CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215841Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 215841, Locametz (kit for preparation of gallium Ga-68 gozetotide injection)
OPQ Integrated Quality Assessment (IQA)

Table of Contents

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215841
Assessment 1

Drug Product Name	Locametz (kit for preparation of gallium Ga 68 gozetotide injection)
Dosage Form	Injection
Strength	25 mcg/vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Advanced Accelerator Applications USA, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	7/29/2021	OPQ-CMC, Microbiology, Process/Facilities, Biopharmaceutics

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Monica Cooper	Suong Tran
Drug Product	John Amartey	Danae Christodoulou
Manufacturing	Krishna Ghosh	Vidya Pai
Microbiology	Laura Wasil	Yeissa Chabrier-Rosello
Biopharmaceutics	Zhuojun Jean Zhao	Kimberley Raines
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Eldon E. Leutzinger	
Laboratory (OTR)	N/A	N/A
Environmental	John Amartey	Danae Christodoulou

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs: See Drug Product review (John Amartey)

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
	II *(if applicable)*					
	III *(if applicable)*					
	IV *(if applicable)*					
	Other					

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
See Drug Product review (John Amartey)		

2. CONSULTS: N/A

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

QUALITY ASSESSMENT
EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

AAA has provided adequate information on the proposed drug product demonstrating that Locametz (kit for the preparation of gallium Ga 68 gozetotide injection)/ 25 µg/vial meets all applicable standards to support the identity, strength, quality and purity it purports.

The Office of Process and Facility has made a recommendation of approval for all the facilities involved in this application.

The proposed labeling and labels have adequate information to meet the regulatory requirements. In summary, no issues remain from the primary reviews for CMC (Chemistry, Manufacturing and Controls) Product Quality, Microbiology Product Quality, Biopharmaceutics and Manufacturing Facility Inspection standpoints.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The product under NDA 215841 is a one-vial multi-dose kit meant to be reconstituted and radiolabeled with a sterile solution of $^{68}GaCl_3$ in HCL from a CGMP-grade $^{68}Ge/^{68}Ga$ generator to obtain the radiopharmaceutical preparation as a solution for injection containing [^{68}Ga]Ga-PSMA-11. It is intended for positron emission tomography (PET) imaging of prostate-specific antigen (PSMA) prostate lesions in adult men with prostate cancer.

The kit is to be stored below (b) (4) and has an expiration of 12 months. After reconstitution and radiolabeling, the solution for injection is to be stored below 30^{0}C and has an expiration of 4 hours.

[^{68}Ga]Ga-PSMA-11 as a "ready-to-use" product is an approved product (12/01/2020) under NDA 212642 granted to the University of California Los Angeles (UCLA) and NDA 212643 to the University of California San Francisco (UCSF) for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in adult men with prostate cancer (with suspected metastasis who are candidates for initial definitive therapy or with suspected recurrence based on elevated serum prostate-specific antigen, PSA, level). In addition to these approvals of the "ready-to-use" product, ^{68}Ga-PSMA-11 radiolabeled solution complies with the Ph. Eur. Monograph (3044) for "Gallium (^{68}Ga) PSMA-11 Injection".

FDA's assessment of safety and effectiveness of NDAs 212642 and 212643, were used to support the registration of PSMA-11 kit for radiopharmaceutical preparation. In conjunction with these assessments was a Study PSMA-617-01 (VISION) using ^{68}Ga-PSMA-11 as a patient selection tool to establish patient eligibility to enter an Endocyte-sponsored study, an international, prospective, open-label, multicenter randomized Phase III study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer. PSMA-617-01 is the largest source of prospective safety data available for ^{68}Ga-PSMA-11, being administered to over 1000 patients, and shows a good safety and tolerability profile.

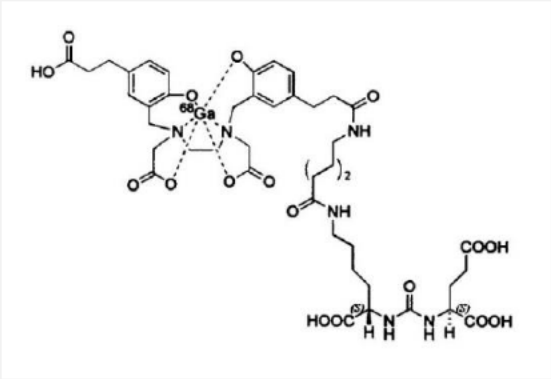
Proposed Indication(s) including Intended Patient Population	For positron emission tomography (PET) imaging of prostate-specific antigen (PSMA) prostate lesions in men with prostate cancer.
Duration of Treatment	Single injection
Maximum Daily Dose	3 – 7 mCi
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

DESCRIPTION.

Locametz is a kit for the preparation of ^{68}Ga-PSMA-11, the second of the kit forms for the preparation of ^{68}Ga-PSMA-11 product. Prior to radiolabeling, the kit ("cold," non-radioactive) contains PSMA-11 (the ligand). During radiolabeling this kit with $^{68}GaCl_3$, the chelating section (HBED) of PSMA-11 sequesters the $^{68}Ga^{3+}$ cation from $^{68}GaCl_3$ to form ^{68}Ga-PSMA-11, the latter as **HBED($^{68}Ga^{3+}$)-CC-Ahx-Lys(OH)-CO-Glu(OH)**, the molecular structure of which is shown below, as reproduced from the literature [*E. Gourni and Gjermund Henriksen, Molecules, 2017, 22(4), 523; Eder, et.al., Bioconjug. Chem, 2012, 23, 688-697*].



In the NDA 215841, PSMA-11 is listed under the drug substance section (3.2.S). (b) (4)

(b) (4)

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Drug Product:

DESCRIPTION:

Locametz is a 1-vial kit that contains a sterile powder for reconstitution (radiolabeling) with an HCl solution of $^{68}GaCl_3$ from a $^{68}Ge/^{68}Ga$ generator (Gallia Pharm Eckert & Ziegler; Galli Ad IRE Elit) to obtain ^{68}Ga-PSMA-11. The powder is comprised of 25 µg of PSMA-11 along with excipients (sodium acetate trihydrate, sodium chloride, gentisic acid (b) (4) in a 10 mL (b) (4) Type 1 Plus glass vial (b) (4) But, the applicant has changed the total radioactivity per vial from (b) (4) to 1369 MBq (37 mCi) (Seq#0026nof 2/07/2022), the change of which is supported by data (Pharmaceutical Development). This is supported by data generated during the pharmaceutical development section and considered acceptable.

Summary of Assessments: Drug Product (^{68}Ga-PSMA-11)

The major issues for the Drug Product are those in 4 major areas, including (1) generators, (2) quality controls (specifications and analytical methods/validation), (3) batch (validation) results and (4) stability.

- **Generators** (the addition of a pump for the IRE GALLI Eo generator.) and some differences in how the reaction vial is handled (b) (4)) between the generators, all of which are **Resolved** (details in Drug Product review).
- Within those for **quality controls** there are an assorted number of concerns that include (b) (4)

  All Resolved.

(b) (4)

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(b) (4)

Labeling:

A substantial part of the prescribing information rests in CMC and there are numerous areas ranging from Dosage Forms and strength (3) to preparation Description (11) to How Supplied/Storage and Handling (16) needing editing for clarity and for accuracy. Applicant responses have taken up several labeling meetings with numerous edits to these sections and to the vial and carton labels. **All have been adequately addressed and there are no remaining issues regarding labeling**.

Manufacturing:

In summary, all facilities involved are acceptable (email of Krishna Ghosh, 3/09/2022). All responses (third round) for AAA have been reviewed and it is concluded that the AAA facility is acceptable as the drug manufacturing site for the NDA. Also, the review of (b) (4) (additional scope – (b) (4) is completed and determined acceptable.

Biopharmaceutics:

Based on the assessment of biopharmaceutics related information, NDA 215841 LOCAMETZ (gallium ^{68}Ga gozetotide) power for injection, 25 µg/vial (kit for preparation of ^{68}Ga-PSMA-11), is recommended for approval from a Biopharmaceutics perspective.

Microbiology (if applicable):

Of the multiple issues for microbiology and multiple IRs, all have been adequately addressed and the final recommendation from Microbiology is Adequate (2/22/2022).

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Radiochemical Identity, HPLC	•Radiolabeling method •Precursor purity •Analytical method • Reference Standard •Acceptance criterion	(H, M, or L) M	Applicant Resolved	Acceptable	N/A
Radiochemical purity, HPLC ITLC	•Radiolabeling Method •Precursor purity •Analytical method •Reference Standard •Acceptance criterion	M	Applicant Resolved	Acceptable	N/A
Chemical purity, HPLC	•Precursor purity •Purity of product Ingredients	M	N/A	Acceptable	N/A
Strength	•Stability •Radionuclide •Radiolysis	M	Applicant Resolved	Acceptable	N/A
Appearance Particulates	•Stability	L	N/A	Acceptable	N/A
Extractables	•Container/closure	L	N/A	Acceptable	N/A
pH	•Formulation	L	N/A	Acceptable	N/A
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	H	Applicant Resolved	Acceptable	N/A

Endotoxin Pyrogen	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	M	Applicant Resolved	Acceptable	N/A

D. List of Deficiencies

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

Overall, all deficiencies initially identified are resolved and no final deficiencies remain that need to be resolved before approval.

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

N/A

4. Labeling Deficiencies

N/A

5. Manufacturing Deficiencies

N/A, see section under manufacturing.

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

N/A

8. Other Deficiencies *(Specify discipline, such as Environmental)*

None

Application Technical Lead Name and Date:

Eldon E. Leutzinger, Ph.D., 3/11/2022

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	215841
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Gallium 68 gozetotide (kit for preparation of 68Ga-PSMA-11)/ 25 µg/vial
Route of Administration	Intravenous injection
Applicant Name	Advanced Accelerator Applications USA, Inc., A Novartis Company
Therapeutic Classification/ OND Division	PET products/DIRM
Manufacturing Site	Advanced Accelerator Applications (Italy) S.r.l. (previously GIPHARMA S.r.l), Via Crescentino, Saluggia (VC) 13040, Italy
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
ECTD Sequence 0000	**7/29/2021**
ECTD Sequence 0014	**11/22/2021**
ECTD Sequence 0018	**12/20/2021**
ECTD Sequence 0021	**1/11/2022**
ECTD Sequence 0025	**1/31/2022**
ECTD Sequence 0027	**2/14/2022**

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This is the original submission of the 505(b)(2) application. The drug product is a cold kit for the preparation of 68Ga-PSMA-11 Injection. The kit consists of one vial of lyophilized PSMA-11. The final drug product, ^{68}Ga-PSMA-11, is produced using ^{68}Ga solution produced from one of two GMP ^{68}Ge/^{68}Ga generators [GalliaPharm generator ((b) (4)) or Galli Ad (Galli Eo) generator ((b) (4))].

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents:

(b) (4)

S DRUG SUBSTANCE

(b) (4) the drug substance is not reviewed.

(b) (4) The applicant stated that two GMP $^{68}Ge/^{68}Ga$ generators can be used to generate ^{68}Ga-PSMA-11: GalliaPharm generator (Eckert and Ziegler, DMF (b) (4) and Galli Eo generator (iRE ELiT, DMF (b) (4) Letters of authorization (LOA) were provided for DMF (b) (4) dated 25 February 2021, and DMF (b) (4) dated 25 May 2021.

Assessment: *Adequate*

For sterility assurance information associated with the GalliaPharm (Eckert and Ziegler) and Galli Eo (iRE ELiT) $^{68}Ge/^{68}Ga$ generators, DMF (b) (4) and DMF (b) (4) respectively, were reviewed and deemed adequate in product quality microbiology reviews (b) (4) docx, dated 1 November 2019, (b) (4) docx, dated 16 April 2021, (b) (4) docx, dated 22 November 2021, (b) (4) docx, dated 26 December 2019, (b) (4) docx, dated 1 July 2021, and (b) (4) docx, dated 22

November 2021, respectively. Please see these reviews for additional information.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(Sequence 0000, Module 3.2.P.1, Description and Composition of the Drug Product – 25 µg [7011242_SM_A_P1_975]

- **Description of the drug product –** the drug product is a kit consisting of 1 vial containing the sterile PSMA-11 powder formulation. It is a multi-dose product.

- **Drug product composition –**

Component	Function	Quantity/vial
PSMA-11	Drug substance	25 µg
Sodium acetate trihydrate, USP-NF	(b) (4)	78 mg
Sodium chloride, USP-NF		40 mg
Gentisic acid		1 mg
(b) (4)		
(b) (4)		

Composition of Radiolabeled Product

Component	Use of GalliaPharm® Generator	Use of Galli Ad®* Generator
PSMA-11	25 µg	25 µg
^{68}Ga-PSMA-11	(b) (4)	
Total radioactivity		
Volume	≤ 5.0 mL	≤ 1.1 mL
Content of excipients	mg/vial	mg/vial
Sodium acetate trihydrate	78	78
Sodium chloride	40	40
Gentisic acid	1	1

*Also called "Galli Eo" generator.

- **Container Closure Systems –**

Component	Description	Manufacturer
Vial	(b) (4)	
Stopper		
Cap		

Assessment: ***Adequate***

The applicant provided an adequate description of the drug product's composition and container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Laura Wasil

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Yeissa Chabrier Rosello

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CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	215841
Assessment Cycle Number	# 1
Drug Product Name/ Strength	LOCAMETZ (gallium ^{68}Ga gozetotide) power for injection, 25 µg/vial (kit for preparation of ^{68}Ga-PSMA-11)
Route of Administration	Intravenous (iv) Injection
Applicant Name	Advanced Accelerator Applications (AAA) USA, Inc.
Therapeutic Classification/OND Division	Positron Emission Tomography (PET) Agent/Division of Imaging and Radiation Medicine (DIRM)
LD Number	NDA 212642 and 212643, ^{68}Ga-PSMA-11 30 mL and 20 mL (0.5-5mCi/mL)
Proposed Indication	For positron emission tomography (PET) of prostate-specific membrane antigen (PSMA)-positive lesions in men with prostate cancer
Primary Assessors	*Zhuojun Joan Zhao, Ph.D.*
Secondary Assessors	*Kimberly Raines, Ph.D.*
Assessment	**Adequate**
Recommendation	Based on the assessment of biopharmaceutics related information, NDA 215841 LOCAMETZ (gallium ^{68}Ga gozetotide) power for injection, 25 µg/vial (kit for preparation of ^{68}Ga-PSMA-11), is recommended for **APPROVAL** from a Biopharmaceutics perspective.

Background

This 505 (b)(2) application seeks approval for LOCAMETZ (gallium ^{68}Ga gozetotide) powder for injection, 25 µg/vial, which is indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA)-positive lesions in men with prostate cancer. The Listed Drugs (LDs) are UCLA's Gallium ^{68}Ga PSMA-11 solution for iv injection (NDA 212642) and UCSF's Gallium ^{68}Ga PMSA-11 solution for iv injection (NDA 212643).

Assessment Summary:

The proposed LOCAMETZ is intended for the same route, same dose, and has the same active ingredient as LD products, however, the amount of the active ingredient is 5 times greater than the listed product and is a lyophilized powder to be reconstituted. The proposed LOCAMETZ was not used in the Endocyte-sponsored PSMA-617-01 Phase 3 clinical trial (VISION), while both LD products were. To support 505(b)(2) approval of LOCAMETZ, the Applicant provided comparative in vitro binding/internalization data between LOCAMETZ and LD product as well as mass dose administration of LOCAMETZ data in the two ongoing phase 3 studies CAAA617B12302 and CAAA617C12301.

This Biopharmaceutics Review evaluated the biopharmaceutics related data supporting the bridge between the proposed drug product and the LDs.

The proposed composition of LOCAMETZ and physicochemical data (pH and osmolality) are acceptable from a Biopharmaceutics perspective, while the adequacy of bridging between the proposed LOCAMETZ and LDs relies on the OCP team's overall assessment of the Applicant's in vitro affinity binding and cellular internalization study results as well as the clinical mass dose data in studies CAAA617B12302 and CAAA617C12301.

Based on the assessment of biopharmaceutics related information, NDA 215841 LOCAMETZ (gallium ^{68}Ga gozetotide) power for injection, 25 µg/vial (kit for preparation of ^{68}Ga-PSMA-11), is recommended for **APPROVAL** from a Biopharmaceutics perspective. under 21CFR 320.24 (b) (6).

List Submissions being assessed:

Document(s) Assessed	Date Received
0001 (1) Original Submission	July 29, 2021
0005 (5) IR Response	September 15, 2021
0013 (15) IR Response	December 1, 2021

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues): None

B.1 DRUG SUBSTANCE

The drug substance, PSMA-11, is a synthetic ligand that contains 2 ureido-linked amino acids (Glu and Lys), the linker Ahx that is bound to the side chain amino acid group of the Lys residue and the chelator HBED-CC.

B.2 DRUG PRODUCT

The proposed drug product PSMA-11 25 µg/vial was developed as a multidose product to be used in combination with a solution of ^{68}Ga in HCl provided by a ^{68}Ge/^{68}Ga generator (Figure 1 and Figure 2) to obtain ^{68}Ga-PSMA-11 solution for injection, being the Radiolabeled Imaging Product for intravenous administration.

Figure 1: Preparation with Eckert & Ziegler GalliaPharm® Generator

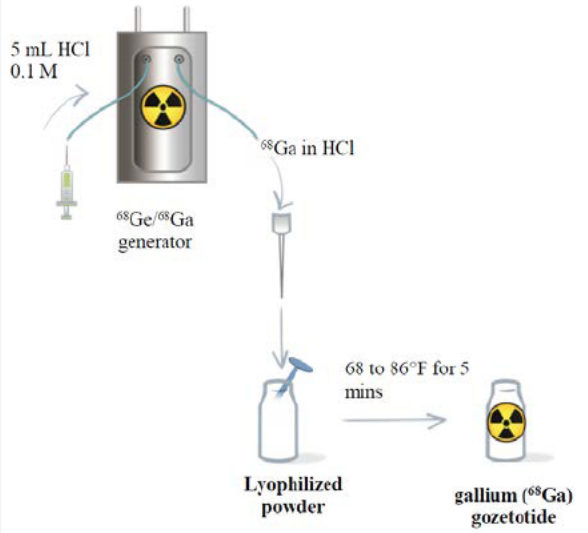
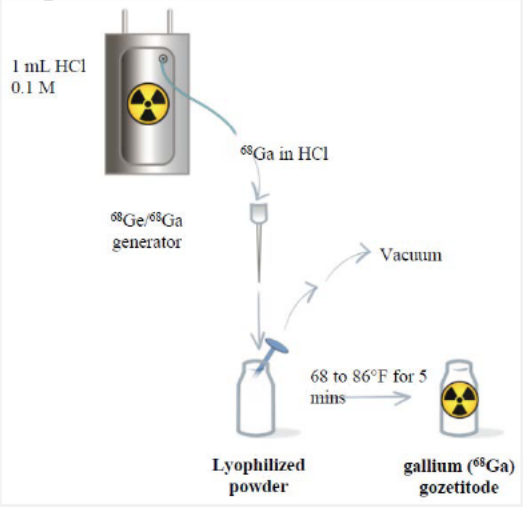


Figure 2: Preparation with IRE ELiT Galli® Eo Generator



The composition of the proposed PSMA-11 25 µg/vial is shown in Table 1.

Table 1: Composition of the powder vial (PSMA-11 25 µg for radiopharmaceutical preparation)

Ingredient	Theoretical amount per vial	Function	Reference to standards
PSMA-11	25 µg	Drug Substance	In-house
Sodium acetate trihydrate[1]	78 mg	(b) (4)	Ph. Eur./ USP/NF
Sodium chloride	40 mg		Ph. Eur./ USP/NF
Gentisic acid	1 mg		In-house
(b) (4)			

The Applicant also provides the composition of the Radiolabeled Imaging Product obtained with the eluate coming from GalliaPharm® generator (Eckert & Ziegler (Radiopharma GmbH)) and Galli Ad® generator (IRE-Elit) shown in Table 2. Generators of (b) (4) MBq have been used as an example.

Table 2: Composition of the Radiolabeled Imaging Product* obtained using the eluate of GalliaPharm® and Galli Ad® generators of (b) (4) MBq

Component	Use of GalliaPharm® Generator	Use of Galli Ad® Generator
PSMA-11 content	25 µg	25 µg
68Ga-PSMA-11 content	(b) (4)	
Total radioactivity		
Volume	≤ 5.0 mL	≤ 1.1 mL
Content of Excipients	mg/vial	mg/vial
Sodium Acetate Trihydrate	78	78
Sodium Chloride	40	40
Gentisic Acid	1	1

* The composition is given for the undiluted radiolabelled imaging product. After reconstitution and radiolabelling, 68Ga-PSMA-11 solution for injection can be diluted with sterile water for injections or with sterile sodium chloride 9 mg/ml (0.9%) solution for infusion to a final volume of 10 mL

(b) (4)

B.3 BRIDGE ETWEEN THE PROPOSED DRUG PRODUCT AND THE LISTED DRUG PRODUCT

^{68}Ga-PSMA-11 was used as diagnostic tool to determine the PSMA-expression status of patients in the Endocyte-sponsored PSMA-617-01 Phase 3 clinical trial (VISION study). However, the proposed LOCAMETZ 25 µg/vial (kit for radiopharmaceutical preparation) has not been used in VISION trial. Therefore, the Applicant was requested to provide the following bridging study/data between the proposed LOCAMETZ and the LD products used in the VISION Study,

at IND stage[1]:

1) *Describe the two formulations along with the active and inactive ingredients side-by-side along with the amounts used.*
2) *Demonstrate the in-vitro binding affinities and internalization (if any) of two formulations are comparable.*
3) *Demonstrate the blood clearance/urine excretion of the two formulations in prostate cancer patients preferably or in healthy volunteers are comparable*
4) *Demonstrate that the biodistribution of two formulations based on imaging (SUVmean) for various critical organs are comparable.*
5) *Demonstrate that the dosimetry (for major target organs and effective dose) of the two formulations are comparable.*

and in the OCP's IR request[2]:

1) *Comparative in-vitro binding, and internalization between LOCAMETZ and the listed drug*
2) *Comparative human pharmacokinetics, biodistribution and dosimetry study between LOCAMETZ and the listed drug*

In the Applicant's response dated September 15, 2021 (Sequence 0005), the Applicant proposed a waiver for the above in vivo BA/BE study under *CFR 320.22*, which was found not applicable for the proposed LOCAMETZ due to the difference in the API amount (5 times of LD). The Applicant was requested to provide in vitro binding/internalization data and PET positivity analysis of approximately 100 patients administered LOCAMETZ in ongoing Phase 3 studies CAAA617B12302 and CAAA614C12301 to support the bridging under *CFR 320.24(b)(6)*[3].

While the Applicant's in vitro binding/internalization study and PSMA-11 peptide mass analysis are currently under reviewer by the nonclinical and clinical teams at the time of this review, the following information is evaluated in support of the bridging between the proposed drug product and the listed drug products from Biopharmaceutics' perspective:

1. Formulation, dosage form

[1] DARRTS: IND-133925, COR-MEET-03 (Meeting Minutes), final date 06/29/2021
[2] DARRTS: NDA 215841, COR-NDAIRT-01 (Information Request), final date 09/09/2021
[3] DARRTS: NDA 215841, REV-CLINPHARM-04 (Filing Review), final date 09/27/2021

2. Physicochemical data

1) Formulation, dosage form and administered volume

The quantitative composition between the proposed PSMA-11 25 µg/vial (kit for radiopharmaceutical preparation and UCLA's Gallium ^{68}Ga PSMA-11 solution for iv injection (NDA 212642) and UCSF's Gallium ^{68}Ga PMSA-11 solution for iv injection (NDA 212643) are shown in Table 3.

Table 3: Qualitative and quantitative composition of the proposed commercial formulation (Applicant) and the formulations used in VISION trial (American clinical centers)

PSMA-11 Formulation Per total volume	AAA's LOCAMETZ (NDA215841)	UCLA's (NDA 212642)	UCSF's (NDA 212643)
^{68}Ga PSMA-11 (API)	25 µg	5 µg	5.5 µg
Sodium Chloride (b) (4))	40 mg	(b) (4)	
Sodium Acetate (b) (4))	(b) (4) *	--	(b) (4)
Gentisic Acid (b) (4)	1.0 mg	--	--
Ethanol	-	(b) (4)	
(b) (4)			

*78 mg of sodium acetate trihydrate is used in the proposed formulation (Table 1), (b) (4)

Reviewer's Assessment:

The composition of the proposed commercial formulation ^{68}Ga-PSMA-11 (Table 1) mainly differs from the LD formulations for the presence of the Gentisic Acid and (b) (4) Sodium Acetate and the amount of PSMA peptide in the kit prior to reconstitution/radiolabeling and administration:

(b) (4)

- Also, refer to the Pharmacology/Toxicology review for the evaluation of the safety of the proposed amount of Gentisic acid and sodium acetate. The non-clinical Reviewer,

Dr. Sunny Awe confirmed that the Applicant demonstrated no relevant differences in the affinity binding and cellular internalization between the proposed LOCAMETZ and the Listed Drug product in study VMGP-01-21.

- The reviewer defers to the clinical team's assessment in vivo disposition or clinical performance of the proposed LOCAMETZ based on PET positivity analysis in ongoing Phase 3 studies CAAA617B12302.

- The reviewer defers to the OCP's team assessment of the difference in API amount in the proposed LOCAMETZ.

For the adequacy of the bridging between the proposed LOCAMETZ and LD products, Biopharmaceutics defers to the OCP's overall assessment on the Applicant's in vitro affinity binding and cellular internalization study results as well as the clinical mass dose data in studies CAAA617B12302 and CAAA617C12301.

2) **Physicochemical Data**

The Applicant provided physicochemical property data of the proposed LOCAMETZ.

Table 4: pH data for Radio-labelled LOCAMETZ Batches

Formulation	AAA's LOCAMETZ (NDA215841)[4]			
pH	**Proposed Specification**	F003920003	F003920004	F003920005
	3.2-6.5	3.6-3.8	3.5-3.8	3.6-3.8

The Applicant notes that the osmolality is not part of the drug product quality specifications and was tested for information-only on three batches of the proposed LOCAMETZ. The Applicant checked the osmolality on non-radioactive samples simulating the radiolabeling solution concentration determined by different volumes of the eluate used in the routine radiolabeling process when using GalliaPharm® and Galli Ad® generators. Therefore, the samples solution was prepared using different volumes of HCl 0.1 being the same as the eluate coming from the generators used for radiolabeling (in the routine practice 1.1 mL eluate coming from Galli Ad® generator and 5 mL eluate coming from GalliaPharm® generator).

In addition, further dilution of the samples with water for injections and sodium chloride 0.9% have been used in order to simulate the conditions of use of the radiopharmaceutical kit which can be also further diluted after radiolabeling.

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Table 5: Osmolality Study Results

Component (quantity/vial)	Components Concentration (when dissolved in 1 mL HCl 0.1M)	Components Concentration (when dissolved in 1 mL HCl 0.1M and diluted with 9mL WFI)	Components Concentration (when dissolved in 5 mL HCl 0.1M)	Components Concentration (when dissolved in 5 mL HCl 0.1M and diluted with 5mL WFI)
PSMA-11 (25µg)	25 µg/mL	2.5 µg/mL	5 µg/mL	2.5 µg/mL
Sodium Acetate Trihydrate (78 mg)	78 µg/mL	7.8 mg/mL	15.6 mg/mL	7.8 mg/mL
Sodium Chloride (40 mg)	40 mg/mL	4.0 mg/mL	8 mg/mL	4.0 mg/mL
Gentisic Acid (1 mg)	1 mg/mL	0.1 mg/mL	0.2 mg/mL	0.1 mg/mL
Osmolality results (mOsm/kg)	Batch F03920003: 2564 Batch F03920004: 2554 Batch F03920005: 2455	Batch F03920003: 243 Batch F03920004: 244 Batch F03920005: 242	Batch F03920003: 570 Batch F03920004: 552 Batch F03920005: 555	Batch F03920003: 277 Batch F03920004: 282 Batch F03920005: 281

Reviewer's Assessment:
Radiolabeling is pH sensitive. The Applicant proposed three pH tests for LOCAMETZ:

Test	Acceptance Criteria
pH (5.0 mL HCl 0.1 N) For preparation with Eckert & Ziegler GalliaPharm Generator	3.2-4.2
pH (1.1 mL HCl 0.1 N) For Preparation with IRE ELiT Galli Eo Generator	4.9-5.4
pH of ^{68}Ga-PSMA-11 solution	3.2-6.5

Although the proposed LOCAMETZ shows slightly lower pH compared to the LD drugs (specification of pH 4-7), the proposed pH range for radio-labelled product is within the common pH ranges for intravenous injection.

As shown in Table 5, the reported osmolality is in the range 2564 – 242 mOsmo/Kg, where the ranging of 2455 to 2564 mOsm/kg is for the eluent dissolved in 1.0 mL of HCl 0.1 M. Per the proposed label, "*after radiolabeling, Gallium ^{68}Ga Gozetotide Injection can be diluted with Sterile Water for Injection, USP or 0.9% Sodium Chloride Injection, USP up to a final volume of 10 mL*" and osmolality range of 242-244 mOsm/kg when diluted with water for injection in a 1:10 ratio is in the acceptable physiological range. Therefore, the observed high osmolality is unlikely to have impact on the behavior of ^{68}Ga-PSMA- due to the further dilution as well as its rapid dilution into the larger blood volume.

Kimberly Raines

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Zhuojun Zhao

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Date: 3/09/2022 04:08:03PM
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ANIKA A LALMANSINGH
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ELDON E LEUTZINGER
03/16/2022 01:51:13 PM