CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215833Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 11, 2022

To: Kelly Chiang, Regulatory Project Manager
Division of Oncology 1 (DO1)

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for PLUVICTO (lutetium Lu 177 vipivotide tetraxetan) injection, for intravenous use

NDA: 215833

In response to DO1's consult request dated August 10, 2021, OPDP has reviewed the proposed product labeling (PI) for the original NDA submission for PLUVICTO (lutetium Lu 177 vipivotide tetraxetan) injection, for intravenous use.

OPDP's comments on the proposed PI are based on the draft PI received by electronic mail from DO1 on February 1, 2022, and are provided below.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

LYNN M PANHOLZER
02/11/2022 11:58:29 AM

Clinical Inspection Summary

Date	January 24, 2022
From	Yang-Min (Max) Ning, M.D., Ph.D. Min Lu, M.D., M.P.H. Philip Kronstein, M.D. Kassa Ayalew, M.D., M.P.H. GCPAB/DCCE/OSI/CDER/FDA
To	Jaleh Fallah, M.D. Sundeep Agrawal, M.D. Kelley Chiang, RPM DO1/OOD/CDER/FDA
NDA #	215833
Applicant	Advanced Accelerator Applications USA, Inc.
Drug	Lutetium (^{177}Lu) vipivotide tetraxetan
NME (Yes/No)	Yes
Therapeutic Classification	Radiopharmaceutical
Proposed Indication	Treatment of prostate-specific membrane antigen (PSMA) expressing, metastatic castration-resistant prostate cancer (mCRPC)
Consultation Request Date	September 1, 2021
Summary Goal Date	January 28, 2022
Action Goal Date	February 4, 2022
PDUFA Date	March 29, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from a randomized trial (Protocol PSMA-617-01) were submitted to the Agency in support of a New Drug Application (NDA) for lutetium (^{177}Lu) vipivotide tetraxetan for use in patients with previously treated, PSMA-expressing mCRPC. Four clinical investigators (CI), Drs. Michael Morris (Site 100104), Nitin Vaishampayan (Site 100029), Scott Tagawa (Site 100152), and Edward Gelmann (Site 100006) and the sponsor (Endocyte, Inc., A Novartis Company) were selected for Good Clinical Practice (GCP) inspections.

Inspections of the four CIs and the study sponsor found no significant regulatory deficiencies. The Applicant's submitted clinical data, including the reported subject PSMA eligibility per the sponsor's prespecified criteria and determination, were verifiable against source records at the sites. Based on the results of these inspections, Study PSMA-617-01 appears to have been conducted adequately, and the clinical data generated by these four CI sites appear reliable and acceptable for this NDA.

II. BACKGROUND

Lutetium (^{177}Lu) vipivotide tetraxetan is a radiopharmaceutical consisting of the radionuclide lutetium-177 bound to a peptidomimetic ligand (PMSA-617) that targets PSMA. The product, named ^{177}Lu-PSMA-617 under IND 133661, has been investigated in patients with advanced prostate cancer. For this NDA, the Applicant submitted clinical data from a randomized trial (Study PSMA-617-01) and proposed an initial indication for the product (b) (4) (b) (4).

Study PSMA-617-01 [NCT03511664] is an ongoing, open-label, randomized (2:1) Phase 3 trial of ^{177}Lu-PSMA-617 in subjects with previously treated, PSMA-expressing mCRPC. To be eligible for the study, subjects were required to have: 1) evidence of pathologically diagnosed prostate cancer and disease progression with at least one metastatic lesion in the mCRPC setting per the prostate cancer clinical trials working group 3 (PCWG3) Guidelines; 2) received at least one novel androgen axis drug (NAAD), i.e., abiraterone acetate or enzalutamide and 1 or 2 taxane-based chemotherapy regimens; 3) have at least one PSMA-positive lesion as determined by the sponsor's designated independent central review (ICR) of gallium (^{68}Ga-PSMA-11) gozetotide positron emission tomography/computed tomography (PET/CT) scan(s) performed at Screening. Subjects who had received other radiotherapeutics (e.g., strontium-89, radium-223) within 6 months prior to randomization or any systemic anti-cancer therapy (e.g., chemotherapy, immunotherapy, or biological therapy) or any investigational agents within 28 days prior to randomization were excluded. Subjects who met all the eligibility criteria were to be randomized (2:1) to receive ^{177}Lu-PSMA-617 plus best standard of care (BSoC) [referred as the lutetium arm thereafter for brevity] or BSoC alone [referred as the control arm thereafter].

The initial primary efficacy endpoint was overall survival (OS), defined as time from the date of randomization to the date of death from any cause. Approximately 8 months after the study initiation, one previously specified secondary endpoint, radiographic progression-free survival (rPFS), was escalated to an alternative primary efficacy endpoint for subjects randomized on or after March 5, 2019. rPFS was defined as the time from the date of randomization to the date of radiographic disease progression as assessed by ICR per the PCWG3 Guidelines or date of death from any cause.

Subjects randomized to the lutetium arm were scheduled to receive ^{177}Lu-PSMA-617 intravenously at a dose of 7.4 GBq (200mCi [±10%]) every 6 weeks (± 1 week) for a total of 6 doses. For subjects in either arm, treatments of BSoC were to be administered at the investigator's discretion, including supportive measures (e.g., pain medications, blood transfusions), other protocol non-prohibited hormonal agents (e.g., ketoconazole), radiation therapy for localized prostate cancer lesions, and bone-targeted agents (i.e., zolendronic acid or denosumab). Study treatment was to be discontinued for unacceptable toxicity, disease progression as assessed by the investigator per the PCWG3 criteria, use of a protocol-specified prohibited treatment, non-compliance, consent withdrawal, or at the investigator's discretion.

Tumor imaging assessments were to be performed with computed tomography

(CT)/magnetic resonance imaging (MRI) scans, bone scans at baseline (within 4 weeks of randomization), every 8 weeks (± 4 days) after initiation of study treatment for the first 24 weeks (independent of dose delays), and then every 12 weeks (± 4 days) through the End of Treatment (EOT) visit. Study scans were to be continued until evidence of disease progression as assessed per the PCWG3 recommendations and related criteria. All scans were required to be submitted to the sponsor's designated imaging laboratory for central review. Following EOT, long-term follow up procedures were to be used every 3 months (± 1 month) for subject survival status, adverse events of special interest, and updates on cancer treatment.

From 05/29/2018 through 01/27/2021 (data cutoff date for analyses included in the current NDA), the study enrolled 831 subjects from 86 investigator sites in eight countries, including Belgium, Canada, Denmark, France, Netherlands, Sweden, United Kingdom, and United States (U.S.). Sixty-three percent of subjects in the study were recruited from the U.S. Of the total enrolled, 551 subjects were randomly assigned to the lutetium arm and 280 to the control arm. This constitutes the population for analysis for the primary endpoint OS. After the key protocol amendment which prospectively included rPFS as the alternative primary endpoint, 581 subjects were enrolled and randomized from 03/09/2019 through the enrollment conclusion. This subpopulation of 581 subjects is the basis for the planned rPFS analysis. Subjects who received at least one dose of study treatment, 529 subjects in the lutetium arm and 205 subjects in the control arm, are included for safety analyses. The study was ongoing as of the above data cutoff date.

The sponsor submitted the Clinsite.xpt dataset necessary for generation of the Clinical Investigator Site Selection Tool (CISST) for Study PSMA-617-01. The Review Division DO1 and OSI reviewed the CISST and selected four investigators for inspection using a risk-based approach. Relative to other domestic sites, these four investigator sites enrolled large numbers of subjects and/or were associated with a considerably lower death rate in the lutetium arm than that in the control arm, favoring treatment with ^{177}Lu-PSMA-617 in terms of primary efficacy results. GCP inspection of the study sponsor was also requested by DO1 given that the product is a new radiopharmaceutical and that the study sponsor has no prior inspection history.

III. RESULTS

1. **Michael Morris, M.D.**
   Site #100104
   1275 York Ave.
   New York, NY 10065
   Inspection Dates: 10/27/2021 – 11/03/2021

   At this site for Protocol PSMA-617-01, 25 subjects were enrolled, with 14 subjects randomized to the lutetium arm and 11 to the control arm. Following randomization, all subjects except for one (Subject (b) (6) in the control arm who died) received study treatment as planned. As of the data cutoff date of (b) (6), 13 subjects in the lutetium arm and 10 subjects in the placebo arm were discontinued due to disease progression, adverse event(s), investigator's discretion, or withdrawal of consent. One subject (# (b) (6)) in the lutetium arm remained on study treatment. Of those who were discontinued, 8 subjects in the lutetium arm and 10 in the control arm have subsequently died since the cutoff date. At the time of this inspection, no subjects were on study treatment, and the study was closed to enrollment but remained open for subjects in survival follow-up.

   Source records for all the enrolled subjects were reviewed during the inspection, and relevant source data were compared with the Applicant's submitted data for the site. The reviewed subject records included the informed consents, eligibility criteria checklists, PSMA eligibility confirmation, enrollment log, randomization allocations, study treatment administration, tumor scans and RECIST worksheets, adverse events (AE) and serious adverse events (SAE), concomitant medications, laboratory reports, protocol deviations, and electronic case report forms (eCRFs). Regulatory binders and procedures for the study administration and oversight were also reviewed, including the institutional review board (IRB) approvals of the protocol/amendments and informed consent forms, delegation of authority log, signed Form FDA 1572s, financial disclosures, training, data entry into eCRFs, study monitoring and reporting to the sponsor, investigational product accountability, and study records retention.

   All the enrolled subjects were found to have met the eligibility criteria and had PSMA-positive lesion(s) per the ICR determination and documentation prior to initiation of study treatment. The Applicant's submitted data, including the primary efficacy endpoint OS, were verified against the source records at the site. No discrepancies were noted. There was no evidence of underreporting of adverse events.

   Of note, the inspection identified that one sub-investigator (Lisa Bodei, M.D., Ph.D.) for this study who signed off an eligibility checklist was found not delegated as per the Delegation of Authority log. This issue was addressed with a Note to File that demonstrated this sub-investigator was fully trained on the study protocol at the study initiation visit and at subsequent amendments, specifically

surrounding the eligibility reviews for this protocol.

2. **Nitin Vaishampayan, M.D.**
   Site #100029
   87 E Canfield St MM05P1
   Detroit, MI 48201
   Inspection Dates: 10/20/2021 – 10/28/2021

   At this site for Protocol PSMA-617-01, 30 subjects were enrolled, with 20 subjects randomized to the lutetium arm and 10 to the control arm. Two subjects (# (b) (6) in the control arm) did not receive the intended treatment(s) following randomization secondary to withdrawal of consent or death. As of the data cutoff date of (b) (6) one subject (# (b) (6) in the lutetium arm) remained on study treatment, and the other subjects had been discontinued from study treatment due to progressive disease, adverse event, death, investigator's decision, or withdrawal of consent. Among the subjects who were discontinued from study treatment, 12 in the lutetium arm and 8 in the control arm died prior to the data cutoff. The remaining subjects were in follow-up visits as per the protocol.

   Source records for all the subjects in the lutetium arm and three randomly selected subjects in the control arm were reviewed during the inspection, and relevant source data were compared with the Applicant's submitted data for the site. The subject records reviewed included, but were not limited to, the signed informed consents, subject eligibility forms and related ^{68}Ga-PSMA-11 scan results, screening and enrollment log, randomization assignment, study treatment administration, imaging documents and local RECIST assessments, AEs and SAEs, laboratory results, follow-up visits, survival status, and protocol deviations. The reviewed regulatory documents included the IRB's approvals of the study protocol/amendments and relevant acknowledgements, Delegation of Authority, signed Form FDA 1572s, financial disclosures, site training throughout the study, monitoring reports and communications, and investigational product administration procedure and accountability records.

   All the subjects underwent ^{68}Ga-PSMA-11 scans prior to randomization and were found to have met the ICR-assessed PSMA positivity criterion and other eligibility criteria of the protocol. The submitted subject data for the site were verifiable with source records reviewed, with no discrepancies noted. In addition, there was no evidence of underreporting adverse events.

3. **Scott Tagawa, M.D.**
   Site #100152
   525 E. 68th St.
   New York, NY 10065
   Inspection Dates: 11/15/2021 – 11/19/2021

   This was the second FDA inspection of the investigator. The first inspection was conducted in December 2018 for another new drug application and was classified as No

Action Indicated.

At this site for Protocol PSMA-617-01, 12 subjects were enrolled, with 6 subjects randomized to each am. All the subjects received study treatment as intended following randomization. As of the data cutoff date of [redacted] one subject (# [redacted] in the lutetium arm) remained on study treatment and one subject (# [redacted] in the lutetium arm) transferred to Site # [redacted] and continued his treatment at the new site. The remaining subjects were discontinued from study treatment due to progressive disease, adverse event, death, withdrawal of consent, or investigator's decision. Of those who discontinued study treatment, one subject in the lutetium arm and four in the control arm died as of the data cutoff. At the time of inspection, no subjects were receiving study treatment, and two subjects on the lutetium arm were in survival follow-up.

Source records for all the enrolled subjects were reviewed during the inspection, and relevant source data were compared with the Applicant's submitted data for the site. The subject records reviewed included the informed consents, screening and enrollment log, eligibility checklists including PSMA eligibility documentation, randomization and study treatment administered, study visit progress notes, imaging assessments and submissions to the central review, AEs, SAEs, concomitant medications, protocol deviations, study product administration documentation and accountability. In addition, the inspection reviewed regulatory binders and study oversight at the investigator site, including the IRB's approvals of the protocol/amendments and informed consents as well as related continuing reviews, training records, signed Form FDA 1572s, financial disclosures, monitoring activities, and reports to the sponsor and related documentation.

All the 12 enrolled subjects were found to have met the eligibility criteria. The Applicant's submitted data, including the primary efficacy endpoint OS, were verified against the source records at the site. No discrepancies were noted. There was no evidence of underreporting of adverse events or protocol deviations.

4. **Edward Gelmann, M.D.**
   Site #100006
   1515 N. Campbell Ave.
   Tucson, AZ 85724
   Inspection Dates: 10/18/2021–10/22/2021

Dr. Gelmann assumed responsibility for the study as the CI in March 2021, when the original CI at the site (Dr. Hani M. Babiker, M.D.) relocated and stopped serving as a CI for the study. This change in CI received IRB's approval and both study sponsor and study subjects were notified accordingly.

At this site for Protocol PSMA-617-01, 15 subjects were enrolled, with 10 subjects randomized to the lutetium arm, 3 to the control arm, and 2 subjects not randomized due to withdrawal of consent. Except for one subject (# [redacted] in the control arm), all subjects received study treatment as intended. As of the data cutoff of

01/27/2021, all treated subjects were discontinued from study treatment due to disease progression, investigation's decision, or other discontinuation criteria. Of those who discontinued study treatment, three subjects in the lutetium arm and two in the control arm died. At the time of this inspection, the remaining subjects at the site were in survival follow-up.

Source records for all the enrolled subjects were reviewed during the inspection, and relevant source data were compared with the Applicant's submitted data for the site. The subject records reviewed included the informed consents, medical history, eligibility documentation, randomization and study treatment administered, scans performed and survival status, AEs/SAEs, concomitant medicines, and protocol deviations. In addition, the inspection reviewed regulatory documents and study oversight at the site, including IRB's approvals of the study protocol/amendments and relevant informed consent forms, Form FDA 1572s, financial disclosure records, training records, data entry and access to eCRFs, monitoring visits, reports to the sponsor, and investigational product accountability records.

The protocol required PSMA eligibility scan and central determination were performed and documented along with other eligibility criteria at the site and in the eCRFs. All subjects met the eligibility criteria. The Applicant's submitted data, including the primary efficacy endpoint OS, were verified against the source records at the site. No discrepancies were noted. There was no evidence of underreporting of adverse events.

5. **Endocyte, Inc.**
   Study Sponsor, acquired by Novartis Pharmaceutical Corporation during study
   8910 Purdue Rd Ste 250
   Indianapolis, IN 46268
   Inspection Dates: 11/15/2021–11/19/2021

   The study sponsor was inspected to evaluate their conduct and oversight of Protocol PSMA-617-01. Of note, after the initiation of Protocol PSMA-617-01 in May 2018, the study sponsor was acquired by Novartis Pharmaceutical Corporation in December 2018. This change was reflected by the addition of "A Novartis Company" following "Endocyte, Inc." in the study protocol amendments implemented after April 2019.

   The inspection reviewed the sponsor's study documents and procedures related to their conduct and management of Protocol PSMA-617-01. The inspection reviewed the sponsor history, standard operating procedures (SOPs), key individuals and their responsibilities, protocol implementation and amendments, Investigator Brochures (IBs) and updates, electronic data systems used for the study, selection of investigators and the contract research organizations (CROs) for the study, training records, Form FDA 1572s, financial disclosures, site monitoring plans and activities, study randomization and data management, the data safety monitoring board and their reports, oversight of the involved CROs and related correspondences, protocol deviation management, quality assurance plans, annual Development Safety Update Reports (DSURs) to the

Agency, and investigational product management and related oversight, including verification of Radioactive Material Programing (RAM) licenses from the participating study sites.

The inspection observed no significant compliance deficiencies in the sponsor's conduct and oversight of Protocol PSMA-617-01. The numbers of participating investigator sites and subjects as well as randomization allocations were consistent with those reported in the NDA. The study data management, including data collection and outsourced study site monitoring, was found to be adequate. Adverse events and relevant reports for the above four CI sites were examined in the safety database (b) (4) with no discrepancies identified.

{See appended electronic signature page}

Yang-Min (Max) Ning, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Team Lead
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {*See appended electronic signature page}*

Philip Kronstein, M.D., Team Lead, acting for
Kassa Ayalew, M.D., M.P.H
Branch Chief and Division Director
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Room
Review Division /Division Director
Review Division /Project Manager
Review Division/Clinical Team Lead
Review Division/Clinical Reviewer
OSI/Office Director
OSI/DCCE/ Division Director
OSI/DCCE/Branch Chief
OSI/DCCE/Acting Team Lead
OSI/DCCE/GCP Reviewer
OSI/ GCP Program Analysts
OSI/Database PM

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/

YANGMIN NING
01/24/2022 06:47:04 PM

MIN LU
01/24/2022 11:05:25 PM

PHILLIP D KRONSTEIN
01/25/2022 04:36:26 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 3, 2022
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 215833
Product Name and Strength:	Pluvicto (lutetium (177Lu) vipivotide tetraxetan) Injection, 1000 MBq/mL (27 mCi/mL)
Applicant/Sponsor Name:	Advanced Accelerator Applications USA, Inc., a Novartis Company
OSE RCM #:	2021-1581-1
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Acting Team Leader:	Janine Stewart, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on December 17, 2021 for Pluvicto. Division of Oncology 1 (DO1) requested that we review the revised container label and carton labeling for Pluvicto (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

[a] Gao, T. Label and Labeling Review for Pluvicto (NDA 215833). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 Dec 1. RCM No.: 2021-1581.

2 DICSUSSION

We noted that the Applicant implemented all of our recommendations except the following recommendations:

1. The Applicant did not include a linear barcode on the container label and carton labeling because 21 CFR 201.25(b)(1)(i)(E) stated that the bar code requirement does not apply to radiopharmaceuticals.[b]
2. The Applicant did not include storage information on the container label due to space constraints. However, the Applicant stated that the storage information is included on the lead shielding label (carton labeling).[c]

We reviewed the Applicant's rationale for not implementing these recommendations and we find their rationale acceptable from a medication error perspective.

3 CONCLUSION

The revised container label and carton labeling received on December 17, 2021 are acceptable from a medication error perspective. We have no additional recommendations at this time.

[b] NDA 215833: PLUVICTO™ 1,000 MBq/mL solution for infusion (lutetium Lu 177 vipivotide tetraxetan) REQUEST FOR EXEMPTION FROM REQUIREMENTS OF 21 CFR § 201.25. Millburn (NJ): Advanced Accelerator Applications USA, Inc., a Novartis Company. 2021 Dec 17. Available from: \\CDSESUB1\evsprod\nda215833\0030\m1\us\fda-response-request-exempt.pdf

[c] Regulatory Affairs. lutetium (177Lu) vipivotide tetraxetan AAA617 / [177Lu]Lu-PSMA-617. Response to Questions. Millburn (NJ): Advanced Accelerator Applications USA, Inc., a Novartis Company. 2021 Dec 17. Available from: \\CDSESUB1\evsprod\nda215833\0030\m1\us\fda-response.pdf

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

TINGTING N GAO
01/03/2022 07:44:58 PM

JANINE A STEWART
01/03/2022 09:30:50 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 1, 2021
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 215833
Product Name, Dosage Form, and Strength:	Pluvicto (lutetium (177Lu) vipivotide tetraxetan) injection, 1000 MBq/mL (27 mCi/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Advanced Accelerator Applications USA, Inc., a Novartis Company
FDA Received Date:	July 29, 2021
OSE RCM #:	2021-1581
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the approval process for Pluvicto (lutetium (177Lu) vipivotide tetraxetan) injection, the Division of Oncology 1 (DO1) requested that we review the proposed Pluvicto prescribing information, container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed PI, container label, and carton labeling and determined that they could be improved for clarity.

4 CONCLUSION & RECOMMENDATIONS

The proposed Pluvicto PI, container label, and carton labeling could be improved for clarity. We provide specific recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 1 (DO1)

A. Prescribing Information

1. Dosage and Administration Section, Section 2.3 Recommended Dose

a. Include the route of administration so that the sentence reads "The recommended TRADENAME dose is 7.4 GBq (200 mCi) intravenously every 6 weeks [redacted]."

b. Consider removing the statement "(± 1 week)" to minimize confusion.

2. Dosage and Administration Section, Section 2.5 Dose Modifications for Adverse Reactions

a. Consider revising the statement [redacted] to "(extending the dosing interval from every 6 weeks up to every 10 weeks)" for clarify.

3. Dosage and Administration Section, Section 2.5 Preparation and Administration

a. Consider specify a specific duration (in minutes) for intravenous push rather than stating "slow intravenous push" for clarity.

4.2 RECOMMENDATIONS FOR ADVANCED ACCELERATOR APPLICATIONS USA, INC., A NOVARTIS COMPANY

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container label & Carton Labeling)

1. As currently presented, the strength presented on the container label and carton labeling only contains the strength in megabecquerels (1000 MBq/mL), while the strength presentation in the prescribing information (PI) contains the strength in megabecquerels (MBq) with the millicurie (mCi) equivalent value presented in parenthesis. We recommend revising the strength presentation to align with the format used in the PI. Revise the strength under the drug product name to read "1,000 MBq/mL (27 mCi/mL)".

2. If the "Batch" is the Lot number, revise the word "Batch:" to "Lot No.:" in accordance with 21 CFR 201.10(i) for clarity.

3. The linear barcode is missing. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual container label and carton labeling as required per 21 CFR 201.25(c)(2).

B. Container Label

1. The storage information on the container label lacks instructions to store the radiopharmaceutical in an appropriately shielded container. Provide a statement on the container label addressing appropriate storage requirements, including appropriate shielding storage requirements, if space permits.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pluvicto received on July 29, 2021 from Advanced Accelerator Applications USA, Inc., a Novartis Company.

Table 2. Relevant Product Information for Pluvicto	
Initial Approval Date	N/A
Active Ingredient	lutetium (177Lu) vipivotide tetraxetan
Indication	treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy (b) (4) (b) (4)
Route of Administration	Intraveous
Dosage Form	injection
Strength	1000 MBq/mL (27 mCi/mL)
Dose and Frequency	7.4 GBq (200 mCi) every 6 weeks (b) (4) Reduce dose by 20% for adverse reactions See \\CDSESUB1\evsprod\nda215833\0000\m1\us\proposed-clean.doc for more information.
How Supplied	One single dose vial in a lead shielded container.
Storage	Store below 30°C (86°F). Do not freeze. Store in the original package to protect from ionizing radiation (lead shielding).
Container Closure	The drug product is supplied in a clear, colorless type I glass 30 mL single-dose vial. The product vial is in a lead shielded container.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Pluvicto labels and labeling submitted by Advanced Accelerator Applications USA, Inc., a Novartis Company.

- Container label received on July 29, 2021
- Carton labeling received on July 29, 2021
- Prescribing Information (Image not shown) received on July 29, 2021, available from \\CDSESUB1\evsprod\nda215833\0000\m1\us\proposed-clean.doc

G.2 Label and Labeling Images

(b) (4)

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

TINGTING N GAO
12/01/2021 10:58:11 AM

ASHLEIGH V LOWERY
12/03/2021 02:05:42 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 215833
Submission Number	# 001
Submission Date	7/29/2021
Date Consult Received	8/11/2021
Drug Name	Lutetium (177Lu) vipivotide tetraxetan
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 (AR) pathway inhibition and taxane-based chemotherapy (b) (4) (b) (4).
Therapeutic Dose	The recommended dose is 7.4 GBq (200 mCi) every 6 weeks for a total of 6 doses.
Clinical Division	OOD/DO1

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 8/11/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Sponsor's statistical analysis plan # PSMA-617-01 (SN0003/SDN4; link);
- Sponsor's cardiac safety report # PSMA-617-01 (SN0003/SDN4; link);
- Sponsor's full study report # PSMA-617-01 (SN0000/SDN1; link);
- Investigator's brochure Edition 6 (SN0003/SDN4; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0003/SDN4; link).

1 SUMMARY

No large QTcF prolongation effect (i.e., >20 msec) of lutetium (177Lu) vipivotide tetraxetan was observed in an alternative design to a thorough QT study. In the absence of a positive control or data characterizing the QTc response at a sufficiently high multiple of the clinically relevant exposure, we are reluctant to draw conclusions of a lack of an effect (ICH E14 Q&A (R3) 5.1 and 6.1).

The effect of lutetium (177Lu) vipivotide tetraxetan on the QTc interval was evaluated in a subset of 30 patients enrolled in Study PSMA-617-01 (VISION Study). This was a Phase III, open-label, randomized study to evaluate the efficacy and safety of lutetium (177Lu) vipivotide tetraxetan in prostate cancer patients with progressive PSMA-positive mCRPC, when administered this drug in addition to Best Supportive or Best Standard of Care (BSC/BSoC) as compared to BSC/BSoC alone. The therapeutic dosing regimen was

evaluated: 7.4 GBq (±10%) administered once every 6 weeks for a maximum of 6 cycles. Data were analyzed using by-time analysis as the primary analysis (results summarized in Table 1). Concentration-QTc analysis was the secondary analysis which suggested a concentration-dependent increase in QTc (Section 3.2.3). Both analyses indicated that lutetium (177Lu) vipivotide tetraxetan is not associated with 20-msec mean increases in the QTc interval. Findings of this analysis are further supported by categorical analysis (Section 4.4).

Table 1: Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	Treatment	Time (h)	ΔQTcF (msec)	90% CI (msec)
QTc	Lu-PSMA-617*	4.0	2.0	(-1.4, 5.4)

**administered with Best Supportive/Best Standard of Care (BSC/BSoC). For further details of the FDA analysis, please see Section 4.*

The design of the QT sub-study has two limitations. Firstly, time-matched PK and ECG sampling was limited with only three time points post-dosing in the first cycle. Secondly, the very first time point was obtained one hour after the end of the infusion and not during or at the end of the infusion; therefore, ECGs at Tmax was not captured. With a rapid distribution phase of the drug this first evaluation time point of one hour shows a concentration that is ~33 % lower than the Cmax that seems to be occurring during the infusion phase. Using the concentration-response relationship, the estimated QTc effect at mean Cmax (6.58 ng/mL) is 8.7 msec (90% UCI 13.6 msec).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN001 from the CSS-IRT. Our changes are highlighted (*addition*, ~~*deletion*~~). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology: (b) (4)

(b) (4) *At the recommended dose, TRADENAME does not cause large mean increases (>20 msec) in the QTc interval.*
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance and the internal draft guidance on "QT Information in Labeling for Oncology Drug and Biological Products."

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

The sponsor, Advanced Accelerator Applications, is developing Lutetium (177Lu) vipivotide tetraxetan intravenous injection for prostate cancer. More specifically, it 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 (AR) pathway inhibition and taxane-based chemotherapy (b) (4) (b) (4). Lutetium (177Lu) vipivotide tetraxetan is a PSMA-binding ligand bound to a peptide with a tetraxetan (4 nitrogen ring) radiolabeled with lutetium-177.

The recommended therapeutic dose is 7.4 GBq (200 mCi) every 6 weeks for a total of 6 doses making the maximum cumulative dose 44.4 GBq; (Bq: becquerel) is a unit of radioactivity). Pharmacokinetics was only obtained at this therapeutic dose (7.4 GBq (200 mCi) and it is also the maximum tested dose from where exposure was obtained. The intravenous injection is a sterile, preservative-free clear, colorless to slightly yellow solution. Lutetium-177 which is an earth metal decays to a stable hafnium-177 with a half-life of 6.6 days by emitting beta-minus radiation.

Mechanism of Action: The active moiety of lutetium (177Lu) vipivotide tetraxetan is the radionuclide lutetium-177 (a medium-energy β-emitter) which is linked to a targeting moiety that binds with high affinity to prostate-specific membrane antigen (PSMA), a transmembrane protein that is highly expressed in prostate cancer, including metastatic castration-resistant prostate cancer (mCRPC). Upon binding to PSMA-expressing cancer cells, the beta-minus emission from lutetium-177 sends therapeutic radiation to the targeted cell inducing DNA damage which leads to cell death and thereby provides for the beneficial treatment of prostate cancer.

PSMA-617-01 (VISION) Study: This was a Phase III, open-label, randomized study to evaluate the efficacy and safety of 177Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered this drug in addition to

Best Supportive/Best Standard of Care (BSC/BSoC) as compared to BSC/BSoC alone. 177Lu-PSMA-617 was administered as a slow i.v. injection at a dose of 7.4 GBq (±10%) once every 6 weeks (±1 week) for a maximum of 6 cycles. The number of patients randomized to 177Lu-PSMA-17 + BSC/BSoC was 551 and for BSC/BSoC alone it was 280 (a 2:1 randomization). The primary objective of this study was to compare the 2

endpoints of radiographic progression-free survival (rPFS) and overall survival (OS) in patients with progressive prostate-specific membrane antigen (PSMA)-positive mCRPC.

QT Sub-study (see Appendix 5.1 for details): In this submission and as a sub-study of the main study described above, the sponsor has also submitted an evaluation of the effect of 177Lu-PSMA-617 on the QTc interval using the Fridericia method (QTcF) in 30 patients with PSMA-positive mCRPC. Also assessed was the effect of 177Lu-PSMA-617 on heart rate, PR and QRS intervals. The primary ECG endpoint was change-from-baseline in QTcF interval (ΔQTcF) using by-timepoint analysis, and secondary was concentration-QTc analysis. Thirty adult patients were enrolled in this single-arm study to receive best supportive/best standard of care along with 177Lu-PSMA-617 administered once every 6 weeks for a maximum of 6 doses.

Twelve-lead ECGs were performed in triplicate at all timepoints for all patients in the sub-study. During Cycle 1 of treatment, ECGs were performed for up to 4 timepoints namely pre-administration and then at 1, 4, and 24 hours post-treatment. ECG monitoring was performed prior to blood collection. For PK during Cycle 1, blood samples (1 mL) were collected immediately before the start of administration, end of administration, then at 20 minutes, 1, 2, 4, 24, 48, 72 hours and Day 6 post-end of infusion.

Pharmacokinetics: The salient Pharmacokinetics of the drug are that it is immediately and completely bioavailable (as a dosage form it is a solution) and that Tmax is reached at the end of the infusion. The mean AUC at the recommended dose is 52.3 ng.h/mL (CV 31.4%). Mean Cmax is 6.58 ng/mL (CV 43.5%). Unlabeled vipivotide tetraxetan and non-radioactive lutetium (175 Lu) vipivotide tetraxetan are each 60% to 70% bound to human plasma proteins. The mean half life is about 41 hours and with an administration cycle of once every 6 weeks the drug does not accumulate. It does not undergo hepatic or renal metabolism and is primarily eliminated renally (> 90%); population pk indicated no effect on Cmax of the mild and moderately impaired patients. Age, body weight, mild and moderate renal impairment are not significant covariates; severe renal impairment has not been studied. No in vivo drug interaction studies have been conducted. Further, in vitro studies show that it is not a substrate of cytochrome P450 (CYP450) enzymes and it neither induces nor inhibits these isozymes. It plays no role with transporter systems either as a substrate or an inhibitor.

Therapeutic dose and exposure: At the therapeutic dose, the mean Cmax was 6.58 ng/mL (CV% 43.5%) and the mean AUCinf was 52.3 ng•h/mL (CV% 43%). Pharmacokinetics was only obtained at the therapeutic dose and it is also therefore the exposure achieved at the maximum tested dose. The main adverse events seen in study PSMA-617-01 (VISION study) were fatigue, dry mouth, nausea, anemia, diarrhea, vomiting, thrombocytopenia, lymphopenia, leukopenia, and urinary tract infection.

Expected High Clinical Exposure Scenario: The sponsor mentions that clinical exposure is unlikely to be affected with them assuming both that there is no error in drug administration and that drug interactions are unlikely. No radiation dose escalation studies were carried out by the sponsor.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

In the sponsor's by-time analysis, 177Lu-PSMA-617 excluded 20 msec threshold at the therapeutic dose level for ΔQTcF.

Reviewer's comment: The sponsor's results are similar to reviewers' analysis results. Please see Section 4.3 for more details.

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (<45 or >100 beats/min), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *The sponsor's results are similar to reviewers' analysis results. Please see Section 4.4 for more details.*

3.2.3 Exposure-Response Analysis

The relationship between 177Lu-PSMA-617 plasma concentrations and ΔQTcF were investigated using a linear mixed-effects modeling approach. The equation describing the relationship is ΔQTcF (msec) = −4.59 (msec) + 2.02 (msec per ng/mL) × 177Lu-PSMA-617 plasma concentration (ng/mL). The slope is 2.02 msec per ng/mL (90% CI: 0.871 to 3.178), with an intercept of -4.59 msec (90% CI: -8.442 to -0.737). Predicted ΔQTcF at the geometric mean peak 177Lu-PSMA-617 concentration (PK/QTc analysis set).

Treatments	GeoMean Cmax (ng/mL)	ΔQTcF (90% CI, msec)
177Lu-PSMA-617	3.80	3.12 (0.69, 5.54)
177Lu-PSMA-617 (POP-PK)	6.58	8.73 (3.82, 13.64)

The predicted QT effect (ΔQTcF) for the 177Lu-PSMA-617 treatment group (mean Cmax 3.8 ng/mL at the first ECG-PK timepoint of 1 hour) was 3.1 msec (with a 90% upper confidence bound of 5.5 msec). The sponsor mentions that the true Tmax for 177Lu-PSMA-617 is likely to have occurred during infusion or very shortly after the end of infusion. The concentration-QTc model predicted a peak QTcF increase of about 8.7 msec (90% UCI 13.6 msec) at a Cmax of 6.58 ng/mL. The concentration-QTc analysis appears to show no evidence of a large effect (20 msec) of 177Lu-PSMA-617 on QTc. The

concentration-QTc analysis results were consistent with those from the by-time point analysis (i.e., no large effect seems to be observed).

Reviewer's Comments: *There are some limitations of this study and they are as follows:*

1) In this study there are only three common PK and ECG time points (i.e., 1, 4 and 24 hours) from where data were obtained and that also from cycle 1 only. Thus, the sampling representation is scant.

2) The first paired ECG and PK sample was obtained 1 hour after the end of infusion which shows the plasma concentration of 177Lu-PSMA-617 of 4 ng/ml. It appears that the distribution phase of the drug is quite rapid to the extent that the 'true' Tmax likely occurred during or at the end of infusion to which the sponsor mentions that they have measured the Cmax to be 6.58 ng/ml. Thus the 'true' Cmax is about 33 % higher than the one measured at the 1-hour timepoint point after the end of the infusion (4 ng/ml). To continue they mention that ECGs were not collected at this timepoint, but the concentration-QTc model predicts a mean QTcF increase of 8.7 msec (90% UCI 13.6 msec).

3.2.4 Cardiac Safety Analysis

In the FAS safety population (N=734), the SOC 'cardiac disorders' was reported in 4.7% patients in the 177Lu-PSMA-617+BSC/BSoC arm compared to 2.9% patients in BSC/BSoC arm.

The was a numerical increase in treatment-emergent AEs in the 177Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arm, respectively, for cardiac failure congestive (0.8% vs. 0.5%), cardiac failure (0.5% vs. 0), arrhythmia (0.4% vs. 0), bradycardia (0.4% vs. 0) and ventricular arrhythmia (0.4% vs. 0). Additional cardiac AEs that were reported in at least 1 subject in the 177Lu-PSMA-617+BSC/BSoC arm were angina pectoris, cardiac flutter, cardiomyopathy, extrasystoles, myocardial infarction and palpitations. No events of 'QT Prolongation' was reported. One fatal case of Cardio-Respiratory Arrest occurred in the BSC/BSoC only arm.

There were only 2 drug-related treatment-emergent AEs occurring in the 177Lu-PSMA-617+BSC/BSoC arm: grade 3 syncope and grade 3 ventricular tachycardia. In both cases, the doses of PSMA-617 and BSC/BSoC were not changed, and the events resolved.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. The statistical reviewer evaluated the ΔQTcF effect using descriptive statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for different treatment groups. The maximum ΔQTcF values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔQTcF Time-course.

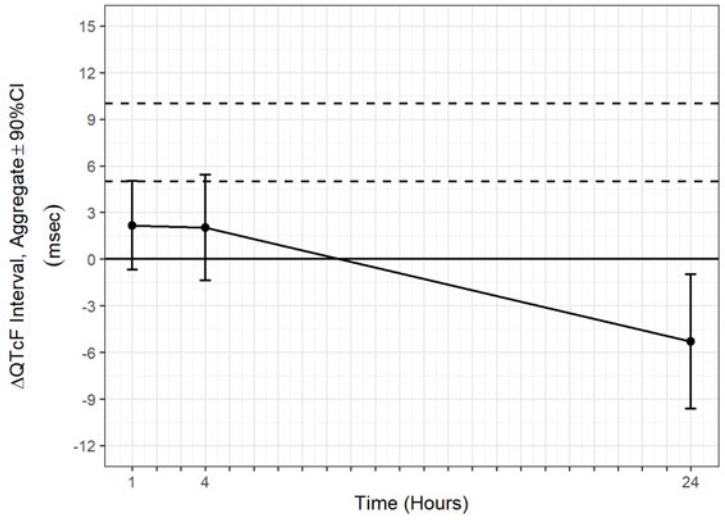


Table 2: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF

Actual Treatment	N	Time (Hours)	ΔQTcF Interval, Aggregate (msec)	90.0% CI (msec)
Lu-PSMA-617+BSC/BSoC	30	4.0	2.0	(-1.4 to 5.4)

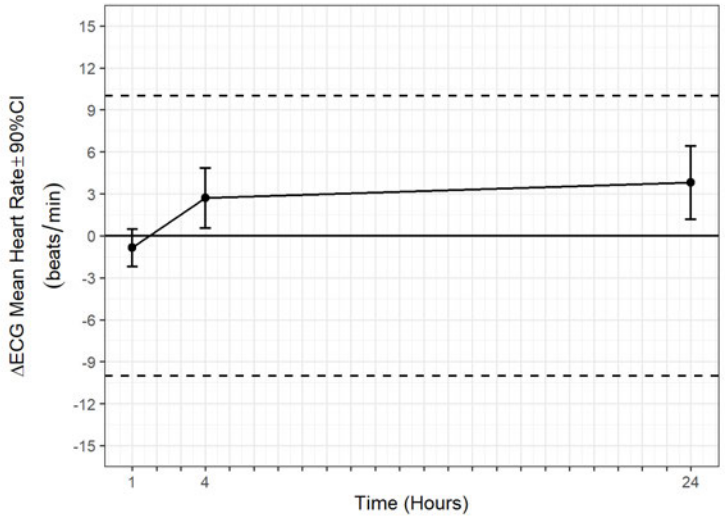
4.3.1.1 Assay Sensitivity

Not applicable

4.3.2 HR

Figure 2 displays the time profile of ΔHR for different treatment groups.

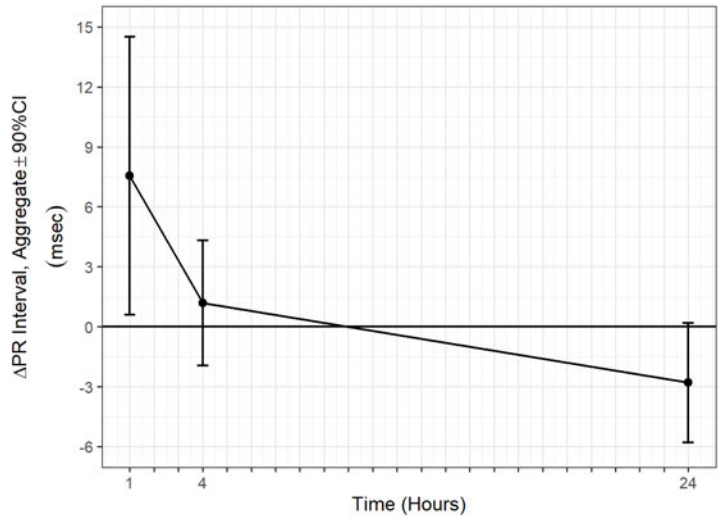
Figure 2: Mean and 90% CI of ΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔPR for different treatment groups.

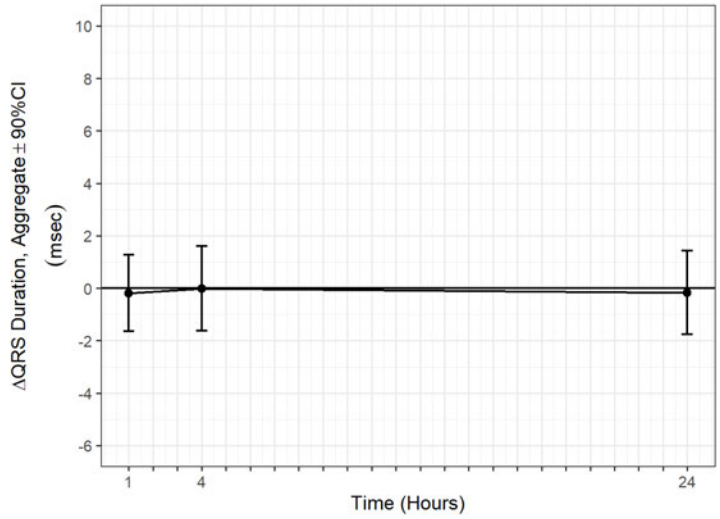
Figure 3: Mean and 90% CI of ΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects received Lu-PSMA-617+BSC/BSoC had observed QTcF above 480 msec or QTcF change from baseline above 30 msec.

4.4.2 HR

None of the subjects had observed HR above 100 beats/min.

4.4.3 PR

Table 3 lists the categorical analysis results for PR (<200 msec, >200 and ≤220 msec, and >220 msec; with and without 25% increase over baseline). One subject (3.7%) had observed PR above 220 msec with 25% increase over time at one time point after receiving Lu-PSMA-617+BSC/BSoC.

Table 3: Categorical Analysis for PR

Actual Treatment	Total (N)		Value <=220 msec		Value >220 msec & <25%		Value >220 msec & >=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Lu-PSMA-617+BSC/BSoC	27	80	25 (92.6%)	78 (97.5%)	1 (3.7%)	1 (1.2%)	1 (3.7%)	1 (1.2%)

4.4.4 QRS

None of the subjects had observed QRS above 120 msec.

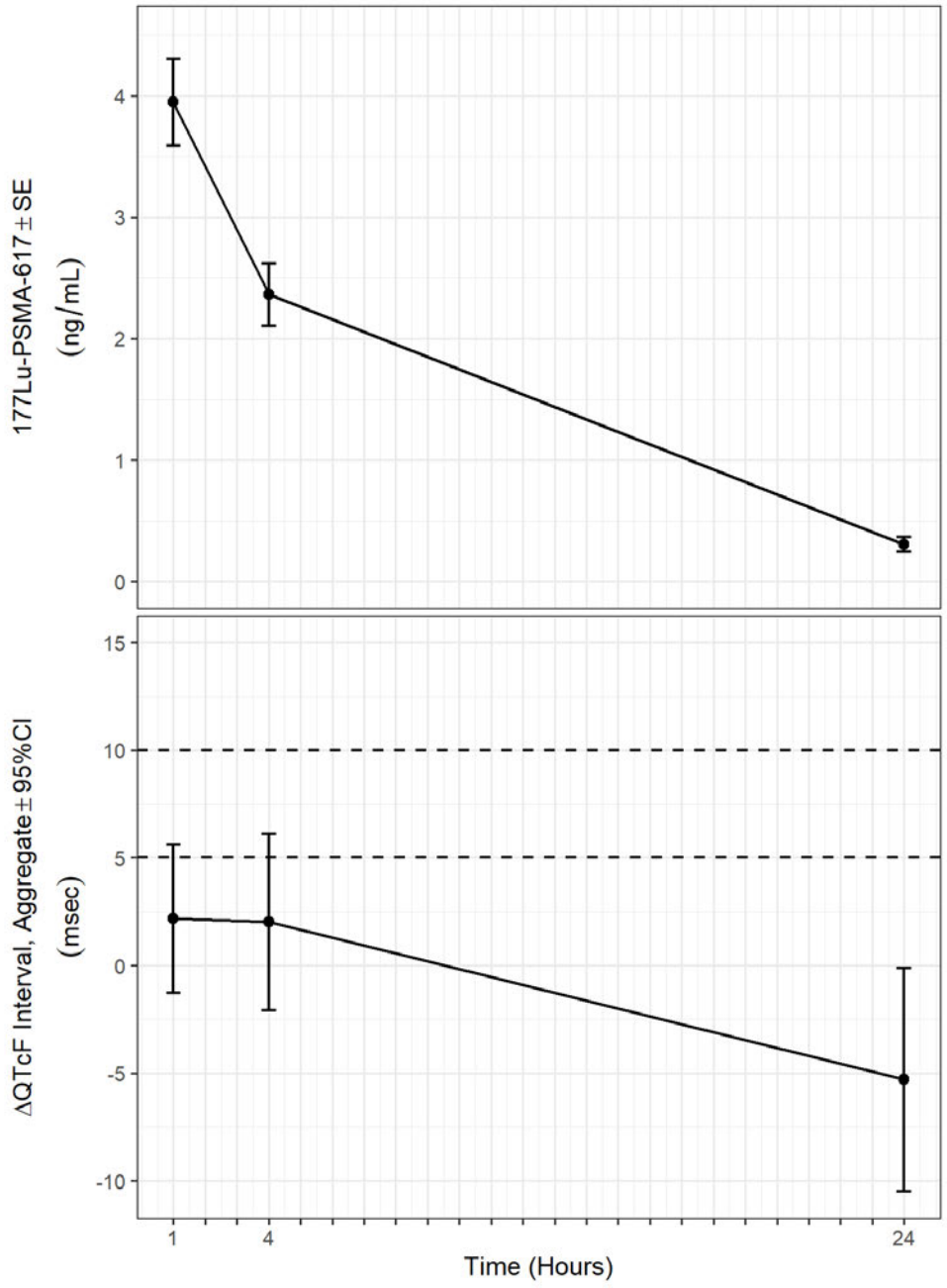
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis was to assess the relationship between plasma concentration of 177Lu-PSMA-617 and ΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship between 177Lu-PSMA-617 concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: absence of - 1) significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between 177Lu-PSMA-617 concentration and ΔQTc and 3) a non-linear relationship.

An evaluation of the time-course of 177Lu-PSMA-617 concentration and changes in ΔQTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect on ΔQTcF and peak concentrations of 177Lu-PSMA-617 indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 7 bpm (Sections 4.3.2 and 4.4.2).

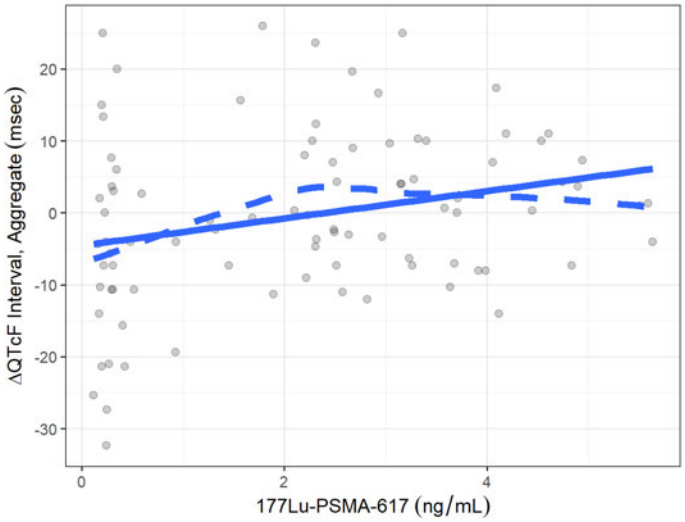
Figure 5: Time-course of 177Lu-PSMA-617 Concentration (top) and QTcF (bottom)[1]



[1] ΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between 177Lu-PSMA-617 concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between 177Lu-PSMA-617 concentration and ΔΔQTc and supports the use of a linear model.

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 4.

Figure 7: Goodness-of-fit Plot for QTcF

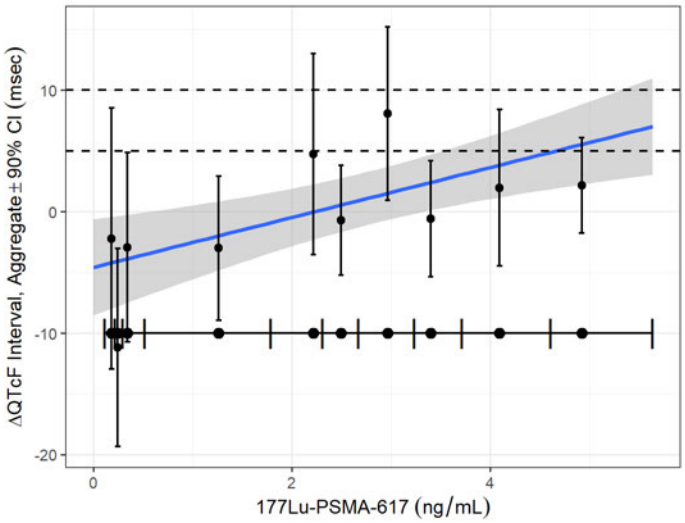


Table 4: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	177Lu-PSMA-617 (ng/mL)	ΔQTcF Interval, Aggregate (msec)	90.0% CI (msec)
Lu-PSMA-617+BSC/BSoC	101	3.8	3.3	(0.8 to 5.7)

5 APPENDIX

5.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

1. Product Information								
Generic Name	Lutetium Vipivotide Tetraxetan			Brand Name	Not Available			
Drug Class	Radiation, Prostrate cancer							
Combination Product	No							
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 (AR) pathway inhibition and taxane-based chemotherapy [redacted (b) (4)].							
Therapeutic Dose	Administer 7.4 GBq (200 mCi) every 6 weeks for a total of 6 doses.							
Maximum Tolerated Dose	NA							
Dosage Form	Solution for Injection			Route of Administration	Intravenous Infusion			
3. QT Studies								
3.1 Primary Studies								
Protocol Number / Population	ECG Quality		Arms		Sample Size		ECG & PK Assessments	
	Assessment	OK?	Arms	High Dose Covers?	No Subjects	OK?	Timing	OK?
Protocol Number: PSMA-617-01	Central Read? No Blinded? No Replicates? Yes	Yes	Highest Dose: 7.4 GBq (every 6 weeks) Placebo: No	Sub-therapeutic	30	Yes	Baseline: Pre-dose baseline. Timing: 1, 4, 24 h post dose.	Yes

Population: Patients Design: Other			Positive Control: No					

The sponsor proposed to exclude large QT effects (i.e., 20 msec) at therapeutic doses.	
3.1 Secondary Studies	
Not Applicable.	
3.3 Data Pooling	
Data pooling?	No
Did sponsor propose an assessment for heterogeneity?	N/A
Is the data pooling appropriate?	N/A
4. Analysis plan	
4.1 Study Objectives Related to QT	
What QTc effect size is the analysis trying to exclude?	20 ms
4.2 Dose Justification	
The sponsor proposed to exclude large QT effects (i.e., 20 msec) at therapeutic doses.	
4.3 QT Correction Method	
Is an HR increase or decrease greater than 10 beats/min?	Unknown
Primary method for QT correction	QTcF
4.4 Assay Sensitivity	
Assay sensitivity methods proposed by sponsor	☐ Moxifloxacin

	☐ Exposure-margin ☐ QT bias assessment ☐ Other ☒ Not applicable (objective is large mean effects)
4.5 By-Time Analysis	
4.5.1 Investigational Drug	
Primary analysis	Yes
Did the sponsor use IUT or descriptive statistics?	IUT
For IUT: Does the sponsor use MMRM to analyze longitudinal values that consider the correlation across time-points, or use ANCOVA by-time-point without considering correlation?	MMRM
For IUT: Is the MMRM model specified correctly with regard to covariance structure, covariates, or if ANCOVA, is the model specified correctly with regard to covariates?	Yes
The data of the sub-study patients will be analyzed descriptively and not considered in the primary and secondary analysis of the main study. Besides the above analysis using descriptive statistics, a by-time point analysis will also be performed using statistical modeling as follows. The analysis for QTcF will be based on a linear mixed-effects model with ΔQTcF as the dependent variable, time (i.e., post-dose time point; categorical), treatment (177Lu-PSMA-617 plus best supportive/best standard of care) and time-by-treatment interaction as fixed effects, and baseline QTcF as a covariate. An unstructured covariance structure will be specified for the repeated measures as post-dose time points within subject.	
4.5.2 Positive Control	
Primary analysis	N/A
Did the sponsor adjust for multiplicity?	N/A
N/A	
4.6 Exposure-Response Analysis	

4.6.1 Investigational Drug			
Primary analysis		No	
What is the dependent variable in the sponsor's model?		Single delta	
White paper model?		Unknown	
Which concentration covariate(s) are included in the model?		Parent	
Did the sponsor propose an assessment of delayed effects?		Yes	
Did the sponsor propose an assessment of linearity?		Yes	
Did the sponsor propose model selection criteria?		Yes	
Which methods did the sponsor use for predicting the QT effect?		☒ Model-based confidence intervals ☐ Bootstrap-derived confidence intervals	
4.6.2 Positive Control			
Primary analysis		N/A	
Same model as investigational drug		N/A	
4.7 Categorical Analysis			
QTcF?	Yes	QRS?	Yes
ΔQTcF?	Yes	HR?	Yes
PR?	Yes	T-wave morphology?	Yes

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/

RAMAN K BAWEJA
11/08/2021 08:50:14 AM

GIRISH K BENDE
11/08/2021 08:56:39 AM

YU YI HSU
11/08/2021 08:57:28 AM

DALONG HUANG
11/08/2021 08:59:55 AM

MICHAEL Y LI
11/08/2021 09:00:54 AM

YANYAN JI
11/08/2021 09:15:35 AM

CHRISTINE E GARNETT
11/08/2021 09:34:26 AM