month follow up for overall survival appears relatively long in this patient population. Please comment.

Sponsor Response [8/15/2018]: As outlined in the statistical powering section of the protocol, 15 months minimum follow-up for OS is a direct consequence of the assumed median OS in this patient population of 10 months and the anticipated median OS with ^{177}Lu-PSMA-617 of 13.7 mo (for a HR of 0.7306) coupled with non-linear patient accrual over 13 months and a reduced alpha due to interim analysis and the division vs rPFS, To generate the required 489 deaths and associated power, a minimum follow-up of 15 months is required. The long term follow up will also provide robust follow up for safety. The profile of recruitment and expected event accrual is shown for information in Figure 1.

Figure 1



Discussion: **No discussion needed.**

Question 2: Endocyte is aware of public reports from other sponsors regarding the use of RECIST Overall Response Rate (ORR) as an endpoint that could support an FDA submission in mCRPC (for example, the TRITON2 study sponsored by Clovis Oncology). Endocyte does not intend to implement ORR as a potential endpoint to support submission without presenting a detailed plan for FDA review. However, we request FDA feedback regarding the use of ORR as an endpoint that
demonstrates clinical benefit in metastatic prostate cancer, either in the setting of a first approval, or a supplemental approval.

a) Is there a scenario where use of ORR (and presumably Duration of Response) could be considered supportive of either accelerated or full approval? As first approval? As supplemental approval?

FDA Response to Question 2a: **Soft tissue response, as measured by confirmed overall response rate, may be acceptable as an endpoint and may be used to support accelerated approval. However, approvability will be a review issue and would additionally depend on the magnitude of the effect, duration of response, and the safety profile. Regular approval would need to be confirmed by an additional efficacy measure such as radiographic progression free survival or overall survival.**

We are concerned that the soft tissue response may not accurately reflect the response within bone. This concern would need to be addressed should any plan for study based on ORR be pursued.

Sponsor Response [8/15/2018]: Thank you for the feedback. We are considering ways to incorporate your feedback into the VISION study. We understand the concern regarding assessing the endpoint, both in the context of multiple endpoints as well as the process of understanding response in bone. In VISION we have the benefit of a control arm for ORR comparison, and rPFS endpoint data that takes into account progression in bone disease and deaths. We will provide additional details as we refine our proposal.

Discussion: The Agency expressed concern about the use of ORR and noted that it would be necessary to allocate alpha to this endpoint comparison.

b) If full approval, are there other considerations regarding data to be collected, secondary study endpoints, and patient population?

FDA Response to Question 2b: Please see answer above.

c) If accelerated approval, would radiographic PFS be considered appropriate for full approval in the confirmatory study?

FDA Response to Question 2c: Yes. However, see FDA Response to Question 1.

Additional Comments:

Please comment on your plans to request Breakthrough Therapy Designation.

Sponsor Response [8/15/2018]: Based on FDA feedback from the End-of-Phase 2 meeting discussion, we have been working with Dr. Hofman to gather data on the full 50 patient data set to support a BTD request. We are also collecting similar data from a parallel prospective study conducted by Dr. Louise Emmett, using a protocol based on Dr. Hofman's study. We intend to confirm Dr. Hofman's data analysis, and then combine the data from Dr. Emmett's study as well, to ensure a robust data set supporting the request. As noted in the briefing document, data analyzed to date on the full 50 patient data at Dr. Hofman's site is consistent with the initial 30 patient data. Data monitoring and analysis activities are in progress, and we hope to complete the data review in the next few weeks. Once complete, we intend to finalize the BTD request for submission to the IND. Our goal is to submit for BTD within the next 2 months.

Discussion: No Discussion needed.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the

FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and

archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf.

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

N/A

5.0 ACTION ITEMS

N/A

6.0 ATTACHMENTS AND HANDOUTS

N/A

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/

JANICE H KIM
09/04/2018

VIRGINIA E MAHER
09/05/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 133661

MEETING MINUTES

Endocyte, Inc.
Attention: Christopher Jordan
Senior Director, Regulatory Affairs
3000 Kent Avenue, Suite A1-100
West Lafayette, IN 47906

Dear Mr. Jordan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ^{177}Lu-PSMA-617.

We also refer to the meeting between representatives of your firm and the FDA on January 30, 2018. The purpose of the meeting was to discuss your proposed development of ^{177}Lu-PSMA-617 for metastatic castration resistant prostate cancer.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Janice Kim, Regulatory Project Manager at (301) 796-9628.

Sincerely,

{See appended electronic signature page}

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Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	EOP2
Meeting Date and Time:	January 30, 2018; 12:00 PM – 1:00 PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Room 1415 Silver Spring, MD
Application Number:	IND 133661
Product Name:	^{177}Lu-PSMA-617
Indication:	metastatic castration resistant prostate cancer
Sponsor/Applicant Name:	Endocyte, Inc.
Meeting Chair:	V. Ellen Maher, MD
Meeting Recorder:	Janice Kim, PharmD, MS

FDA ATTENDEES
Julia Beaver, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
V. Ellen Maher, MD, Clinical Team Leader, DOP1
Sundeep Agrawal, MD, Clinical Reviewer, DOP1
Jason Schroeder, PhD, Biostatistics Team Leader, DBV
Todd Palmby, PhD, Non-clinical Team Leader, DHOT
Wimolnut Manheng, PhD, Non-clinical Reviewer, DHOT
Stanley Stern, PhD, Imaging Reviewer, DMIP
Janice Kim, PharmD, MS, Regulatory Project Manager, DOP1
Fatima Rizvi, PharmD, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES
Alison Armour, MD, Chief Medical Officer
(b) (4), Consultant - Statistics
Erik Chelius, PhD, Senior Director, CMC
Johannes Czernin, MD; Co-Primary Investigator, Phase 2 RESIST-PC trial
Mike Groaning, PhD; Director, Strategic Development
Christopher Jordan, MSHS; Senior Director, Regulatory Affairs
Patrick Klein, PhD, Senior Director, Toxicology
David McAvoy, JD, Senior Director, Legal Affairs
Tim Mitchell, BS, Senior Director, Quality

Mike Sherman, MBA, CEO, President

1.0 BACKGROUND

The Sponsor is seeking FDA guidance on the proposed development of ^{177}Lu-PSMA-617 for metastatic castration resistant prostate cancer in patients expressing PSMA, as determined by an FDA approved imaging agent, who have already received abiraterone and/or enzalutamide and at least one prior taxane-containing regimen. Specifically, the sponsor's inquiry focuses on the phase 3 study and overall clinical plan for this therapeutic agent, as well as the proposed development plan of the radioactive diagnostic agent ^{68}Ga-PSMA-11, with intention to support registration.

^{177}Lu-PSMA-177

^{177}Lu-PSMA-617 is a beta particle-emitting radioactive therapeutic agent that the sponsor plans to administer intravenously at a dose of 7.4 GBq +/- 10% (200 mCi) every 6 weeks for up to 6 cycles. It is composed of 3 components: a pharmacophore ligand, (b) (4) that enables the radioisotope to bind to PSMA; a chelator DOTA; and a linker connecting these 2. PSMA is a trans-membrane protein that is noted by the sponsor to be expressed in prostate cancer. The proposed mechanism of action of this drug is that binding of the ligand to PSMA can lead to internalization and sustained retention of ^{177}Lu-PSMA-617, which then causes DNA strand damage in prostate cancer cells.

This therapy has been evaluated in Phase 1 dosimetry trials and compassionate use patients. A prospective Phase II study by Hofman has also been reported in 30 patients with metastatic castration resistant prostate cancer. Further details below.

Summary of exposure

The sponsor estimates that ^{177}Lu-PSMA-617 has been used to treat approximately 500 patients, with doses ranging from 2 to 9.3 GBq, and schedules of administration every 4 to 12 weeks for 1-7 cycles. The most common regimen used has been 4 cycles of 6 GBq every 8 weeks, which was published by the German Radiopharmaceutical Society in 2015. The most common parameter for efficacy used has been PSA response, with some reports also providing information on overall survival.

The table below summarizes efficacy findings from various studies involving this therapeutic agent. The Rahbar 2017 study was a compassionate use series summary of 145 patients. The Hofman 2017 study is the first prospective phase 2 study in 30 metastatic CRPC patients dosed with up to 4 cycles of 4-8 GBq given every 6 weeks. In this study, 87% patients had already been exposed to taxane chemotherapy, 47% to 2 taxanes, and 83% had received either abiraterone or enzalutamide.

	Rahbar et al. 2017	Demirci** et al. 2017	Rahbat** et al. 2018	Hofman et al 2017	Hofman** et al 2017

# Patients	145	43	104	30	21 (subset of 30)
# Cycles	1-4 cycles, every 8-12 weeks	2-4 cycles	Median 3 cycles (1-8) every 8 weeks	1-4 cycles, every 6 weeks	Not reported
Mean Dose	5.9 (2-8) GBq	Cumulative dose 21 + 7.2 GBq	Median dose 6.1 GBq	Mean dose 7.5 (4.4-8.7) GBq 8-6 GBq q 6 wks x 4	Not reported
Efficacy PSA decline ≥50%	PSA decline ≥50% in 45% of patients	PSA decline ≥50% in 54% of patients median PFS 6.5 mo (95% CI 4-8.9) median OS 15 mo (95% CI 12.1-17.8)	PSA decline ≥50% after first cycle in 33% patients Median OS 56 weeks (95% CI: 50.5-61.5)	PSA decline ≥50% in 57% of patients	PSA decline ≥50% in 57% of patients ORR by RECIST in 17 patients with measurable disease was 71%.

All patients had PSMA-expressing metastatic CRPC with progression after abiraterone or enzlutamide and a taxane, or were ineligible for chemotherapy

**In the Hofman study, 21 out of 30 patients are the subset that meet criteria for the sponsor's proposed Phase III study population. Also, 42 out of 43 patients in the Demirci study, and all 104 patients in the Rahbar 2018 OS analysis listed above meet inclusion criteria for the proposed Phase III study. However, these pts were not treated at the phase 3 dose and schedule.

Safety

Current radiation dose limits for normal tissue radioligand therapy exposure have been taken directly from limits defined for high dose external beam radiation. Areas of normal tissue PSMA expression, including the proximal renal tubules, duodenal mucosa, and salivary glands may be sites of toxicity from this therapeutic agent, in addition to the metastatic sites involved which is predominantly bone.

Adverse events noted with in the Hofman study have been reported as mostly Grade 1 and 2, including Grade 1 and 2 xerostomia in 63% of patients. Common grade 3 and 4 events include anemia (23%), neutropenia (10%), and thrombocytopenia (27%). The only other Grade 3-4

toxicities reported were fatigue (3%) and bone pain (3%). Retrospective analyses also demonstrated Grade 1-2 AST elevation in 19% of patients and ALT elevation in 8% of patients. The schedule for laboratory testing in the Hofman study is unknown. Safety reports from other series also note hematologic toxicities, xerostomia, fatigue, and bone pain, as well as nausea. The sponsor notes that hematologic impairment, likely due to bone metastatic disease and heavy pre-treatment combined with transient exposure to radioactivity, was present in 65-92% of patients at baseline. No significant nephrotoxicity signal has been noted, per the sponsor.

^{68}Ga-PSMA-11

The sponsor also is inquiring about diagnostic imaging to use in conjunction with this experimental treatment, to select patients who express PSMA. They note that multiple small molecule-based, radioactive diagnostic agents are in development globally for the localization of PSMA expression, and they may use one of these agents in conjunction with ^{177}Lu-PSMA if they any of them are approved at the time of their submission. Further, they plan to study ^{177}Lu-PSMA with multiple imaging agents. If none are approved, the sponsor plans to submit its own PSMA targeted diagnostic agent, ^{68}Ga-PSMA-11.

^{68}Ga-PSMA-11 is a radiopharmaceutical with proposed use for localizing PSMA-expressing metastatic prostate cancer. The sponsor plans for this to be used with PET for localization of PSMA-expressing metastatic prostate cancer in adult patients. It will be administered intravenously at a dose of 111 (b) (4) MBq (3 (b) (4) mCi) prior to ^{177}Lu-PSMA-617.
As noted above, in the event that no other small molecule PSMA-targeted imaging agent is approved at the time of ^{177}Lu-PSMA-617 submission, the sponsor plans to submit ^{68}Ga-PSMA-11 for approval to be used to select patients with PSMA expressing tumors for treatment with ^{177}Lu-PSMA-617.

Proposed Phase 3 Study

Patients will be randomized 2:1 to receive either ^{177}Lu-PSMA-617 plus physician's choice or physician's choice only. Physician's choice will exclude other investigational agents, cytotoxic chemotherapy, other systemic radioisotopes, and hemi-body radiotherapy. The sponsor has provided the following examples of agents that may be used in combination with study drug: enzalutamide/abiraterone (in pts who have not received both), focal radiation therapy, steroids, first generation anti-androgens, estramustine, or ketoconazole. The study will be open-label, and the planned enrollment is 750 patients. As mentioned above, patients will be those with metastatic CRPC who have progressed on either abiraterone or enzalutamide and at least one prior taxane (and if patient's physician deems patient is unsuitable for or patient refuses to receive a second taxane). Patients must also show PSMA uptake on imaging studies.
^{177}Lu-PSMA-617 will be administered intravenously at a dose of 7.4 GBq +/- 10% (200 mCi) every 6 weeks for up to 6 cycles. After the 4th cycle, the investigator will determine whether the patient will go on to receive 6 cycles of study drug. Patients with a PSA or radiological response and those thought to be receiving clinical benefit will remain on study for 6 cycles. The agent used in combination with study drug (or another agent) will be continued beyond 6 cycles.

The primary endpoint is overall survival. Key secondary endpoints include radiographic PFS, ORR, and time to first skeletal related event. Radiographic imaging will take place every 8 weeks during the first 24 weeks of treatment and every 12 weeks thereafter. The total duration of the study will be approximately 30 months.

Statistical Analysis Plan Summary:

With 750 patients and 489 events at the time of the final analysis, the study can detect a HR of 0.82 with a one-sided p value of 0.023. This would result in a median OS of 10 months in the control and 12.1 months in the treatment arm. There will be 2 interim analyses at 50% (~18 mos) and 70% (~22 mos) of events that will use one-sided alphas of 0.00153 and 0.0069, respectively.

2. DISCUSSION

Question 1: Significant clinical safety and dosimetry information has been collected for ^{177}Lu-PSMA-617 through compassionate use and clinical trials (See Section 10.1.3 and Appendix A). Does FDA agree that the proposed nonclinical data package (See Section 10.2.1), as supported by the current and planned clinical studies, is sufficient to support registration of ^{177}Lu-PSMA-617 in this patient population?

FDA Response to Question 1: It does not appear at this time, that additional nonclinical studies will be needed to support submission of an NDA for ^{177}Lu-PSMA-617 in the intended patient population. A final decision on what nonclinical studies will constitute a complete NDA submission will be made at the time of a future pre-NDA meeting.

Question 2: Does FDA agree that the design of the planned Phase 3 study for ^{177}Lu-PSMA-617 is sufficient to meet its stated objectives and that it can be considered an adequate and well controlled trial supporting approval? Specifically, does the Agency agree with the following aspects of the study:
a. Study design, including primary and secondary endpoints
b. Planned patient population and comparator arm
c. Patient selection process
d. Dose and schedule of ^{177}Lu-PSMA-617
e. Statistical analysis plan

FDA Response to Question 2: We have the following comments regarding the design and treatment plan of your planned Phase 3 study:

1. **Given the wide variety of physician's choice therapy options, the specified design may not reliably estimate the treatment effect for ^{177}Lu-PSMA-617. If the physician's choice therapies used in the two arms are not comparable (e.g., enzalutamide versus radiation), then the magnitude of any observed treatment effect may not be attributable to the ^{177}Lu-PSMA-617 therapy.**
    a. **We recommend that you limit the number of options (2 to 3 drugs) included in the physician's choice therapies. This will allow a larger number of**

patients to be enrolled to each group and will permit examination of the contribution of each physician's choice therapy to study outcome.

Sponsor Response to Question 2 Response 1(a): The decision to provide the physician's choice in each arm was based on a number of factors recommended by health care practitioners experienced in the development of prostate cancer therapies, including (i) variability in global prescribing patterns and agent availability (to ensure the trial can be international in scope), (ii) the desire to provide good palliation and best standard of care (since placebo is not an ethical option), and (iii) the concern that some investigators will not randomize patients to a physician's choice arm if access to a novel androgen axis drug (NAAD) is not provided. The options described for physician's choice fall into two broad categories – a second NAAD for patients who are eligible and palliative care alternatives. None of the palliative care options included in physician's choice have been shown to impact overall survival. The agents most likely to provide meaningful efficacy in this population are abiraterone and enzalutamide. Therefore, we propose to adjust the original stratification related to number of prior novel androgen axis drugs (abiraterone or enzalutamide – 1 vs 2), and change that to a stratification related to use of a second NAAD in the comparator arm, yes versus no. This will maintain balance between the arms of the study.

Discussion: The sponsor's proposal to randomize patients to study drug plus possible abiraterone/enzalutamide or possible abiraterone/enzalutamide is acceptable. Patients will be stratified by whether or not they would use abiraterone/enzalutamide.

b. We also recommend that Investigator's pre-specify the physician's choice therapy they plan to use and that you use this as a stratification factor during randomization.

Sponsor Response to Question 2 Response 1(b): We agree to have investigators pre-specify the physician's choice therapy – please see response to the previous point regarding stratification based on physician's choice administered.

2. **Your choice of primary and secondary endpoints is acceptable.**
3. **We have the following additional comments about the choice of comparators. Some combinations could result in unintended adverse events.**
    a. **Given these concerns and difficulty standardizing focal external beam radiation, including modalities used, we recommend you limit physician's choice to drug therapies. If you choose to use external radiation, given the possible synergistic toxicity that may result from your treatment and focal external beam radiation therapy, you should provide a plan for the DMC to monitor the safety of patients receiving these therapies concomitantly.**

Sponsor Response to Question 2 Response 3(a): We believe this is an important treatment option for certain patients in this setting, and focal external beam radiation therapy does not reduce blood counts. To ensure patient safety, we agree to careful safety monitoring, and will provide a safety monitoring plan in the DMC charter.

b. Combining a radiation-based therapy with abiraterone (or enzalutamide) may cause synergistic toxicity (see DHCP Letter from Bayer dated November 30, 2017. It is noted that 45 patients have received study treatment concomitantly with abiraterone or enzalutamide in the Rahbar 2016 and Ahmadzadehfar 2017 studies. Please provide a plan for the DMC to monitor for synergistic toxicity with combination treatment of your study agent with abiraterone and enzalutamide.

Sponsor Response Question 2 Response 3(b): We have previously noted the excess numbers of fractures
25% v 7% and deaths 27% v 20% in the radium/abiraterone/prednisolone arm compared to the abiraterone/prednisolone arm, and discussed the findings with our clinical advisors in relation to the proposed Phase 3. No bone fracture safety signal has been detected to date in the large number of patients treated with ^{177}Lu–PSMA-617. To ensure patient safety, we agree to careful safety monitoring, and will provide a safety monitoring plan in the DMC charter.

4. **Inclusion criteria #11a, serum PSA progression definition should be consistent with the Prostate Cancer Working Group definition; in their definition, 2 ng/mL is the minimal starting value. Please record the type (PSA, bone scan, RECIST) of disease progression. You should exclude patients with a super scan.**

Sponsor Response to Question 2 Response 4: With regard to these requests: (1) There is some ambiguity in the PCWG3 paper between the columns in Table 3 regarding the minimal starting value – our intent is to be consistent with the PCWG3 criteria. We agree with a definition of 2 ng/mL as the minimal starting value. (2) We agree to record the type of disease progression (PSA, bone scan, RECIST). (3) We also agree with excluding patients with a super scan, and will add that as an exclusion criterion.

5. **FDA encourages broadening eligibility criteria when safe and appropriate. Specifically, consider allowing enrollment of the following patients:**
   a. **Patients with treated/stable brain metastases (e.g., no progression for at least 4 weeks after local prior therapy). If there are specific safety concerns, consider tailoring specific criteria to the concern rather than generally excluding all patients with brain metastases.**

Sponsor Response to Question 2 Response 5(a): We agree to broadening eligibility criteria per these comments. We will revise the inclusion criteria regarding brain metastases to the following: "Patients with a history of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired. For patients with parenchymal CNS metastasis (or a history of CNS metastasis), baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast)."

b. Patients with HIV infection who are healthy and have a low risk of AIDS-related outcomes.

Sponsor Response to Question 2 Response 5(b): We propose to revise the inclusion and exclusion criteria as follows:
INCLUSION CRITERIA: HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial.

EXCLUSION CRITERIA: Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, New York Heart Association Class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, active hepatitis B, or C, or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.

6. **For further comments regarding patient selection, specifically in regards to the use of a PSMA targeted small molecule diagnostic agent, please FDA Response to Question 4 and 6 below.**
7. **You should ensure that in the absence of disease progression or excess toxicity that all patients receive the same number of cycles of study drug.**

Sponsor Response to Question 2 Response 7: All patients will receive 6 cycles of ^{177}Lu-PSMA-617 in the absence of disease progression or excess toxicity.

8. **You have not provided sufficient information regarding your choice of dosage regimen and number of cycles you proposed to use or the expected toxicity. Please state the number of patients who have been treated with the proposed phase 3 dose and schedule, the schedule of laboratory monitoring, and the adverse events and laboratory abnormalities reported in these patients.**

Sponsor Response to Question 2 Response 8: The selection of 7.4 GBq every 6 weeks for 6 cycles is based on data from the prospective Phase 2 trial by Dr. Hofman, and is further supported by compassionate use studies, dosimetry data, and by the development of ^{177}Lu-DOTATATE (Lutathera). The principle behind the Phase 3 treatment regimen is to replicate the safety and efficacy of ^{177}Lu-PSMA-617 as demonstrated in the prospective Phase 2 study by Dr. Hofman, and to maximize the potential survival for these patients by allowing a total of 6 cycles to be administered to patients who are receiving benefit.

The prospective Phase 2 trial conducted by Dr. Hofman has the most relevant data supporting the dosage regimen proposed for the phase 3 study. Thirty patients had been treated at the time of the ESMO presentation with 7.4 GBq, administered every 6 weeks. Laboratory evaluations of hematology and blood chemistry occurred every 2 weeks, including on the day of subsequent treatment. The tables below describe the adverse events and laboratory abnormalities reported in the phase 2 study, and demonstrates a favorable safety profile.

Toxicity	G1/2 (%) (baseline)	G1/2 (%) any cause	G3/4 (%) any cause	G3/4 (%) (LuPSMA617)
Hemoglobin	80	73	23	7
Neutrophils *	0	40	10	7
Platelets	17	43	27	13

* No episodes of febrile neutropenia

Toxicity	G1/2 (%)	G3/4 (%)
Dry mouth	63	0
Nausea*	50	0
Vomiting*	20	0
Fatigue	17	3
Dry Eyes	7	0
Bone pain	7	3
Anorexia	7	0
Infusion related reactions	0	0
Renal toxicity	0	0

* transient and self-limiting within first 24 hours

This study has been expanded to 50 patients and discussions with Dr. Hofman indicate that the safety profile noted above is consistent in the additional 20 patients. In this study, Dr. Hofman has given a maximum of 4 cycles of therapy and, on the basis of the safety information generated, suggested that in the phase 3 trial therapy be given up to 6 cycles, barring disease progression.

In addition, Haug, et al has previously administered 3 cycles of ^{177}Lu-PSMA-617 at a dose of 7.4GBq every 4 weeks with no excess hematological toxicity. Higher doses of 8.7 GBq have also been administered by Baum, et al, every 8 weeks, again with no excess hematological toxicity. Overall, the available ^{177}Lu-PSMA-617 literature indicates that 4 cycles of 7.4 GBq ^{177}Lu-PSMA-617 can be given every 4, 6 or 8 weeks with low grade reversible hematologic toxicity and an acceptable safety profile.

The current radiation dose limits for normal tissue exposure are derived from external beam radiotherapy rather than directly from radioligand therapy. These thresholds, particularly for

kidney exposure, have provided a conservative backdrop for both ^{177}Lu-PSMA-617 as well as Lutathera development, as described in the EOP2 briefing document. Four cycles of 7.4 GBq results in an estimated kidney radiation exposure of approximately 23 Gy, in line with the external beam radiotherapy recommendations. However, in this patient population, and given the uncertainty of translating external beam radiation limits to radioligand therapy, the additional 2 cycles are warranted as they may provide an additional survival benefit to patients that have been found to respond favorably following the first 4 cycles of therapy. Up to six cycles (in the absence of disease progression or excess toxicity) of 6-8.5 GBq per dose, administered every 6 weeks, are being administered in the recently started randomized phase 2 study at sites in Australia and New Zealand, based on the Hofman prospective study.

Based on all these inputs, we intend to administer a maximum of 6 cycles of ^{177}Lu-PSMA-617 at a dose of 7.4GBq, every 6 weeks, in Study PSMA-617-01.

Sponsor References:
Haug et al, Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S212 EPW11.
Baum et al, J Nucl Med. 2016 Jul;57(7):1006-13.

Discussion: Your choice of dose and schedule appear to be acceptable. However, you should develop a plan to have your DMC closely monitor the initial 30 patients on study drug for toxicity.

9. **In the proposed phase 3 protocol, please provide a plan for follow up of patients for renal dysfunction, MDS, AML, etc. after administration of 6 cycles of study drug. We realize these patients have a limited life expectancy, but would like to collect as much data as possible.**

Sponsor Response to Question 2 Response 9: We agree, and will update the Phase 3 protocol to include hematological and biochemical laboratory assessments every 3 months as part of the planned long term follow up, to screen for hematological and/or renal dysfunction, MDS and AML.

10. **We recommend that you use the stratified log-rank test for your primary analysis. We will provide more comments once you submit a detailed statistical analysis plan.**

Sponsor Response to Question 2 Response 10: We are concerned with loss of statistical power based on a log rank test that can occur as the number of strata increases, increasing the possibility of empty cells. An identically structured stratified Cox analysis with randomized treatment as the sole covariate does not suffer from this power loss.

Question 3: Assuming positive results from the planned Phase 3 study of ^{177}Lu-PSMA-617 and demonstration of positive benefit/risk in the proposed patient population (which Endocyte recognizes is a review issue), does FDA agree that the overall registration plan as outlined in Section 10.2.3 is sufficient to support approval?

FDA Response to Question 3: Your registrational plan appears generally acceptable. However, see our responses in this document.

Question 4: Multiple small molecule-based, radioactive diagnostic agents are in development globally for the localization of PSMA expression (DCFPyL, PSMA-11, PSMA-1007, EC0652, PSMA-617, Progenics 1404/MIP-1404, etc). This class of imaging agents all identify PSMA expression through the use of radiolabeled targeting ligands that bind to PSMA, and where tested, preliminary data indicates comparable tumor distribution results. There is the potential that one or more of these agents may be submitted and/or approved prior to the approval of the therapeutic ^{177}Lu-PSMA-617. Endocyte proposes that (b) (4) ^{177}Lu-PSMA-617 (assuming eventual approval) includes use of any FDA approved PSMA-targeted small molecule-based radioactive diagnostic agent to characterize the PSMA status of mCRPC patients who may be eligible for ^{177}Lu-PSMA-617 therapy. Does FDA agree that an FDA-approved PSMA-targeted small molecule based radioactive diagnostic agent would be suitable for determining PSMA status of mCRPC patients?

FDA Response to Question 4: No.

1. **You have stated that PSMA is highly expressed on prostate cancer cells and that it continues to be expressed in patients with castration-resistant prostate cancer. Please comment on the need to determine PSMA-targeted uptake on imaging, to predict response, prior to administration of ^{177}Lu-PSMA. If possible, please provide data concerning patient outcome among those who did not have PSMA-targeted uptake prior to dosing.**

Sponsor Response to Question 4 Response 1: The expression of PSMA and uptake and retention of ^{177}Lu-PSMA-617 into prostate cancer cells is an important part of the mechanism of cell kill. This mechanism has been demonstrated in preclinical studies using PSMA-positive and PSMA-negative xenografts. In addition, dosimetry studies have confirmed that ^{177}Lu-PSMA-617 uptake occurs in PSMA positive tumor and tissue. Data from the Hofman study demonstrates that up to 15% of patients who might otherwise be eligible for the study are not good candidates for ^{177}Lu-PSMA-617 therapy based on lack of PSMA-expressing disease. It should be noted that Dr. Hofman performed a rigorous assessment of PSMA-positivity and observed the highest response rates for PSA reduction and ORR per RECIST criteria, relative to compassionate use studies where more liberal criteria were used. We believe that PSMA-imaging to assess patient's disease is important for inclusion in the study.

We do not have data regarding patient outcome for patients who do not have PSMA-targeted uptake at this time.

2. **It is necessary to demonstrate that the use of each imaging agent results in the same decision concerning treatment with ^{177}Lu-PSMA. It is then necessary to demonstrate that these treatment decisions result in similar outcome for the patients. We recommend you use a single imaging agent and a single imaging modality. Alternatively, you could provide a plan to examine the role of imaging in**

patient outcome with a small number of imaging agents. This plan will be subject to review.

Sponsor Response to Question 4 Response 2: We would like to discuss this further in the meeting. Our approach is modeled off the use of in vitro diagnostic tests for patient selection, where an FDA-approved test is sufficient for patient selection and the test approval/clearance is provided by CDRH. We believe that if a PSMA-targeted imaging agent is approved by DMIP for PSMA-expressing disease that the approval addresses issues such as sensitivity/specificity, truth standard comparisons, etc.

We also note the newly granted approval of Lutathera (January 26, 2018), which is indicated for somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors. Two imaging agents for detection of somatostatin receptor positive disease are approved (Octreoscan and NETSPOT), and per the approved Lutathera labeling either can be used for patient selection.

We are also concerned with the suggestion that it is necessary to demonstrate that treatment decisions result in similar outcomes. The use of a PSMA-targeted imaging agent is used to make a treatment decision regarding ^{177}Lu-PSMA-617 administration. However, patient outcome as a result of ^{177}Lu-PSMA-617 therapy is based on multiple other factors, such as the inherent radiosensitivity of the tumor and individual patient tolerability. Further, the requirement to demonstrate treatment decisions result in similar outcomes will necessitate new efficacy studies to be conducted with each PSMA-targeted imaging agent that may be approved, either before or after a ^{177}Lu-PSMA-617 approval is received. We are concerned that this will limit access to ^{177}Lu-PSMA-617 should it be approved, even in the case of an approved imaging agent for PSMA-expressing disease.

3. **Please provide detailed information on the method that will be used to read the imaging scans and how the decision will be made to administer the therapeutic agent.**

Sponsor Response to Question 4 Response 3: We have drafted our read rules and are currently evaluating them using the Phase 2 data from the Hofman study. The current read rules and patient selection process are outlined below:

Each subject passing initial screening for the Phase 3 study will be evaluated with an appropriate PSMA-targeted imaging agent. Images will be collected from each site electronically by a pre-selected imaging CRO, processed and checked for quality. After clearing the quality check, images will be read by a trained radiologist or nuclear medicine physician. The reads will be performed by viewing the MIP or coronal images. Each reader will have completed reader training and will ensure adherence to pre-selected read rules that will be detailed in the imaging charter.

The read rules have been designed to exclude patients who are unlikely to receive benefit from ^{177}Lu-PSMA-617 treatment. Inclusion into the study requires that patients have PSMA-positive disease (as defined in Rule 1 below) without significant presence of PSMA-negative disease as

determined by rules 2-4. The draft rules will categorize patients as eligible or ineligible for treatment with ^{177}Lu-PSMA-617 as follows:

1. Patients must have PSMA-positive disease by PSMA-targeted imaging. Positivity will be defined based on a visual comparison, with uptake greater than liver required.
2. Patients with large PSMA-negative lymph nodes (>2.5 cm) will be ineligible for ^{177}Lu-PSMA-617 therapy.
3. Patients with bone metastasis with a PSMA negative soft tissue component (≥1 cm) will be ineligible for ^{177}Lu-PSMA-617 therapy.
4. Patients with a PSMA-negative solid organ metastasis (i.e., lung, liver, adrenal glands, etc.) that are ≥1 cm, will be ineligible for ^{177}Lu-PSMA-617 therapy.

Because PSMA-positivity is a requirement for study entry/randomization, reads will be performed within 48-72 hours. The central read will consist of a single read from any one of a pool of 3 readers pre-selected for the study. After the read is performed centrally, the imaging CRO will input the read result (eligible/ineligible for ^{177}Lu-PSMA-617 therapy) for each subject and that will be communicated to the corresponding study site.

The final version of the read rules will be submitted to the IND prior to study implementation.

Discussion: FDA expressed their concerns about the sponsor's approach. The sponsor will provide additional rationale and literature and their decision concerning the final study design.

Question 5: Significant clinical safety and dosimetry information has been collected for ^{68}Ga-PSMA-11 through compassionate use and clinical trials (See Section 10.1.4). Does FDA agree that the proposed nonclinical data package (See Section 10.3.1), as supported by the current and planned clinical studies, is sufficient to support registration of ^{68}Ga-PSMA-11?

FDA Response to Question 5: We have insufficient information to provide an answer to this question. We recommend that you clarify whether ^{68}Ga-PSMA-11 is being developed strictly as a companion diagnostic for use with ^{177}Lu-PSMA-617 or as a "stand-alone" diagnostic imaging drug. Assuming the latter, we recommend that you submit a meeting request to DMIP for discussion of your imaging drug development.

Question 6: In the event that a PSMA-targeted small molecule imaging agent is not approved at the time of ^{177}Lu-PSMA-617 submission and Endocyte proceeds forward with registration of a PSMA-targeted imaging agent, does FDA agree that the overall registration plan (as outlined in Section 10.3.2) is sufficient to support approval of ^{68}Ga-PSMA-11 for localization of PSMA-expressing metastatic prostate cancer?

FDA Response to Question 6: Please see FDA Response to Question 5. The "registration plan" would have to include adequate product quality data and demonstrate substantial evidence of safety and effectiveness of their product.

Additional Comments:

1. **We recommended that you revise the exclusion criteria in the proposed clinical protocol for ^{177}Lu-PSMA-617 for patients who have partners of childbearing potential to be consistent with the recommendation in the Investigator's Brochure. Advise male patients who have female partners of reproductive potential to use effective contraception during treatment and for at least 3 months following the last dose.**
2. **Please comment on the rationale for using an add on trial design instead of using study drug as single agent compared to physician's choice.**

Sponsor Response to Additional Comments (2): Multiple discussions with investigators and advisors have indicated that in this patient population, physician's choice of best standard of care should not be withheld from any patient enrolled in the study, for both ethical and practical reasons. In addition, there are no overlapping toxicities between the agents in physician's choice and ^{177}Lu-PSMA-617 therapy, which supports the currently proposed trial design.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format.

This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do

not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:

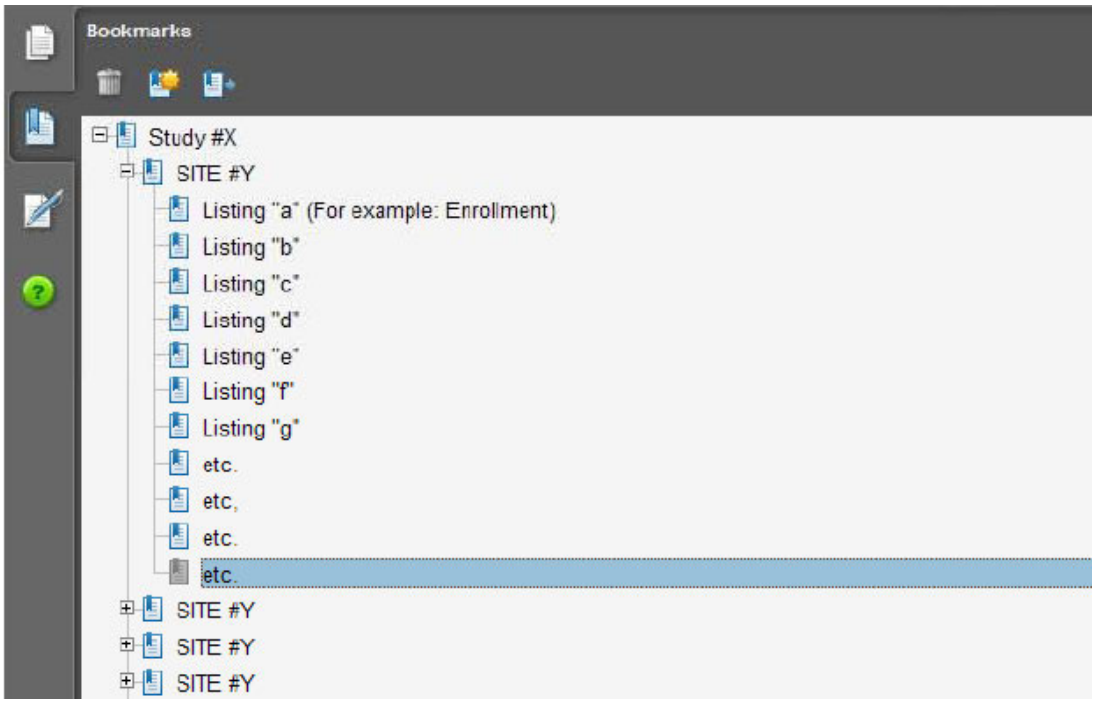
a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

N/A

5.0 ACTION ITEMS

N/A

6.0 ATTACHMENTS AND HANDOUTS

N/A

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANICE H KIM
02/08/2018

VIRGINIA E MAHER
02/09/2018