

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208547Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208547

SUPPL #

HFD # 160

Trade Name: Netspot

Generic Name: Kit for the preparation of gallium Ga 68 dotatate injection

Applicant Name: Advanced Accelerated Applications (AAA)

Approval Date, If Known: June 1, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

YES

! NO

Explain:

! Explain:

Work was conducted by sponsor or designee.

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====
Name of person completing form: Modupe Fagbami

Title: Regulatory Project Manager

Date: May 9, 2016

Name of Office/Division Director signing form: Libero Marzella, M.D., Ph.D.

Title: Division of Medical Imaging Products; Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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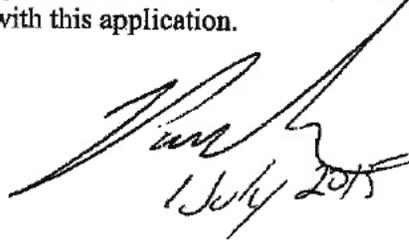
/s/

MODUPE O FAGBAMI
05/19/2016

LIBERO L MARZELLA
05/19/2016

DEBARMENT CERTIFICATION

Advanced Accelerator Applications USA Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



1 July 2015

ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION ¹ | | |
|--|---|--|
| NDA 208547 | NDA Supplement # N/A BLA Supplement # N/A | If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i> |
| Proprietary Name: Netspot Established/Proper Name: Kit for the preparation of gallium Ga 68 dotatate injection Dosage Form: Intravenous Injection | | Applicant: Advanced Accelerator Applications Agent for Applicant (if applicable): N/A |
| RPM: Modupe Fagbami | | Division: Division of Medical Imaging Products |
| NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) | <p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: _____</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p> | |
| ❖ Actions | | |
| <ul style="list-style-type: none"> Proposed action User Fee Goal Date is: June 1, 2016 | | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR |
| <ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> | | <input checked="" type="checkbox"/> None |
| ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ | | <input type="checkbox"/> Received |
| ❖ Application Characteristics ³ | | |

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

| | |
|---|---|
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>) | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| ❖ Public communications (<i>approvals only</i>) | |
| • Office of Executive Programs (OEP) liaison has been notified of action | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| • Indicate what types (if any) of information were issued | <input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other |
| ❖ Exclusivity | |
| • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes |
| ❖ Patent Information (NDAs only) | |
| • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. | <input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic. N/A |
| CONTENTS OF ACTION PACKAGE | |
| Officer/Employee List | |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>) | <input checked="" type="checkbox"/> Included |
| Documentation of consent/non-consent by officers/employees | <input checked="" type="checkbox"/> Included |

| Action Letters | |
|--|---|
| ❖ Copies of all action letters <i>(including approval letter with final labeling)</i> | Action: June 1, 2016 |
| Labeling | |
| ❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i> | |
| <ul style="list-style-type: none"> Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> | <input checked="" type="checkbox"/> Included |
| <ul style="list-style-type: none"> Original applicant-proposed labeling | <input checked="" type="checkbox"/> Included |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i> | <input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None |
| <ul style="list-style-type: none"> Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> | <input type="checkbox"/> Included |
| <ul style="list-style-type: none"> Original applicant-proposed labeling | <input type="checkbox"/> Included |
| ❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i> | |
| <ul style="list-style-type: none"> Most-recent draft labeling | <input checked="" type="checkbox"/> Included |
| ❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> Review(s) <i>(indicate date(s))</i> | Non-Acceptability letter: September 24, 2015; 1/22/2016 Acceptability: January 22, 2016 Reviews: January 14, 2016; September 18, 2015 |
| ❖ Labeling reviews <i>(indicate dates of reviews)</i> | RPM: <input type="checkbox"/> June 1, 2016; December 9, 2015 DMEPA: <input checked="" type="checkbox"/> February 17, 2016 DMPP/PLT (DRISK): <input type="checkbox"/> None OPDP: <input type="checkbox"/> May 23, 2016 SEALD: <input type="checkbox"/> None CSS: <input type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> May 16, 2016 Other: <input type="checkbox"/> None |
| Administrative / Regulatory Documents | |
| ❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i> | November 23, 2015 |
| ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee Cleared on May 9, 2016 | <input checked="" type="checkbox"/> June 1, 2016 |
| ❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i> | <input checked="" type="checkbox"/> Included |
| ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| <ul style="list-style-type: none"> Applicant is on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

| | |
|---|--|
| <ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action |
| ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC _____ If PeRC review not necessary, explain: | <u>This Application has Orphan Drug Designation</u> |
| ❖ Breakthrough Therapy Designation | <input checked="" type="checkbox"/> N/A |
| <ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) | |
| <ul style="list-style-type: none"> CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) | |
| <ul style="list-style-type: none"> CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p> | |
| ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package</i>) | Included |
| ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) | May 23(2), March 21, January 15, 2016, and December 22, 2015 |
| ❖ Minutes of Meetings | |
| <ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> |
| <ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> November 19, 17, 2014; July 1, 2014 |
| <ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> No mtg |
| <ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) | November 24, 2015 |
| <ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> January 28, 2016 |
| <ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) | |
| ❖ Advisory Committee Meeting(s) | No AC meeting |
| <ul style="list-style-type: none"> Date(s) of Meeting(s) | |
| Decisional and Summary Memos | |
| ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None June 1, 2016 |
| Division Director Summary Review (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None May 31, 2016 |
| Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None May 26, 2016 |
| PMR/PMC Development Templates (<i>indicate total number</i>) | <input type="checkbox"/> None |

| Clinical | |
|---|---|
| ❖ Clinical Reviews | |
| • Clinical Team Leader Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> No separate review |
| • Clinical review(s) (indicate date for each review) | December 4, 2015 |
| • Social scientist review(s) (if OTC drug) (indicate date for each review) | <input checked="" type="checkbox"/> None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo) | Reference Page 50 of December 4, 2015 Clinical Review |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) | N/A |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review) | N/A |
| ❖ Risk Management | |
| • REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) | N/A |
| • REMS Memo(s) and letter(s) (indicate date(s)) | N/A |
| • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) | December 7, 2015 |
| ❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators) | May 23, 2016; April 18, and February 18, 2016 |
| Clinical Microbiology <input checked="" type="checkbox"/> None | |
| ❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review) | <input type="checkbox"/> No separate review |
| Clinical Microbiology Review(s) (indicate date for each review) | <input type="checkbox"/> None |
| Biostatistics <input type="checkbox"/> None | |
| ❖ Statistical Division Director Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> December 16, 2015 |
| Statistical Team Leader Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> December 14, 2015 |
| Statistical Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> December 15, 2015 |
| Clinical Pharmacology <input type="checkbox"/> None | |
| ❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review) | |
| Clinical Pharmacology Team Leader Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> No separate review |
| Clinical Pharmacology review(s) (indicate date for each review) | <input checked="" type="checkbox"/> December 3, 2015; and September 8, 2015 |
| ❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters) | <input checked="" type="checkbox"/> None requested |

| Nonclinical <input type="checkbox"/> None | |
|---|---|
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> May 26, 2016 |
| • Supervisory Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> No separate review |
| • Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> December 4, 2015 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) | N/A |
| ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) | N/A |
| ❖ ECAC/CAC report/memo of meeting | <input type="checkbox"/> None Included in P/T review, page |
| ❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>) | <input type="checkbox"/> None requested |
| Product Quality <input type="checkbox"/> None | |
| ❖ Product Quality Discipline Reviews | |
| • Tertiary review (<i>indicate date for each review</i>) | |
| • Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>) | <input type="checkbox"/> No separate Review |
| • Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> May 2, April 28, 26(2) , 122016; February 11, 24, October 23, 2015 |
| ❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>) | <input type="checkbox"/> None |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) | Reference OPQ N208547 Integrated Quality Assessment Final Review of 4/28/2016 |
| <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) | |
| <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) | |
| ❖ Facilities Review/Inspection | |
| <input checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>) | <input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> |

| Day of Approval Activities | |
|---|---|
| ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) | <input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>) |
| <ul style="list-style-type: none"> • Finalize 505(b)(2) assessment | <input checked="" type="checkbox"/> Done |
| ❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager | <input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>) |
| ❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications | <input type="checkbox"/> Done |
| ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email | <input checked="" type="checkbox"/> Done |
| ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter | <input checked="" type="checkbox"/> Done |
| ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name | <input checked="" type="checkbox"/> Done |
| ❖ Ensure Pediatric Record is accurate | <input type="checkbox"/> Done |
| ❖ Send approval email within one business day to CDER-APPROVALS | <input checked="" type="checkbox"/> Done |

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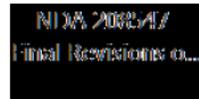
/s/

MODUPE O FAGBAMI
06/03/2016

From: Fagbami, Modupe
Sent: Tuesday, May 31, 2016 11:29 AM
To: victor.paulus@adacap.com
Cc: Davis-Warren, Alberta E
Subject: NDA 208547 Ga 68 dotatate FDA Revisions to PI
Importance: High

Good morning Victor,

As discussed earlier today, please find the FDA revisions to the PI for NDA 208547 Ga 68 dotatate.



Kindly review and ensure that you send your response by COB today, May 31, 2016.

Please ensure that you conform to all the formatting requirements on this label when sending your response.

Please confirm receipt of this email and let me know if you have any questions.

Thank you

Modupe O. Fagbami

RPM

Division of Medical Imaging Products

Office of Drug Evaluation IV

CDER, FDA

10903 New Hampshire Avenue

WO-22, Room 5439

Silver Spring, Maryland 20993

Phone: 301-796-1348

Fax: 301-796-9899

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/s/

MODUPE O FAGBAMI
05/31/2016

From: Fagbami, Modupe
Sent: Friday, May 27, 2016 10:22 AM
To: victor.paulus@adacap.com
Subject: NDA 208547 Ga 68 dotatate Request for Revision to LOA language
Importance: High

Hi Victor,

Kindly request Eckert and Ziegler to revise the language of the 2nd paragraph of their LOAs dated March 4, and May 25, 2016 as indicated in red below:

“Eckert & Ziegler Radiopharma GmbH states that DMF (b)(4) is current and will be promptly updated to reflect any labeling and manufacturing changes associated with the GalliaPharm generator, including changes related to the target material, to facilitate compliance with the requirements of the Federal Food, Drug, and Cosmetic Act and FDA regulations, including Title 21 of the Code of Federal Regulations part 314. In addition, Eckert & Ziegler Radiopharma GmbH will comply with the statements made within DMF (b)(4). Eckert & Ziegler Radiopharma GmbH will promptly notify FDA through an amendment to DMF (b)(4) of any addition, change, or deletion of information in the DMF. Eckert & Ziegler Radiopharma GmbH will also promptly notify in writing Mr. Victor G. Paulus, PhD and Advanced Accelerator Applications, that an addition, change, or deletion of information has been made to the DMF.”

Please send me the response to this request today, May 27, 2016, by latest 4:00 pm.

Kindly acknowledge receipt of this communication and let me know if you have any questions.

Thank you.

Modupe O. Fagbami

RPM

Division of Medical Imaging Products

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Silver Spring, Maryland 20993

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MODUPE O FAGBAMI
05/27/2016

From: Fagbami, Modupe
Sent: Tuesday, May 24, 2016 3:01 PM
To: victor.paulus@adacap.com
Subject: NDA 208547 NETSPOT Ga 68 dotatate FDA Revision to Applicant's label
Importance: High

Hi Victor,

Please find attached FDA's further revisions to the NDA 208547 NETSPOT Ga 68 dotatate label.



Kindly respond to the following Comments:

1. Corresponding to the yellow highlight on the label:
Please request permission from the supplier of GalliaPharm, Eckert and Ziegler, to allow you to include the Ge 68 breakthrough specification of NMT (b) (4)% in the PI for their product, NETSPOT and amend your NDA with the Eckert & Ziegler response.
2. We request the following changes to Figure 1:
 - Change the wording in VIAL 1 to Reaction Vial with Lyophilized Powder and in VIAL 2 to Buffer Vial;
 - State more clearly: (b) (4)

NOTE: We may have additional comments to the current version of label. However, we are requesting that you send us your response to this version on or before 10:00 am on Thursday, May 26, 2016.

Kindly let me know if you have any questions.

Thank you.

Modupe O. Fagbami

*RPM
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MODUPE O FAGBAMI
05/24/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: May 3, 2016 at 1:30 pm

Application Number: NDA 208547

Product Name: Ga 68 dotatate

Applicant Name: Advanced Accelerator Applications (AAA)

Subject: T-Con to confirm letter of Authorization from GIpharma and Eckert & Ziegler

FDA Participants

Libero Marzella, M.D., Ph.D., Director, DMIP

Alex Gorovets, M.D., Deputy Director, DMIP (CDTL)

Eric Duffy, Ph.D., Division Director, OPQ/ONDP/DNDPII

Danae Christodoulou, Ph.D., CMC Branch Chief, OPQ/ONDP/DNDPII/NDPBVI

Eldon Leutzinger, Ph.D., CMC Team Leader, OPQ/ONDP/DNDPII/NDPBVI

John Amartey, Ph.D., CMC Reviewer, OPQ/ONDP/DNDPII/NDPBVI

Jagjit Grewal, Associate Director, Regulatory Affairs, ODEIV

Modupe Fagbami, Regulatory Project Manager, DMIP

Applicant Participants

Victor Paulus, Ph.D., Head, Regulatory Affairs, AAA

Mark Ibrahim, Regulatory Specialist, AAA

Jack Erion, V.P., and Deputy CEO, AAA

Huw Jones V.P., Marketing, AAA

Zhang, M.D., Project Manager

BACKGROUND:

Eckert and Ziegler generator is to be cited in the Package Insert for NDA 208547. It was noted that there is no direct LOA from GIpharma to Advanced Accelerator Applications (AAA). This t-con was requested by the Agency to discuss the letter of authorization for DMF (b) (4) with the Applicant.

DISCUSSION:

Jagjit Grewal, ADRA, ODEIV informed the Applicant that the LOA on file was addressed to Victor Paulus and not to Advanced Accelerated Applications (AAA).

Also, that the Eckert and Ziegler generator will be cited for producing Ga 68 dotatate in the package insert, the Applicant will need the Eckert and Ziegler permission/authorization to make this claim.

The updated LOA should include information that the Agency will be notified through an amendment to the DMF of any addition, change or deletion of information to the DMF.

Applicant agreed to submitting the updated GIpharma LOA within a week and to providing the Eckert and Ziegler authorization letter within 7 days from this t-con.

Post Meeting Note:

The Applicant, Advanced Accelerated Applications (AAA) submitted the required documents as promised.

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/s/

ALEXANDER GOROVETS
05/23/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: April 25, 2016 at 2:30 pm

Application Number: NDA 208547

Product Name: Ga 68 dotatate

Applicant Name: Advanced Accelerator Applications (AAA)

Subject: Discussion of Established name for the drug substance Ga 68 dotatate

FDA Participants

Alex Gorovets, M.D., Deputy Director, DMIP (CDTL)

Eric Duffy, Ph.D., Division Director, OPQ/ONDP/DNDPII

Danae Christodoulou, Ph.D., CMC Branch Chief, OPQ/ONDP/DNDPII/NDPBVI

Eldon Leutzinger, Ph.D., CMC Team Leader, OPQ/ONDP/DNDPII/NDPBVI

John Amarty, Ph.D., CMC Reviewer, OPQ/ONDP/DNDPII/NDPBVI

Modupe Fagbami, Regulatory Project Manager, DMIP

Applicant Participants

Victor Paulus, Ph.D., Head, Regulatory Affairs, AAA

Claude Hariton, Ph.D. Global Head, Research and Development

Michael Zhang, M.D. Project Manager

BACKGROUND:

FDA initiated this t-con following the message from the Applicant that they “will revise the established/generic name of their product to be in-line with USAN naming guidelines and following the precedent set by other diagnostic test kits such as “Kit for the Preparation of Technetium Tc 99m Sestamibi”. The revision will be: Netspot (Kit for the Preparation of Gallium Ga 68 Dotatate).” This is to ensure that the Applicant has applied for an established name for the drug substance.

DISCUSSION:

Danae Christodoulou started the discussion by letting the Applicant know of the need for a USAN application for the Established/Generic name of their product.

Applicant confirmed that they are very familiar with the process and that there is already a process in place with USAN where they have proposed the name gallium Ga 68 dotatate.

It was agreed that this will be adopted and used in all the text and communication regarding their product.

In addition, the Agency requested the Applicant to:

- Forward a copy of the USAN submission
- Refer the Ceretec™ (Kit for the Preparation of Technetium Tc99m Exametazime Injection) label as a potential example for product labeling
- Update the flow diagram in the label under Drug Preparation of Dosage and Administration as will be instructed when the label is sent to the Applicant by the Division.

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/s/

ALEXANDER GOROVETS
05/23/2016

From: Fagbami, Modupe
Sent: Monday, May 23, 2016 3:15 PM
To: victor.paulus@adacap.com
Subject: NDA 208547 NETSPOT Ga 68 dotatate FDA revision to Labelling
Importance: High

Dear Dr. Paulus,

Reference your submission of May 20, 2016, please find the FDA revision.

Kindly submit your response to the FDA by latest Wednesday, May 25, 2016.

Carton Label: NDA208547

- Change [REDACTED] (b) (4) to "20 mg of (b) (4) Mannitol"



Please let me know if you have any questions.

Thank you.

Modupe O. Fagbami

RPM

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Reference ID: 3935375

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MODUPE O FAGBAMI
05/23/2016

From: Fagbami, Modupe
Sent: Monday, May 16, 2016 2:48 PM
To: victor.paulus@adacap.com
Subject: NDA 208547 Ga68 dotatate Carton and Container Labels FDA Revisions and Comments
Importance: High

Hello Victor,

Please find below the FDA revisions and comments regarding the Carton and Container labels for NDA 208547 Ga 68 dotatate.

Kindly submit the updated version on or before 12:00 pm, Friday May 20, 2016.

They are:

Carton Label for the kit

Front panel

- Change [REDACTED] (b) (4) to NETSPOT (kit for reparation of Ga 68 dotatate injection)
- Delete [REDACTED] (b) (4)
- Change **all** DOTATATE to dotatate
- Move "For Intravenous Use Only" under the strength and increase the font or bold it.

First bullet: Remove [REDACTED] (b) (4) from contents of Vial

Third bullet: "Porous" should read "porous" no capital P

Add fifth bullet: 1 drug product label for radiopharmacy use

Add sixth bullet: 1 drug product syringe label for the radiopharmacy

Left panel:

Remove [REDACTED] (b) (4)

Right panel: No edits.

Container Label

Vial 1 (Reaction vial with lyophilized powder): Should be on vial 1.

- Change all (b) (4) to NETSPOT
- Change all Octreotate to dotatate, 40 mcg
- Ensure proprietary name and established name and strength is displayed prominently e.g.
NETSPOT
40 mcg dotatate per vial
- CFR reference to established name N/A here, we are not using established name
- Unbold "Usual dosage"
- Revise (b) (4)
(b) (4). For intravenous Use Only After reconstitution with Ga 68 chloride and pH adjustment with Reaction Buffer prior to use.
- Unbold the storage statement: Do not agree with DMEPA's recommendation, storage statement should be prominent (because of the leaded container and the within 4h use.)
(b) (4): Revise to "Single dose vial".

Vial 2 (Buffer): Should be on vial 2

- Change (b) (4) to "1 mL in 10 mL Vial"
- Delete (b) (4) and replace with "Reaction Buffer for preparation of Ga 68 dotatate injection"
- Revise (b) (4) to read such as: "For Adjusting pH of Ga 68 dotatate injection" to ensure that the Reaction Buffer will not be used alone instead of Ga 68 dotatate injection

- Directly under the above statement, add a sentence to read such as: For pH adjustment of radiolabeled Netspot only
- Add the statement “Not for Direct administration”
- Revise (b) (4) To read such as: See package insert for preparation and administration instructions.
- Revise (b) (4) information to read such as “Single Dose Vial”. Discard Unused Portion
- Unbold the storage information to help improve the prominence of the most important information on the display panel.

Accessory Cartridge Label

- Revise (b) (4) information to read such as “Cartridge for preparation of Ga 68 dotatate injection” to ensure that the accessory cartridge will be used appropriately in the preparation of Ga 68 dotatate.
- Revise “single –Use Vial” to read such as “Single Use Cartridge” Discard after Use.

Drug Product Label (Ga 68 dotatate) for the radiopharmacy

- Revise “(b) (4)” to “Ga 68 dotatate injection”
- Revise (b) (4) to “EOS” =End of synthesis



Syringe Label for Drug Product

This was requested by CMC drug product during review – the firm agreed but did not include here. The syringe label should be included in the box for the kit.

- Add radioactive symbol to the syringe label

- Revise [REDACTED] (b) (4) to “NETSPOT (Kit for preparation of Ga 68 dotatate injection”
- Add Ga 68 dotatate injection



Let me know if you have any questions.

Thank you.

Modupe O. Fagbami

RPM

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MODUPE O FAGBAMI
05/16/2016

From: Fagbami, Modupe
Sent: Friday, April 29, 2016 5:09 PM
To: victor.paulus@adacap.com
Subject: NDA 208547 Ga 68 dotatate FDA Revised Label
Importance: High

Dear Dr. Paulus,

Please find attached the clean copy of the FDA revised label for your review.



Below are the following information requests and comments on the Revised Label for your response on or before 12:00 noon on Thursday, May 5, 2016.

They are:

1. The approved proprietary name is Netspot.
2. Update the TOC in accordance with the revised FPI.
3. Conduct a search for dosimetry data for the pediatric age groups for inclusion in the PI.
4. We plan to discuss with you how to reference in the PI the source of the Ga 68 eluate.
5. We will provide comments to the carton and vial labeling in a separate communications

Kindly confirm receipt of this email and let me know if you have any questions.

Thank you.

Modupe O. Fagbami

RPM

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/s/

MODUPE O FAGBAMI
04/29/2016

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Regulatory Briefing
Meeting Date and Time: February 5, 2016; 11:00 a.m. – 1:00 p.m.
Meeting Topic: A new PET agent [NETspot (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection)] for an uncommon disease (Neuro-Endocrine Tumors)
Meeting Chair: John Jenkins, M.D.

PRESENTERS

1. Libero Marzella, M.D., Ph.D., Director, Division of Medical Imaging Products (DMIP), ODEIV, Office of New Drugs
2. Alex Gorovets, M.D., Deputy Director, DMIP
3. John Amartey, Ph.D., CMC Reviewer, OPQ/ONDP/DNDPII/NDPBVI
4. Thomas Gwise, Ph.D., Deputy Director, OTS/OB/DBV
5. Cynthia Welsh, M.D., Medical Officer, DMIP

Purpose of Regulatory Briefing:

The purpose of this Regulatory Briefing was to discuss the adequacy of the clinical efficacy and product quality data for a 505 (b)(2) new drug application (NDA) for a kit for the preparation of ⁶⁸Ga-Dotatate for injection. The radiopharmaceutical product is intended for use with Positron Emission Tomography (PET) for [REDACTED] (b) (4)

The NDA relies on two sources of information: review of literature and clinical data from an expanded access study being conducted under IND 111972 at Vanderbilt University Medical Center (VUMC) to which the NDA applicant has obtained the right of reference.

I. Summary of the Issue

The focus of this briefing was to critically evaluate the regulatory approach for bridging the clinical and commercial product and to consider whether the totality of the data including five clinical studies provide substantial evidence of clinical utility for the purpose of tumor visualization in patients with known primary or recurrent NETs.

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NETs are heterogeneous, uncommon malignancies. The tumors express somatostatin receptor to variable degrees. This receptor is the target for molecular imaging. Management of this disease is variable. Heterogeneity of this disease and the number of patients affected are major challenges to drug development

The regulatory briefing focused on two competing molecular imaging technologies. The first is single photon emission tomography (SPECT) which detects single gamma ray photons and the second is PET, which detects the dual photon signal produced by the annihilation of a positron and electron. Advantages in imaging hardware and software favor positron emission tomography and are stimulating the development of new PET imaging drugs. Advances in radiochemistry represent a game changer in favor of PET-based somatostatin receptor imaging.

Drug Product Considerations

^{68}Ga is a novel radionuclide for PET imaging. The radionuclide is obtained by elution of Germanium-68/Gallium-68 ($^{68}\text{Ge}/^{68}\text{Ga}$) generators. In the most common form of the generator, ^{68}Ge (the parent radionuclide, half-life = 271 days) is absorbed on solid matrices in a small column and continuously decays to ^{68}Ga (the daughter radionuclide, half-life = 68 minutes). ^{68}Ga Dotatate is the first in this class of diagnostic radiopharmaceuticals submitted to the Agency for market approval.

To encourage the development of these investigational drug products the Division recommended the submission of drug master files (DMFs) for the ^{68}Ga generators and for the drug substance precursors and the development of kit formulations for reproducible production of the drug product.

The drug substance precursor is a somatostatin derivative (TATE) conjugated to a metal chelating group (DOTA) forming the Dotatate. The components for producing the ^{68}Ga Dotatate are supplied as a two-vial kit with an accessory cartridge. Vial 1 contains lyophilized Dotatate with excipients and Vial 2 contains a reaction buffer solution for the reconstitution process with the $^{68}\text{GaCl}_3$ generator eluate. The kit formulation is prepared to be radiolabeled with the $^{68}\text{GaCl}_3$ generator eluate. The final preparation of the drug product injection is performed at the end-user radiopharmacy in a nuclear medicine facility. The lyophilized vial of Dotatate is reconstituted by adding the generator eluate followed by addition of the required amount of the buffer solution. The vial is then heated at a pre-set temperature. The product is then tested for purity before administration.

The proposed commercial formulation which consists of the drug substance ^{68}Ga Dotatate and excipients was not used in clinical trials. The literature studies cited in the NDA were conducted with ^{68}Ga Dotatate formulated with different excipients. The clinical formulation used in the Vanderbilt trial and the commercial formulation of the drug product also differ.

The CMC reviewers confirmed the identity of the drug substance, ^{68}Ga Dotatate by comparison to authentic, physico-chemically characterized reference standard, the “cold” Ga Dotatate. The

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reviewers concluded that the active ingredient is the same in both products. In addition, the reviewers evaluated the excipients to determine the potential for interactions between excipients and the active ingredient. The reviewers concluded that the small amounts of excipients do not alter the nature, disposition and performance of the drug. Specifically gentisic acid (b) (4) and has been used in other approved radiopharmaceuticals and mannitol (b) (4) commonly used in pharmaceuticals.

The Division concluded that the investigational and proposed commercial products are equivalent and sought confirmation at the regulatory briefing that the approach used for the evaluation of commercial product quality is acceptable.

Clinical Utility

Certain types of NETs express somatostatin receptors. The receptors are the target for radiopharmaceutical-based molecular imaging. Somatostatin receptor imaging (SRI) might be useful as an aid in the detection of primary NETs where a tumor is suspected based on clinical manifestations but the tumor's location has not been identified through conventional imaging. SRI is also an aid for localization of tumors in patients with known primary or recurrent NETs for the purpose of tumor staging.

The drug Indium 111 (111In) labelled Pentetreotide (OctreoScan) was approved on January 2, 1994 for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors. There have been no new developments in single photon emission tomography for SRI. On the other hand, 68Ga Dotatate is the first of three investigational SRI drugs that rely on positron emission tomography.

The development of these new SRI drugs has been driven by major advances in 68Ga radiochemistry. The image quality and resolution of anatomy is greater using PET-based SRI. Additional advantages of 68Ga radiopharmaceuticals are a reduction in radiation absorbed dose to patients and more rapid image acquisition. The initial investigational use of 68Ga somatostatin receptor imaging in patients with NETs was carried out in Europe and publications describing this clinical experience generated great interest in the radiology community and patient support groups in the US.

However, the marketing prospects for 68Ga Dotatate were insufficient to generate commercial interest because of the relatively small size of the patient population, the anticipated single use of the diagnostic, and the uncertain prospects for reimbursement by third-party payers. In the absence of commercial interest in drug development and lack of feasibility of multi-center studies, the Division encouraged single-center expanded access INDs sponsored by academic investigators and a review of the scientific literature as sources of evidence for an eventual NDA.

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Sources of Clinical Evidence

The NDA relies on a review of the scientific literature and on a single-center study conducted at the Vanderbilt University Medical Center.

(b) (4)
The applicant proposed the following indication for use:

(b) (4)
However, the literature review contained no randomized, prospective trials with independent blinded image review designed for drug development. Incomplete information in the articles did not allow one to determine precise diagnostic test performance (sensitivity/specificity) or to evaluate the role of new imaging information on patient management and patient outcomes. Nevertheless the reviewers determined that the totality of the clinical experience as demonstrated in the literature and other supporting studies for this rare, heterogeneous disease may be used to support approval.

The clinical and statistical reviewers relied on five studies that demonstrate the ability of 68 Ga Dotatate to localize disease.

Study 1. Srirajaskanthan (2010)

In this study 51 patients with NET, who were negative or faintly positive by OctreoScan imaging, underwent 68Ga Dotatate scanning. The PET images were evaluated by retrospective consensus reads blinded to OctreoScan results. The PET scans were positive in 41 of the 51 patients. PET scans localized disease and provided adjunct diagnostic information. Clinical management was altered in 36 of 51 patients. The majority of the tumors were upstaged and judged to be inoperable and these patients were therefore treated with systemic chemotherapy.

Study 2. Hoffman (2012)

The study design and the patient population were similar to those in study 1. In 33 of 40 patients the PET 68Ga Dotatate scans localized disease and provided adjunct diagnostic information resulting in unspecified changes in patient management.

Study 3. Haug (2012)

In this retrospective study 104 consecutive patients with suspected NET received 68Ga Dotatate scans. A total of 36 patients were histologically positive for NET and 68 were considered negative by histology or clinical criteria. The diagnostic findings based on consensus reads were: Sensitivity = 81%, 95%CI (64%, 92%) Specificity = 90%, 95%CI (80%, 96%)

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Study 4. Haug (2014)

In this retrospective study 63 consecutive patients with history of resection of primary NET received 68Ga Dotatate scans. The diagnostic findings based on consensus reads were: Sensitivity = 90% (74%, 97%); Specificity = 83% (67%, 92%).

Study 5. VUMC (IND 111972)

This prospective study enrolled 97 patients requiring scanning for clinical management. A total of 78 patients were evaluable for comparison to a previous OctreoScan performed within the previous three years. Ga68 Dotatate images were interpreted by consensus between two readers blinded to prior clinical information. The truth standard was a composite consisting of conventional imaging, clinical information and histopathology. A total of 50 patients were positive and 28 patients were negative for NET. Ga68 Dotatate identified correctly 48 of the positive and 26 of the negative patients.

In a total of 17 patients with discordant scan results (14 positive and 3 negative for NET by truth standard) 68Ga-Dotatate correctly identified 13/14 positives and 2/3 negatives. On the other hand, OctreoScan correctly identified 1/14 positives and 1/3 negatives.

The reviewers concluded that the overall scientific literature supports product efficacy, but the level of evidence is generally low. Two of the studies cited above are borderline adequate to estimate the diagnostic performance of 68Ga Dotatate. It is difficult to estimate performance metrics from the VUMC clinical study data.

In addition the reviewers determined that 68Ga Dotatate PET imaging relative to 111In Pentetreotide SPECT imaging has advantages that include: greater spatial resolution (3–6 mm vs. 10–15 mm), greater affinity of Dotatate (10-fold) for the somatostatin receptor 2, lower radiation exposure to the patient (3.15 mSv vs. 26 mSv for an adult weighing 75 kg), and faster image acquisition process post-administration (approximately 2 hours vs. 2 days).

The Division concluded that a number of published studies support the utility of 68Ga Dotatate for use in patients with NETs. However study design and conduct issues including patient selection bias (e.g. selection of patients with negative or weakly positive SPECT imaging) and incomplete ascertainment of false positive rates might not allow reliable determination of absolute or relative diagnostic performance characteristics. These data although insufficient for the indication proposed by the sponsor, appear to support an indication similar to that for OctreoScan, i.e. localization of tumors in patients with NETs. The Division sought confirmation at the regulatory briefing that this assessment is justified.

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II. Discussion

Question 1

The AAA kit has not been used in any human or animal study. Identity and quality of the injection produced with the kit are being extrapolated from a comparison to the VUMC investigational product and general considerations about products from published studies. Is this acceptable?

Meeting Discussion:

There was a discussion of whether or not additional analytical work is needed to achieve a complete characterization of the product. The Division confirmed that the active pharmaceutical ingredient (API) and the final product in the kit are adequately characterized. The Division is confident of the quality of the product and cited the experience with numerous INDs that use similar API and final drug products and for which adequate characterization has been provided. These data are in line with the data provided by the applicant in the NDA. A question was raised about the adequacy of the specifications for free and DOTA-bound ⁶⁸Ga in the final product because of the implications of altered biodistribution of imaging signal for diagnostic image quality. It was confirmed that the linkage is very stable, and that the final product is tested for identity of the labelled gallium Dotatate and the excess Dotatate that is in the final formulation. This is shown analytically by means of the HPLC or ITLC used in the testing of the products.

The question was raised about safety concerns because this product has not been tested in humans. It was pointed out that the product is administered in microdose quantities and there is significant experience in IND studies with human safety. It was mentioned that the bridging approach for establishing product quality is consistent with the approach used for generic products for IV use which are eligible for a biowaiver and are not evaluated in humans.

Question 2

Are submitted clinical data sufficient for assessing risk and benefit of this product?

Meeting Discussion:

DMIP explained that it expects to rely on evidence from adequate and well controlled clinical trials for diagnostic and patient management claims for imaging drugs. DMIP explained that for this NDA it is relying on the totality of evidence of benefit in the setting of negligible risk to make ⁶⁸Ga dotatate available to a rare disease population.

Parallels were drawn to other drugs approved for uses in patients with rare disease where case series and retrospective data have been used. In these cases evidentiary standards are lessened. It was mentioned that in addition to other clinical development issues, the wide availability and experience with ⁶⁸Ga dotatate make a comparative clinical study difficult to carry out.

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It was mentioned that the Agency has an interest in using data from real clinical world experience for NDAs. This application provides an example of the challenges with this approach. The Division stated that academic investigators and professional societies in the medical imaging field are interested in developing a clinical trial infrastructure that might support the development of other radiopharmaceuticals for which commercial interest is lacking. DMIP has developed guidance for imaging standards and actively encourages standardizing product manufacturing and specifications for investigational drugs and the use of uniform clinical protocols.

(b) (4)

How do these data compare to what is done for visualization claims for other imaging drugs. It was agreed that image quality seems greater with PET but how does this package of data compare to other imaging NDAs.

DMIP used the example of contrast agents and explained that for a structure delineation claim objective evidence of improved image quality such as improved visualization of anatomy with the use of contrast is acceptable. For a structure delineation claim evidence of diagnostic performance (i.e. sensitivity and specificity) is not necessary.

For 68Ga Dotatate the lack of prospective design, potential for bias in patient selection and image assessment, and uncertainties about truth standard and false positive rates argue against the use of diagnostic accuracy data in the prescribing information. In particular data on comparison of performance of SPECT and PET are not adequate. Even though there is no reliable accuracy data, the totality of the evidences available shows that the risk-benefit is favorable.

Concern was expressed about the need to provide guidance to clinicians about the possibility of false positives and negatives. DMIP will consider this advice.

Question 3

If yes, the product appears to be useful for lesion localization in patients with NETs. (b) (4)
Do you agree?

Meeting Discussion:

See discussion above.

Regulatory Briefing Meeting

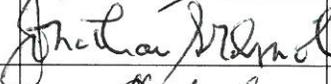
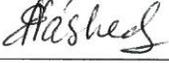
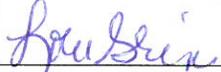
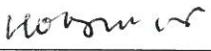
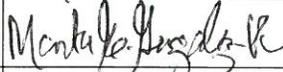
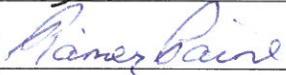
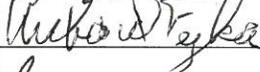
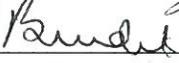
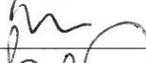
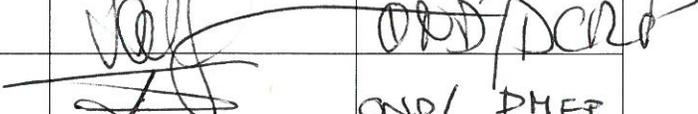
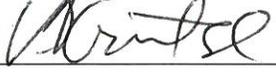
**A new PET agent (Ga68 Dotatate) for an uncommon disease
(Neuro-Endocrine Tumors)**

February 5, 2016

Sign In Sheet

| # | Name | Sign-In | Division/Office |
|-----|-------------------------|--------------------|-----------------|
| 1. | Adebayo Laniyonu | <i>[Signature]</i> | DMIP |
| 2. | Alex Gorovets | ✓ | |
| 3. | Bob Temple | <i>[Signature]</i> | OEI |
| 4. | Charles Ganley | ✓ | |
| 5. | Christy John | | |
| 6. | Cynthia Welsh | ✓ | |
| 7. | Danae Christodoulou | <i>[Signature]</i> | ONDP |
| 8. | David Jacobson-Kram | | |
| 9. | Dhanalakshmi Kasi | | |
| 10. | Donna Christner | | |
| 11. | Douglas C. Throckmorton | | |
| 12. | Eldon Leutzinger | <i>[Signature]</i> | ONDP |
| 13. | Eric Duffy | | |
| 14. | Gene Williams | | |

| | | | |
|-----|-------------------|--------------|-----------|
| 15. | Helen Ngai | ✓ | Phone |
| 16. | Jagjit Grewal | ✓ | |
| 17. | Janet Anderson | | |
| 18. | Janet Woodcock | | |
| 19. | Jesse Wells | | |
| 20. | John Amartey | John | BPO / ADP |
| 21. | John Jenkins | ✓ | |
| 22. | Jyoti Zalkikar | ✓ | Phone |
| 23. | Kate Gelperin | ✓ | Phone |
| 24. | Kate Phelan | | |
| 25. | Kathleen Uhi | | |
| 26. | Krishnakali Ghosh | ✓ | Phone |
| 27. | Libero Marzella | ✓ | |
| 28. | Lisa LaVange | | |
| 29. | Martin Haber | | |
| 30. | Naomi Redd | | |
| 31. | Nushin Todd | ✓ | |
| 32. | Ron Honchel | | |
| 33. | Rosemary Roberts | | |
| 34. | Sandy Kweder | | |
| 35. | Sara Camilli | | |
| 36. | Satish Misra | Satish Misra | DBV / DB |
| 37. | Steven Bird | | |
| 38. | Sukhminder Sandhu | | |

| | | | |
|-----|-----------------------------|---|-------------|
| 39. | Thao Vu | | |
| 40. | Thomas Gwise |  | OS |
| 41. | Tien Mien Chen | | |
| 42. | Vidula Kolhatkar | | |
| 43. | Yelena Maslov | | |
| 44. | Adam George |  | OPDP |
| 45. | SONATHAN GOLDSMITH |  | RDP/OND |
| 46. | Eugenia Nashed |  | OPQ / OPPQ |
| 47. | Levi Griner |  | NDP |
| 48 | HONGLIU DING |  | OSE |
| | Albrecht, Renata |  | DTOP |
| | Stanley H. Stern |  | DMIP |
| | Marista E. Gonzalez-Pineiro |  | ODSIC |
| | Wiley Chambers |  | DTOP |
| | Rainer Paine |  | CND/OND |
| | Roselyn Epps |  | OND/ODDP |
| | RICHARD FEJKA |  | OND/DMIP |
| | Bandu Karapure |  | OND/DMIP |
| | Ronald Howard |  | OND DMIP |
| | Katie Sokolowski |  | ODEII/DAAAP |
| | Jon Kretting |  | OND/DMIP |
| | Shari Talfree |  | OND/DCR |
| | Jean-Marc Guettier |  | OND/DMIP |
| | VICTOR CRENTSIL |  | OND/ODE III |

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/s/

LIBERO L MARZELLA
03/21/2016



NDA 208547

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head, Regulatory Affairs
350 Fifth Avenue, Floor 69, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) dated July 1, 2015, received July 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NETspot (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection).

On February 12, 2016, we received your February 12, 2016, major amendments to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is June 1, 2016.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 15, 2016.

If you have any questions, call Modupe Fagbami, Regulatory Project Manager, at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Libero Marzella, Ph.D., M.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

LIBERO L MARZELLA
02/18/2016

From: Fagbami, Modupe
Sent: Friday, January 22, 2016 1:01 PM
To: victor.paulus@adacap.com
Subject: NDA 208547- (b) (4) (Kit for the Preparation of 68Ga-DOTATATE for Injection)
Information Request
Importance: High

Dear Dr. Paulus,

Please provide a letter of clarification and commitment by COB Tuesday, January 26, 2016, listing the following:

- All of the remaining data to be submitted to the NDA 208547.
- Outstanding Applicant's responses to our information requests.

Please let us know in the letter your best estimate of when such data will be submitted.

Kindly confirm receipt of this email.

Thank you.

Modupe O. Fagbami

RPM

Division of Medical Imaging Products

Office of Drug Evaluation IV

CDER, FDA

10903 New Hampshire Avenue

WO-22, Room 5439

Silver Spring, Maryland 20993

Phone: 301-796-1348

Fax: 301-796-9899

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/s/

MODUPE O FAGBAMI
01/22/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208547

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Advanced Accelerator Applications USA, Inc.
350 Fifth Avenue, Suite 6902
New York, NY 10118

ATTENTION: Victor G. Paulus, Ph.D.
Head of Regulatory Affairs

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA), dated and received July 1, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for ⁶⁸GA-DOTATATE Injection, 40 mcg/vial.

We also refer to your correspondence, dated and received November 3, 2015, requesting review of your proposed proprietary name, Netspot.

We have completed our review of the proposed proprietary name, Netspot and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your November 3, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Modupe Fagbami, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
01/22/2016



INADVERTENT DISCLOSURE

Advanced Accelerator Applications USA, Inc.
Attention: Mark Ibrahim, M.S.C.R.
Empire State Building
350 Fifth Ave, Suite 6902
New York, NY 10118

Dear Mr. Ibrahim:

On December 17, 2015, at 7:41 AM, you were inadvertently sent an email that contained information regarding a third-party. Thank you for notifying us of the error. On December 21, 2015, we contacted you to request that you delete the email, and that you agree to not retain any copies of the email or use, distribute, or disclose the document or the contents thereof.

By January 8, 2015, please send a letter: (1) confirming deletion of the email; and (2) stating your agreement to not use, distribute, or disclose the email or the contents thereof. The letter should be sent to my attention at the following address:

Thao M. Vu, R.Ph
10903 New Hampshire Ave
WO75, Room 4509
Silver Spring, MD 20993

We apologize for the inadvertent disclosure of this information to you. We will be informing the third-party of this inadvertent disclosure of information. CDER takes its disclosure responsibilities very seriously and we make every effort to ensure that information is disclosed only in accordance with applicable laws and regulations. If you have any questions, please call me at (240) 402-2690.

Thank you for your cooperation, and prompt attention to this matter.

Sincerely,

{See appended electronic signature page}

Thao M. Vu, R.Ph
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Office of Program and Regulatory Operation
Center of Drug Evaluation and Research

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/s/

THAO M VU
12/22/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date and Time: December 7, 2015, 2:00-2:30pm, EST.

Application Number: 208547

Product Name: (b) (4) (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection)

Sponsor/Applicant Name: Advanced Accelerator Applications (AAA)

Subject: To address CMC residual issues.

FDA Participants

| | |
|------------------------------|--|
| Libero Marzella, M.D., Ph.D. | Director, Division of Medical Imaging Products |
| Modupe Faqbami | Regulatory Project Manager, DMIP, OND |
| Alex Gorovets, MD. | Deputy Director, DMIP, OND |
| Cynthia Welsh, MD. | Medical Officer, DMIP, OND |
| Danae Christodoulou, Ph.D. | Branch Chief, Acting |
| Eldon Leutzinger, Ph.D. | Application Technical Lead, CMC |
| Thao M. Vu, R.Ph | Regulatory Business Process Manager |
| John Amartey, Ph.D. | Drug Product reviewer |
| Dhanalakshmi Kasi | Drug Process reviewer |

Sponsor/Applicant Participants

| | |
|------------------------------|--|
| Mark Ibrahim | Regulatory Specialist |
| Michael Zhang, MD. | Clinical Project Manager |
| Lorenza Fugazza, Ph.D. | Development Scientist & Head of Radiochemistry |
| Isabelle Gilbert-Chan | Pharmaceutical Development Manager |
| Maurizio Mariani, MD., Ph.D. | Head, Non-Clinical R&D |
| Victor G. Paulus, Ph.D. | Head, Regulatory Affairs |

1.0 BACKGROUND:

CMC requested AAA (in the 74 days letter and during Mid-cycle) to submit the following information for review:

1. Executed batch records and results for 3 runs for radiolabeling of the kit.
The translations of the records for the components of the kit are the master (blank) records. The batch records submitted in Italian are executed batch records – at least one executed record of each kit component should be provided in English.
2. Submit the validation of ITLCs test method against HPLC approved method with regards to radiochemical purity for review.
3. Define fill volume range.

Thus far, the information submitted by AAA was not complete.

2.0 DISCUSSION:

1. FDA reinstated that the submitted information post mid-cycle were blank master records. Therefore, AAA will need to provide translations for executed batch records for at least one batch (vial 1, 2, and cartridge) by December 21, 2015. In addition, the notes that were in Italian executed batch record has to be captured in the English translation. The remainder translation for the executed batch records may be provided post-action date.
2. AAA will need to provide data to demonstrate the validation of ITLC QC test methods against HPLC approved method in performing radiochemical purity. The data will need to be submitted by December 21, 2015
3. Fill volume limit provided for vial 2 in Table 1 (In process tests and corresponding limit) is (b) (4) which is not acceptable. Revise your fill volume limit as not less than 1 ml as per USP <1>. Also, fill volume range has to be included in the in process test table for vial 2 as per USP <1151>.

AAA acknowledged and concurred with FDA's requests and will provide the above three items by December 21, 2015

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/s/

THAO M VU
12/22/2015

From: Fagbami, Modupe
Sent: Wednesday, December 16, 2015 12:04 PM
To: victor.paulus@adacap.com
Subject: NDA 208547- (b) (4) (Kit for the Preparation of 68Ga-DOTATATE for Injection)
Importance: High

Dear Dr. Paulus,

You responded to the clinical IR on 11/24/15 stating that the information on the 17 discordant would be submitted by VUMC and that they were sent out by VUMC to FDA:

2. For the 17 patients with discordant OctreoScan and DOTATATE PET scan results, please provide the following for our review: copies of the CRFs, the individual blinded reader results, change in management data and information, as well as the adjudication data/information. Please respond to this request by COB 11/23/15.

Your Response:

“The requested information for the 17 patients was sent to the Agency by mail yesterday Monday November 23rd from the University and should be received shortly.”

Please note that we have not received the information on the 17 patients. Let us know urgently when, and to which IND or NDA the information was sent.

Thanks you.

Modupe O. Fagbami

*RPM
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA
10903 New Hampshire Avenue
WO-22, Room 5439
Silver Spring, Maryland 20993
Phone: 301-796-1348
Fax: 301-796-9899*

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/s/

MODUPE O FAGBAMI
12/16/2015

From: Fagbami, Modupe
Sent: Tuesday, December 15, 2015 11:56 AM
To: victor.paulus@adacap.com
Subject: FW: NDA 208547- [REDACTED] (b) (4) (Kit for the Preparation of 68Ga-DOTATATE for Injection)
Discipline Review Letter
Importance: High

Dear Dr. Paulus,

The below is a clarification to the Biopharmaceutical item listed in the attached Discipline Review letter of December 11, 2015.

- Provide the calculated osmolality value for the formulation and support the information with at least one measured value of the reconstituted drug product [⁶⁸Ga]-DOTATATE.

Kindly confirm receipt of this communication and let me know if you have any questions.

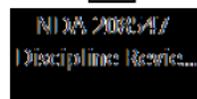
Thank you.

Modupe Fagbami

From: Fagbami, Modupe
Sent: Friday, December 11, 2015 2:10 PM
To: victor.paulus@adacap.com
Subject: NDA 208547- [REDACTED] (b) (4) (Kit for the Preparation of 68Ga-DOTATATE for Injection) Discipline Review Letter
Importance: High

Dear Dr. Paulus,

Please find attached an electronic copy of the Discipline Review Letter for NDA 208547- [REDACTED] (b) (4) (Kit for the Preparation of 68Ga-DOTATATE for Injection).



Kindly let me know if you have any questions.

Thanks

Modupe O. Fagbami

RPM

Division of Medical Imaging Products

Office of Drug Evaluation IV

CDER, FDA

10903 New Hampshire Avenue

WO-22, Room 5439

Silver Spring, Maryland 20993

Phone: 301-796-1348

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/s/

MODUPE O FAGBAMI
12/15/2015



NDA 208547

MID-CYCLE COMMUNICATION

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head, Regulatory Affairs
350 Fifth Avenue, Floor 69, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [REDACTED]^{(b) (4)} (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection).

We also refer to the teleconference between representatives of your firm and the FDA on October 27, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Modupe Fagbami
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: October 27, 2015 at 3:30 pm

Application Number: NDA 208547

Product Name: (b) (4) (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection

Indication: Diagnostic for (b) (4) neuroendocrine tumors (b) (4) NETs)

Applicant Name: Advanced Accelerator Applications (AAA)

Meeting Chair: Libero Marzella, M.D., Ph.D., Director, DMIP

Meeting Recorder: Modupe Fagbami, Regulatory Project Manager, DMIP

FDA ATTENDEES

Charles Ganley, M.D., Office Director ODE IV
Libero Marzella, M.D., Ph.D., Director, DMIP
Alex Gorovets, M.D., Deputy Director, DMIP
Nushin Todd, M.D., Associate Director, Labeling, DMIP
Cynthia Welsh, M.D., Medical Officer, DMIP
Jagjit Grewal, Associate Director of Regulatory Affairs, ODEIV
Danae Christodoulou, Ph.D., CMC Branch Chief, OPQ
Eldon Leutzinger, Ph.D., CMC Team Leader, OPQ
Vinayak Pawar, Ph.D., CMC Microbiology Reviewer, OPQ/OPF/DMA
Krishnakali Ghosh, Ph.D., Senior Policy Advisor/CSO, CDER/OPQ/OPF/DIA
John Amartey, Ph.D., CMC Reviewer, OPQ
Ronald Honchel, Ph.D., Nonclinical Reviewer, DMIP
Christy John, Ph.D., Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Satish Misra, Ph.D., Biostatistician Reviewer, OTS/OB/DBV
Jyoti Zalkikar, Ph.D., Biostatistician, Reviewer, OTS/OB/DBV
Helen Ngai, Ph.D., Microbiologist, OMPT/CDER/OPQ/OPF/DMA/MABI
Michelle Rutledge, Ph.D., OSE/OMEPRM/DMEPA
Vidula Kolhatkar, Ph.D., Biopharmaceutics Reviewer, OPQ/ONDP
Dhanalakshmi Kasi, Ph.D. Staff Fellow, OPF/Division III
Alberta Davis-Warren, Regulatory Project Manager, DMIP
Diane Hanner, Regulatory Project Manager, DMIP
Modupe Fagbami, Regulatory Project Manager, DMIP

APPLICANT ATTENDEES

(b) (4)

Maribel Lopera Sierra, M.D., Chief Medical Officer
Maurizio Mariani, M.D., Ph.D., Head, Non-Clinical Research
Camelia Cercel, Regulatory Affairs
Daniela Chicco, Ph.D. Preclinical Research
Claude Hariton, Ph.D., Head, Clinical Research
Thomas Thevenet, Clinical Development Scientist
Jack Erion, Ph.D., Vice President and Deputy CEO
Izabela Rejdych, Manager, EU Regulatory Affairs
Michael Zhang, M.D., Clinical Project Manager
Mark Ibrahim, Regulatory Specialist
Victor Paulus, Ph.D., Head, Regulatory Affairs

INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

SIGNIFICANT ISSUES

1. Clinical:

In the VUMC protocol, there is no mention in the eligibility criteria if subjects were allowed to be scanned with concomitant use of long or short acting somatostatin analogs. Please clarify if subjects had the somatostatin analogs discontinued prior to scanning with DOTATATE.

Meeting Discussion:

Response to the above information request was received on October 26, 2015. It is under review.

2. Chemistry, Manufacturing and Controls (CMC):

- a. In your response to our previous CMC information request #9, you have presented only an HPLC analysis of the [^{nat}Ga]-DOTATATE (in-house standard). Present the

mass spectrum of the reference standard to support the mass analysis in figure 2 of 3.2.P.6 presented in the application.

- b. Provide a Letter of Authorization (LoA) to the IND study conducted, i.e., the VUMC protocol.
- c. You have provided batch record translations for ct002-13002-v1, ct002-13003-v1, ct002-14001-v1, ct0031 14001-v2, ct0031 14002-v2 and ct003114003-v2 in responses to the information request dated 10/07/2015. These exhibit batch records in English are incomplete. Provide the complete batch records in English, including all of the in-process test and release test results.
- d. In your response to question 21 in the information request (10/07/2015), you have stated that the product is a cold kit which is labeled in a licensed pharmacy. But, you have not provided any evidence of assurance that the kits on radiolabeling will produce [68Ga]-DOTATATE reproducibly meeting the established release specifications. Provide the following information 1. Test results (batch analysis data, COA) from three validation batches of [68Ga]-DOTATATE produced from the kits. 2. All peaks in the Radio/UV HPLC chromatograms for the three validation batches should be identified and appropriately integrated to provide an unambiguous account of the chemical and radio chemical purity of the drug product. 3. Chemical purity, based on the UV HPLC chromatograms, should take into account all chemical impurities, including related substances. 4. The test results from the three validation batches should also include the quantitative levels of (b) (4) present in your final product.
- e. Provide lyophilization sampling plan used for your exhibit batches to ensure uniformity of units in different locations on each shelf with respect to the lyophilized product properties, such as (b) (4), can be adequately captured. Also include how this information from your exhibit batch will be used to control your commercial batches.
- f. Your manufacturing process for vial 1 involves the (b) (4) content limit in your release specification for vial 1.
- g. Your target fill weight for vial 1 is (b) (4) mL and the range is (b) (4) mL. Your lower fill limit ((b) (4) ml) is (b) (4) the target fill which is not acceptable. Revise your lower limit to NLT 1 mL as per USP <1>.
- h. Your pharmaceutical development report provided in section 3.2.P.2 shows that buffer addition time (10 min delay), radiolabeling temperature (95°C) and time (7 min) are critical process parameters for which any change in these parameters may lead to decomposition of the drug product. Since there is no batch sheet for radiolabeling, explain how these critical process parameters are communicated to the radio pharmacist.

Meeting Discussion:

Response to the above information request was received on October 26, 2015. It is under review.

3. Biopharmaceutics:

Submit a formal biowaiver request for the requirement to conduct in vivo bioavailability or bioequivalence studies to bridge the proposed commercial formulation and the clinically tested formulation used under the VUMC protocol.

Your biowaiver request should include the following:

- A detailed side-by-side table comparing the proposed commercial formulation and the clinically tested formulation used under the VUMC protocol including the osmolality and pH values.
- Scientific justification that the two products are similar, despite any differences between the two formulations, in terms of the in vivo pharmacokinetic performance and the clinical performance. You may include literature references and/or your study reports to support your justification.

Meeting Discussion:

Response to the above information request was received on October 26, 2015. It is under review

4. Clinical Pharmacology:

In **Section 7.1. Somatostatin Analogs**, the package inserts states: “Non-radioactive somatostatin analogs competitively bind to the same somatostatin receptors (b)(4) long acting analogs of somatostatin (b)(4) Short acting analogs of somatostatin can be used up to 24 hours before (b)(4) imaging (b)(4).”

- Please provide a listing of relevant long acting and short acting analogs of somatostatin commonly used. Also, please provide justification for avoiding long acting analogs (b)(4) and short acting analogs 24 hours before imaging study. What is the basis for the recommendations? Are there empirical (i.e., imaging) data available to support that it is necessary to avoid analogs? If yes, are there empirical (i.e., imaging) data to support that (b)(4) 24 hours are the proper timeframes?

Meeting Discussion:

Response to the above information request was received on October 26, 2015. It is under review.

5. Division of Medication Error Prevention and Analysis: (DMEPA)

Please provide 3 representative samples of the product with attached proposed commercial labels and labeling for our review. This will help us to inform the review of the labels, labeling and product design from the medication error perspective.

Meeting Discussion:

Response to the above information request was received on October 26, 2015. It is under review. The Agency agreed that the Applicant could send the labeling without the proprietary name since that is yet to be approved.

MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major Safety Concerns identified at this time and there is currently no need for REMS.

ADVISORY COMMITTEE MEETING

There are no plans at this time for an Advisory meeting.

LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

It is anticipated that the Agency will be discussing labelling before the end of the year 2015, and Late Cycle meeting is planned for late January 2016. The meeting package will be sent to the Applicant two weeks before the late cycle meeting.

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/s/

LIBERO L MARZELLA
11/24/2015

From: Fagbami, Modupe
Sent: Tuesday, November 24, 2015 10:18 AM
To: victor.paulus@adacap.com
Subject: NDA 208547- (b) (4) (Kit for the Preparation of 68Ga-DOTATATE for Injection)
Importance: High

Dear Dr. Paulus,

We are still waiting for your response regarding the following which we had earlier sent to you. Please provide response to us ASAP.

1. Provide complete translation of all exhibit batch records including in process test and release test results in English for the manufacture of vial 1 (ct002-13002-v1, ct002-13003-v1, ct002-14001-v1), vial 2 (ct0031 14001-v2, ct0031 14002-v2 and ct003114003-v2) and cartridge.
2. In your response to question 21 in the information request (10/07/2015), you have stated that the product is a cold kit which is labeled in a licensed pharmacy. But, you have not provided any evidence of assurance that the kits on radiolabeling will produce [68Ga]-DOTATATE reproducibly meeting the established release specifications. Provide the following information 1. Test results (batch analysis data, COA) from three validation batches of [68Ga]-DOTATATE produced from the kits. 2. All peaks in the Radio/UV HPLC chromatograms for the three validation batches should be identified and appropriately integrated to provide an unambiguous account of the chemical and radio chemical purity of the drug product. 3. Chemical purity, based on the UV HPLC chromatograms, should take into account all chemical impurities, including related substances. 4. The test results from the three validation batches should also include the quantitative levels of (b) (4) present in your final product.

Please confirm receipt and let me know if you have any questions.

Thank you.

Modupe O. Fagbami

RPM

Division of Medical Imaging Products

Office of Drug Evaluation IV

CDER, FDA

10903 New Hampshire Avenue

WO-22, Room 5473

Silver Spring, Maryland 20993

Phone: 301-796-1348

Fax: 301-796-9899

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/s/

MODUPE O FAGBAMI
11/24/2015

From: Fagbami, Modupe
Sent: Tuesday, November 17, 2015 1:41 PM
To: victor.paulus@adacap.com
Subject: NDA 208547- (b) (4) (Kit for the Preparation of 68Ga-DOTATATE for Injection)
Information Requests Clinical Information Request
Importance: High

Hello Dr. Paulus,

Please find the following Clinical Information Request for your response as indicated:

1. Please confirm that all patient records, including data collection and/or case report forms (CRF), related to the conduct of the VUMC expanded access program, as well as all records related to the conduct of the blinded reads, are available at the Vanderbilt clinical site. If so, please provide the specific address. If not, please provide the location and specific address. Please respond to this request by COB 11/18/15 (within 24-48 hours.)
2. For the 17 patients with discordant OctreoScan and DOTATATE PET scan results, please provide the following for our review: copies of the CRFs, the individual blinded reader results, change in management data and information, as well as the adjudication data/information. Please respond to this request by COB 11/23/15.

Kindly confirm receipt and let me know if you have any questions.

Thank you

Modupe O. Fagbami

*RPM
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA
10903 New Hampshire Avenue
WO-22, Room 5473
Silver Spring, Maryland 20993
Phone: 301-796-1348
Fax: 301-796-9899*

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/s/

MODUPE O FAGBAMI
11/17/2015

From: Fagbami, Modupe

Sent: Tuesday, November 10, 2015 11:56 AM

To: victor.paulus@adacap.com

Subject: NDA 208547- (b) (4) (Kit for the Preparation of 68Ga-DOTATATE for Injection) CMC Information Requests

Importance: High

Hello Victor,

Please find the following information request for your response on or before COB, Thursday, November 12, 2015.

1. The (b) (4) label presented for the drug product is lacking a lot number. Revise the label to include this information.
2. There is no syringe label in the application package insert. Provide an individual syringe label with all the relevant product information space permitting.

Kindly confirm receipt of this email.

Thank you.

Modupe O. Fagbami

RPM

Division of Medical Imaging Products

Office of Drug Evaluation IV

CDER, FDA

10903 New Hampshire Avenue

WO-22, Room 5473

Silver Spring, Maryland 20993

Phone: 301-796-1348

Fax: 301-796-9899

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/s/

MODUPE O FAGBAMI
11/10/2015



NDA 208547

INFORMATION REQUEST

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head, Regulatory Affairs
350 Fifth Avenue, Floor 69, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) dated July 1, 2015, received July 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [REDACTED] (b)(4) [REDACTED] (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection).

We are reviewing the Clinical, Chemistry Manufacturing and Controls (CMC), Biopharmaceutics and Clinical Pharmacology sections of your submission and have the following comments and information requests. We request a prompt written response on or before COB, Monday October 26, 2015, in order to continue our evaluation of your NDA.

They are:

1. Clinical:

In the VUMC protocol, there is no mention in the eligibility criteria if subjects were allowed to be scanned with concomitant use of long or short acting somatostatin analogs. Please clarify if subjects had the somatostatin analogs discontinued prior to scanning with DOTATATE.

2. Chemistry, Manufacturing and Controls (CMC):

- a. In your response to our previous CMC information request #9, you have presented only an HPLC analysis of the [^{nat}Ga]-DOTATATE (in-house standard). Present the mass spectrum of the reference standard to support the mass analysis in figure 2 of 3.2.P.6 presented in the application.
- b. Provide a Letter of Authorization (LoA) to the IND study conducted, i.e., the VUMC protocol.

- c. You have provided batch record translations for ct002-13002-v1, ct002-13003-v1, ct002-14001-v1, ct0031 14001-v2, ct0031 14002-v2 and ct003114003-v2 in responses to the information request dated 10/07/2015. These exhibit batch records in English are incomplete. Provide the complete batch records in English, including all of the in-process test and release test results.
- d. In your response to question 21 in the information request (10/07/2015), you have stated that the product is a cold kit which is labeled in a licensed pharmacy. But, you have not provided any evidence of assurance that the kits on radiolabeling will produce [68Ga]-DOTATATE reproducibly meeting the established release specifications. Provide the following information 1. Test results (batch analysis data, COA) from three validation batches of [68Ga]-DOTATATE produced from the kits. 2. All peaks in the Radio/UV HPLC chromatograms for the three validation batches should be identified and appropriately integrated to provide an unambiguous account of the chemical and radio chemical purity of the drug product. 3. Chemical purity, based on the UV HPLC chromatograms, should take into account all chemical impurities, including related substances. 4. The test results from the three validation batches should also include the quantitative levels of (b) (4) present in your final product.
- e. Provide lyophilization sampling plan used for your exhibit batches to ensure uniformity of units in different locations on each shelf with respect to the lyophilized product properties, such as (b) (4), can be adequately captured. Also include how this information from your exhibit batch will be used to control your commercial batches.
- f. Your manufacturing process for vial 1 involves (b) (4) content limit in your release specification for vial 1.
- g. Your target fill weight for vial 1 is (b) (4) mL and the range is (b) (4) mL. Your lower fill limit (b) (4) ml) is (b) (4) the target fill which is not acceptable. Revise your lower limit to NLT 1 mL as per USP <1>.
- h. Your pharmaceutical development report provided in section 3.2.P.2 shows that buffer addition time (10 min delay), radiolabeling temperature (95°C) and time (7 min) are critical process parameters for which any change in these parameters may lead to decomposition of the drug product. Since there is no batch sheet for radiolabeling, explain how these critical process parameters are communicated to the radio pharmacist.

3. Biopharmaceutics:

Submit a formal biowaiver request for the requirement to conduct in vivo bioavailability or bioequivalence studies to bridge the proposed commercial formulation and the clinically tested formulation used under the VUMC protocol.

Your biowaiver request should include the following:

- A detailed side-by-side table comparing the proposed commercial formulation and the clinically tested formulation used under the VUMC protocol including the osmolality and pH values.
- Scientific justification that the two products are similar, despite any differences between the two formulations, in terms of the in vivo pharmacokinetic performance and the clinical performance. You may include literature references and/or your study reports to support your justification.

4. Clinical Pharmacology:

In Section 7.1. **Somatostatin Analogs**, the package inserts states: “Non-radioactive somatostatin analogs competitively bind to the same somatostatin receptors (b) (4) long acting analogs of somatostatin (b) (4) Short acting analogs of somatostatin can be used up to 24 hours before the imaging study.”

- Please provide a listing of relevant long acting and short acting analogs of somatostatin commonly used. Also, please provide justification for avoiding long acting analogs (b) (4) and short acting analogs 24 hours before imaging study. What is the basis for the recommendations? Are there empirical (i.e., imaging) data available to support that it is necessary to avoid analogs? If yes, are there empirical (i.e., imaging) data to support that (b) (4) 24 hours are the proper timeframes?

5. Division of Medication Error Prevention and Analysis: (DMEPA)

Please provide 3 representative samples of the product with attached proposed commercial labels and labeling for our review. This will help us to inform the review of the labels, labeling and product design from the medication error perspective.

If you have any questions, please contact Modupe Fagbami, Regulatory Project Manager, at 301-796-1348.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

LIBERO L MARZELLA
10/16/2015

From: Fagbami, Modupe
Sent: Wednesday, October 07, 2015 9:05 AM
To: victor.paulus@adacap.com
Subject: NDA 208547 (b) (4) (Kit for the Preparation of 68Ga-DOTATATE for Injection)
Information Request
Importance: High

Dear Dr. Paulus,

We refer you to NDA 208547, IND 111972 referenced in your NDA, the protocol entitled “Use of 68Ga-DOTATATE PET scanning for diagnosis and treatment of metastatic neuroendocrine tumors” (dated 5/25/11) and to the Statistical Analysis Report – Vanderbilt University found in module 5. We have the following information requests:

1. Please clarify the standard of truth used in this protocol. It is our understanding that it is standard of care imaging previously performed including SPECT. Please state if you conducted the following comparisons:
 - a. PET performance compared to conventional imaging (without SPECT)
 - b. SPECT performance compared to conventional imaging (without PET)
 - c. performance results of ‘a’ compared to results of ‘b’

If not, please describe what was performed and how it was used to arrive at the primary endpoint. Were there any cases where histopathology could serve as a standard of truth? If so, please identify such cases.

[This is the division’s current thinking: For assessment of the test’s performance, we recommend measuring patient level disease detection (“sensitivity”) using blinded readers and a specified standard of truth (histopathology or a composite of conventional imaging, clinical information and histopathology). Demonstrating statistically significant superiority or non-inferiority in relation to a comparator (111-In-octreotide) or superiority over a pre-defined threshold is acceptable. We are particularly concerned about false positive detections and recommend measuring “specificity” as a co-primary endpoint. Enrolling patients with a suspected NET and a negative SOT would contribute to the patient-level “specificity population”].

2. Please clarify the primary endpoint(s) for the overall patient population.
3. We recommend also analyzing data in the following sub-populations, if available:
 - Patients who underwent curative primary resection and are imaged to assess adequacy of resection or for surveillance
 - Patients who are undergoing evaluation of clinical recurrence and in whom other imaging modalities are negative
 - Patients who are scheduled for surgery and are undergoing primary staging

4. Please describe the procedure that was used for PET/CT scan interpretation and the extent of blinding. It is our understanding that 2 readers were each blinded to the other reader's interpretation but otherwise fully cognizant of other clinical, imaging and laboratory data as noted in 3b on page 33/34 of the protocol and that discrepancies were resolved by consensus and a patient level majority read was utilized for determination of the primary endpoint. Note that this conflicts with the main body of the protocol – see scan interpretation page 20.
 - Provide the patient level data for each reader; identify the scans that required adjudication, the reason for the adjudication, and the result.
 - Provide a flow chart for how you assessed a change in management.
 - Provide the step by step results of the management decisions.

5. With respect to assessing changes in patient management we recommend considering the following evaluations:
 - Octreoscan results 'a' leading to patient management decision 'b'
 - Dotatate scan results 'c' leading to patient management decision 'd'
 - Comparative assessment between "d" and "b"

A non-comparative assessment of a proportion of patients in whom a clinically meaningful change in management has occurred as a result of the imaging test could also be acceptable as a secondary analysis.

Please note that your protocol should have provided details for the methodology used in your study to make the clinical management determinations in order to minimize bias. For example, please clarify:

- Who independently/blinded read the comparator scan
 - Who independently/blinded made the management decision using the results of the comparator scan
 - Who independently/blinded read the Dotatate scan
 - The information that was made available to make these clinical decisions
 - Who independently/blinded made the management decision using the results of the Dotatate scan
 - A definition of 'change in patient management'
 - Randomization and blinding of images
6. Please submit the case narratives for subjects who had an AE.
 7. Define the term "harm levels" found in your discussion of the safety results.
 8. Explain appendix 2.2 column entitled "reason from imaging review".

Additional Information Requests:

In relation to your drug product, please address the following and send response by Friday October 9, 2015:

- Has your product (kit) been used in any of the submitted publications
- Has your kit been used at Vanderbilt?
- Has your product been administered to a human?
- Has your product been used in a non-clinical setting?

In relation to the currently submitted meta-analysis please address the following:

1. There are many analyses described in the primary analysis section. Please specify the secondary endpoints and their analyses one by one clearly.
2. We strongly recommend evaluating the performance (sensitivity and specificity) of the 68Ga-DOTATATE with respect to well defined standard of truth as the primary endpoint. The lower bounds of 95% confidence intervals (LCL) for the sensitivity and specificity (pooled by taking into consideration the heterogeneity among the studies) greater than 50% would imply reasonable diagnostic characteristics of the 68Ga-DOTATATE PET.
3. Clarify the analytical approach for comparing the two imaging modalities (68GADOTATATE vs. 111In-octreotide) for non-inferiority. The margin must be justified.
4. Clarify and justify the definition of change in patient in management.
5. In data extraction, please clarify if the following factors are considered:
 - Study completion date and study publication date
 - Study design (n, age, sex, drug, dose)
 - Characteristics of study population
 - country
 - Assessment procedures (imaging and SOT)
 - Covariates, if available (such as demographics, prior therapy, unknown primary vs. known primary)
6. Different analysis populations can be specified for analyzing the primary and secondary endpoints according to the availability of the data (results from 68Ga-DATATE, results from Octreotide, and SOT). Please clearly define the analysis populations for different analyses.

7. Clarify how the missing data were imputed.
8. Clarify the agreement evaluation for the reviewers. How many reviewers are included for the inter-rater reliability evaluation?
9. Clarify how the publication bias is evaluated.

Please respond to the additional requests related to the drug product by COB, Friday, October 9, 2015, and you could respond to the rest of the requests within the next 1 to 2 weeks.

Let me know if you have any questions.

Thank you.

Modupe O. Fagbami

RPM

Division of Medical Imaging Products

Office of Drug Evaluation IV

CDER, FDA

10903 New Hampshire Avenue

WO-22, Room 5473

Silver Spring, Maryland 20993

Phone: 301-796-1348

Fax: 301-796-9899

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/s/

MODUPE O FAGBAMI
10/07/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208547

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Advanced Accelerator Applications USA, Inc.
350 Fifth Avenue, Suite 6902
New York, NY 10118

ATTENTION: Victor Paulus, Ph.D.
Head of Regulatory Affairs

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) dated and received July 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection, 40 mcg of Dotatate.

We also refer to:

- Your correspondence, dated and received July 1, 2015, requesting review of your proposed proprietary name, (b) (4)
- Our correspondence, dated July 7, 2015, requesting clarification of the established name
- Your correspondence, dated and received July 10, 2015, providing clarification of the established name

We have completed our review of this proposed proprietary name, (b) (4) and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name, (b) (4) is unacceptable because (b) (4)

Please be advised that our proprietary name review does not consider the presentation of the proposed proprietary name (e.g. Name, NAME, NaMe). We defer evaluation of text presentation (i.e. letter case, font size, etc.) of the proposed proprietary name to our label and labeling review.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Modupe Fagbami, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR on behalf of TODD D BRIDGES
09/24/2015

From: Anderson, Janet
To: ["Victor Paulus"](#)
Subject: RE: NDA-208547 - Request for Clarification of Established Name
Date: Friday, July 10, 2015 3:52:00 PM

Thank you for the update. You have a great weekend too.

Janet

From: Victor Paulus [mailto:victor.paulus@adacap.com]
Sent: Friday, July 10, 2015 3:21 PM
To: Anderson, Janet; Fagbami, Modupe
Subject: Re: NDA-208547 - Request for Clarification of Established Name

Dear Janet and Modupe,

Sequence 0001 was submitted via the gateway with only the Amendment to Request Proprietary Name Review. RegOps staff just sent me a copy of the receipt.

Revised labeling which incorporates reproduction and lactation will be sent on Monday along with SPL.

I hope you both have a pleasant and relaxing weekend.

All the best,

Victor

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From: <Anderson>, Janet <Janet.Anderson@fda.hhs.gov>
Date: Friday, July 10, 2015 at 9:31 AM
To: victor paulus <victor.paulus@adacap.com>
Cc: "Fagbami, Modupe" <Modupe.Fagbami@fda.hhs.gov>
Subject: RE: NDA-208547 - Request for Clarification of Established Name

Hello Victor,

The amendment can just be a clarification of the established name and as mentioned below please include the statement **"AMENDMENT TO REQUEST FOR PROPRIETARY NAME REVIEW"** in bold capital letters, at the top of your cover letter and on the first page of the main submission document.

Thanks,
Janet

*Janet L. Anderson, Pharm.D.
Safety Regulatory Project Manager*

*FDA CDER Office of Surveillance and Epidemiology
White Oak, Bldg. 22, Rm 4484
10903 New Hampshire Ave
Silver Spring, Maryland 20993-0002
301-796-0675*

From: Victor Paulus [<mailto:victor.paulus@adacap.com>]
Sent: Friday, July 10, 2015 7:49 AM
To: Anderson, Janet
Cc: Fagbami, Modupe
Subject: Re: NDA-208547 - Request for Clarification of Established Name
Importance: High

Dear Janet,

Should the amendment be a resubmission of all of the information already provided with the amended clarification or juts the clarification?

Thanks and best regards,

Victor

Victor G. Paulus, PhD

Head, Regulatory Affairs
Advanced Accelerator Applications

www.adacap.com

The Empire State Building
350 Fifth Avenue, Suite 6902
69th Floor
New York, NY 10118

tel. 212.235.2391

Bridging Science with Life

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From: <Anderson>, Janet <Janet.Anderson@fda.hhs.gov>
Date: Tuesday, July 7, 2015 at 4:14 PM
To: victor paulus <victor.paulus@adacap.com>
Cc: "Fagbami, Modupe" <Modupe.Fagbami@fda.hhs.gov>
Subject: NDA-208547 - Request for Clarification of Established Name

Dear Dr. Paulus,

We are in receipt of your July 1, 2015 submission for NDA 208547. Please clarify the established name for NDA 208547. The 356h, Request for Proprietary Name Request, and Package Insert uses different variations of the established name (e.g., [68Ga-DOTATATE](#), [DOTATATE](#), [68Ga-DOTA₀-Tyr₃-Octreotate](#), Gallium-68 (⁶⁸GA) DOTA₀-Tyr₃-Octreotate . Please submit an amendment to your PNR with the clarified established name.

*To submit an amendment to a proprietary name request, please include the statement "**AMENDMENT TO REQUEST FOR PROPRIETARY NAME REVIEW**" in bold capital letters, at the top of your cover letter and on the first page of the main submission document (please refer to the complete submission guidance link below). The review of this name will be initiated when the amendment is received.*

If you require additional information on developing proprietary names for drugs or proposing alternative proprietary names for consideration, we refer you to the following:

Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>

.

Sincerely,
Janet

*Janet L. Anderson, Pharm.D.
Safety Regulatory Project Manager
FDA CDER Office of Surveillance and Epidemiology
White Oak, Bldg. 22, Rm 4484
10903 New Hampshire Ave
Silver Spring, Maryland 20993-0002
301-796-0675*

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/s/

JANET L ANDERSON
09/18/2015



NDA 208547

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head, Regulatory Affairs
350 Fifth Avenue, Floor 69, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) dated July 1, 2015, received July 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (b) (4) (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection).

We also refer to your submissions dated July 10, 13, 23, 27; September 3 and 8, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is **March 1, 2016**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

In addition, the planned date for our internal mid-cycle review meeting is **October 7, 2015**. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- 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 in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

If you have any questions, call Modupe Fagbami, Regulatory Project Manager, at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

ALEXANDER GOROVETS
09/11/2015

From: Davis-Warren, Alberta E
To: "victor.paulus@adacap.com"
Cc: [Fagbami, Modupe](#)
Subject: NDA 208547- (b) (4) (Kit for the Preparation of 68Ga-DOTATATE for Injection) - Information Request
Date: Thursday, September 10, 2015 12:40:00 PM

Dear Dr. Paulus,

Reference your submission dated July 1, 2015, for NDA 208547- (b) (4) (Kit for the Preparation of 68Ga-DOTATATE for Injection). During our review of the Clinical section of the submission, we have the following information request:

Please submit a copy of the VUMC clinical protocol (PDF Format is fine).

Please respond to this request by no later than **September 17, 2015**. Please submit an amendment to your application with your response to the request using the official channels. To expedite the review process, please send me and Ms. Modupe Fagbami a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) and (Modupe.Fagbami@fda.hhs.gov) by **September 17, 2015**.

Please contact me if you have any questions.

Thank you,

Alberta providing coverage for Ms. Modupe Fagbami

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-595-7922 fax
Alberta.Davis-Warren@fda.hhs.gov

FDA does not ensure the security of email communications. If you desire to communicate by secure email, please establish a secure email channel by contacting SecureEmail@fda.hhs.gov.

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/s/

ALBERTA E DAVIS WARREN
09/10/2015



NDA 208547

PRIORITY REVIEW DESIGNATION

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head, Regulatory Affairs
350 Fifth Avenue, Floor 69, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) dated July 1, 2015, received July 1, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for [REDACTED]^{(b)(4)} (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection)

We also refer to your submissions dated July 10, 13, 23, and 27, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is March 1, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 1, 2015.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before September 13, 2015.

If you have any questions, call Modupe Fagbami, Regulatory Project Manager,
at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Division Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

LIBERO L MARZELLA
08/28/2015



NDA 208547

INFORMATION REQUEST

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head, Regulatory Affairs
350 Fifth Avenue, Floor 69, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) dated July 1, 2015, received July 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [REDACTED]^{(b) (4)} [REDACTED] (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection).

We also refer to your July 1, 2015, submission, containing documentation of your New Drug Application (NDA).

We are reviewing the clinical and statistics sections of your submission and have the following comments and information requests. We request a prompt written response on or before COB, Thursday, August 27, 2015, in order to continue our evaluation of your NDA.

Clinical:

According to the following Guidance for Industry “Integrated Summaries of Effectiveness (ISE) and Safety (ISS): Location Within the Common Technical Document”, your application should include integrated summaries of effectiveness and safety which should be located in module 5, section 5.3.5.3.
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm136174.pdf>

We note that there are instances, particularly for Orphan drugs with small studies, in which the textual information for the module 2 summary may be complete as well as the identical to the textual information for the integrated summary. However, the tables, appendices, and datasets and detailed analyses should be submitted in module 5.

If you have included all the required information in module 2, please insert categories for an ISE and ISS in module 5 in which you hyperlink or make reference back to the appropriate section(s) of module 2.

Statistics:

We note that you have included a tabular listing of the VUMC data in module 5. Unfortunately, the data in that format is not able to be manipulated in order for the agency to conduct analyses. Please submit the data from the VUMC experience in .xpt sortable and searchable datasets.

If you have any questions, please contact NAME, Regulatory Project Manager, at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Alexander Gorovets, M.D.
Deputy Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

ALEXANDER GOROVETS
08/26/2015



NDA 208547

NDA ACKNOWLEDGMENT

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head, Regulatory Affairs
350 Fifth Avenue, Floor 69, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: [REDACTED] ^{(b)(4)} (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection)

Date of Application: July 1, 2015

Date of Receipt: July 1, 2015

Our Reference Number: NDA 208547

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 30, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

The content of labeling must conform to the content and format requirements of revised 21CFR 201.56-57

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 208547** submitted on **July 1, 2015**, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, Regulatory Project Manager, at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Modupe Fagbami
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

MODUPE O FAGBAMI
08/24/2015

From: Fagbami, Modupe

Sent: Tuesday, July 07, 2015 5:24 PM

To: victor.paulus@adacap.com

Subject: NDA 208547 - (b) (4) (Kit for the Preparation of 68Ga-DOTATATE for Injection Information Request

Importance: High

Dear Dr. Paulus,

Reference your submission dated July 1, 2015, for NDA 208547 - (b) (4) (Kit for the Preparation of 68Ga-DOTATATE for Injection.

It was observed that you included the pregnancy and lactation information in your proposed label in the old format. Applications submitted on or after June 30th, 2015, must include such information consistent with the new format and content requirements as specified under PLLR. Failure to do so can result to a Refuse To File.

Kindly submit a revised pregnancy/lactation information in the label per the new PLLR requirements on or before COB, Tuesday, July 14, 2015 to comply with all labeling requirements specified in 21 CFR 201.56 and 201.57.

Let me know if you have any questions.

Thank you

Modupe O. Fagbami

RPM

Division of Medical Imaging Products

Office of Drug Evaluation IV

CDER, FDA

10903 New Hampshire Avenue

WO-22, Room 5473

Silver Spring, Maryland 20993

Phone: 301-796-1348

Fax: 301-796-9899

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/s/

MODUPE O FAGBAMI
07/07/2015



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PIND 122818

**MEETING REQUEST-
WRITTEN RESPONSES**

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head, Regulatory Affairs
350 Fifth Avenue, Floor 69, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ^{68}Ga -DOTA⁰-Tyr³-Octreotate.

We also refer to your submission dated October 7, 2014, containing an IND review request that was reclassified as a Type C Guidance meeting request by the Division of Medical Imaging Products after reviewing the contents of the submission and found that the submission does not include a clinical protocol. The purpose of the meeting became obtaining feedback from the division regarding the proposed literature review protocol.

Further reference is made to our Meeting Granted letter dated November 10, 2014, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses (Clinical and Statistics) to the questions contained in your submission. Additional responses from CMC will be communicated to you in a separate letter at a later date.

If you have any questions, call Modupe Fagbami, Regulatory Project Manager at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging and Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Written Responses

WRITTEN RESPONSES

Meeting Type: C
Meeting Category: Guidance

Application Number: IND 122818
Product Name: $^{68}\text{Ga-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$.

Indication: Diagnostic for [REDACTED] (b) (4) neuroendocrine tumors [REDACTED] (b) (4) NETs).

Sponsor: Advanced Accelerator Applications (AAA)
Regulatory Pathway: 505(b)(2)

BACKGROUND

The Sponsor made this submission for an IND review on October 7, 2014. In order to provide full responses to the Sponsor, the Division of Medical Imaging Products reclassified the submission as a Type C, guidance Meeting request, Written Response Only (WRO), on November 10, 2014, when the clinical review team found that the submission does not include a clinical protocol.

$^{68}\text{Ga-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ is indicated as a diagnostic for [REDACTED] (b) (4) neuroendocrine tumors [REDACTED] (b) (4) NETs).

Prior to this submission, a Type B Pre-IND meeting was requested by the Sponsor for the product and the meeting was held on July 1, 2014, to discuss the requirements for an IND submission to conduct a confirmatory bridging study

QUESTIONS AND RESPONSES:

We reiterate that for your IND and eventual NDA, evidence of safety and efficacy may be based on literature with supportive data supplied by the clinical data (with appropriate rights of reference to VUMC IND) from the completed VUMC study. If available, please provide an update of the VUMC study results. The VUMC study is important because it provides clinical data that can be subject to inspection and verification. We refer you to the July 1, 2014, meeting minutes.

Primary deficiency of the current submission (SDN 4 dated 10/7/14) is that there is no Statistical Analysis Plan (SAP) with which to conduct your review and analysis of the literature. We recommend that you choose an indication, design a SAP to capture your chosen endpoints (see discussion below) that will support that indication, and then prospectively perform the literature search and analysis. If not performed in a prospective fashion, the information obtained from your analyses would be exploratory in nature only.

The SAP should prespecify endpoints, performance criteria, the truth standard, and the methodology and definition of meaningful changes in patient management. With respect to the literature review protocol, we recommend that you:

- **Prospectively perform your literature search and review *after* you have designed and written your statistical analysis plan.**
- **Modify your adverse event toxicity scale.** (b) (4)

We recommend that you consider the following toxicity scale:

- **Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf>**
- **Modify your case report forms to capture changes in patient management found with the information made available from the Ga-68 DOTATATE scan.**

We recommend a primary efficacy endpoint of assessment of the test's performance. For assessment of the test's performance, we recommend measuring patient level disease detection ("sensitivity") using blinded readers and a specified standard of truth (histopathology or a composite of conventional imaging, clinical information and histopathology). Alternatively a "within patient sensitivity" would be acceptable if the standard of truth (SOT) is available on a lesion by lesion basis. Demonstrating statistically significant superiority or non-inferiority in relation to a comparator (111-In-octreotide) or superiority over a pre-defined threshold would be acceptable.

We do not object to a primary efficacy endpoint involving changes in patient management and consider such an endpoint to be important in establishing the test's clinical utility. However based on the information you have provided, this endpoint might be difficult to achieve. Therefore, we recommend using this endpoint for a secondary analysis and designating the test's performance as the primary analysis.

We are particularly concerned about false positive detections and recommend measuring "specificity" as a co-primary endpoint. Enrolling patients with a suspected NET and a negative SOT would contribute to the patient-level "specificity population". Measuring lesion-level false detection rate would also be acceptable. Here again we recommend a pre-specified comparison to 111-Inoctreotide or to a threshold.

As for the "patient management" endpoint, we recommend evaluating a change in management prospectively for the VUMC trial (and in the articles if possible) in the following fashion:

- **Octreoscan (or comparator(s) of your choice) results 'a' leading to patient management decision 'b'**
- **Dotatate scan results 'c' leading to patient management decision 'd'**
- **Comparative assessment between "d" and "b"**

- **Please note that your protocol should provide details for the methodology used in your study to make the clinical management determinations in order to minimize bias. For example, you should describe:**
 - **Who will independently/blinded read the comparator scan**
 - **Who will independently/blinded make the management decision using the results of the comparator scan**
 - **Who will independently/blinded read the Dotatate scan**
 - **The information that will be made available to make these clinical decisions**
 - **Who will independently/blinded make the management decision using the results of the Dotatate scan**
 - **A definition of ‘change in patient management’**
 - **Randomization and blinding of images**
 - **Design of a case report form to capture these data**

Specific Statistical Comments:

We strongly recommend you submit a statistical analysis plan (SAP) with pre-specified analysis approaches before conducting the systematic review and meta-analysis. Please clearly provide the following information in the SAP.

- 1. Specify the clinically well-defined patient population, standard of truth, and the measures taken (in the studies) to minimize bias in the image interpretation such as prospective design, and blinded readers.**
- 2. Specify the endpoints (primary and secondary), the statistical approaches, and how you will collect the data to support the primary and other analyses.**
- 3. Provide a clear summary table with the definitions of sensitivity and specificity for the studies in the review articles.**
- 4. Provide the details of the forest plots and the hierarchical summary receiver operator curves, and the other methods for heterogeneity.**
- 5. Clarify the analytical approach in its entirety for comparing the two imaging modalities (68GA-DATATE vs. 111In-octreotide) for either superiority or non-inferiority. In testing non-inferiority, margin must be pre-specified and justified. If Hierarchical SROC will be used, please provide the complete details.**
- 6. Pre-specify the response variables, and the independent variables for fixed effect and random effect included in the generalized linear mixed models.**
- 7. Sensitivity analyses should be conducted for different missing data approaches.**
- 8. If the doses are variable in different studies, please consider it in the efficacy and safety evaluations.**

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies 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 PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP 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 pdit@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

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.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 [CDER/CBER Position on Use of SI Units for Lab Tests \(http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm\)](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the

application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

| List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature | |
|--|--|
| Source of information (e.g., published literature, name of listed drug) | Information Provided (e.g., specific sections of the 505(b)(2) application or labeling) |
| <i>1. Example: Published literature</i> | <i>Nonclinical toxicology</i> |
| <i>2. Example: NDA XXXXXX “TRADENAME”</i> | <i>Previous finding of effectiveness for indication X</i> |
| <i>3. Example: NDA YYYYYY “TRADENAME”</i> | <i>Previous finding of safety for Carcinogenicity, labeling section XXX</i> |

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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/s/

MODUPE O FAGBAMI
11/19/2014

LIBERO L MARZELLA
11/19/2014

PIND 122818

**MEETING REQUEST-
WRITTEN RESPONSES**

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head, Regulatory Affairs
350 Fifth Avenue, Floor 69, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your Pre-Investigational New Drug Application (PIND) file for $^{68}\text{Ga-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$.

We also refer to your submission dated October 7, 2014, containing an IND review request that was reclassified as a Type C Guidance meeting request by the Division of Medical Imaging Products after reviewing the contents of the submission and found that the submission does not include a clinical protocol. The purpose of the meeting became obtaining feedback from the division regarding the proposed literature review protocol.

Further reference is made to our Meeting Granted letter dated November 10, 2014, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses (Clinical and Statistics) to the questions contained in your submission. Additional responses from CMC will be communicated to you in a separate letter at a later date.

If you have any questions, call Modupe Fagbami, Regulatory Project Manager at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging and Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Written Responses

WRITTEN RESPONSES

Meeting Type: C
Meeting Category: Guidance

Application Number: IND 122818
Product Name: $^{68}\text{Ga-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$.

Indication: Diagnostic for [REDACTED] (b) (4) neuroendocrine tumors [REDACTED] (b) (4) NETs).

Sponsor: Advanced Accelerator Applications (AAA)
Regulatory Pathway: 505(b)(2)

BACKGROUND

The Sponsor made this submission for an IND review on October 7, 2014. In order to provide full responses to the Sponsor, the Division of Medical Imaging Products reclassified the submission as a Type C, guidance Meeting request, Written Response Only (WRO), on November 10, 2014, when the clinical review team found that the submission does not include a clinical protocol.

$^{68}\text{Ga-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ is indicated as a diagnostic for [REDACTED] (b) (4) neuroendocrine tumors [REDACTED] (b) (4) NETs).

Prior to this submission, a Type B Pre-IND meeting was requested by the Sponsor for the product and the meeting was held on July 1, 2014, to discuss the requirements for an IND submission to conduct a confirmatory bridging study.

QUESTIONS AND RESPONSES:

We reiterate that for your IND and eventual NDA, evidence of safety and efficacy may be based on literature with supportive data supplied by the clinical data (with appropriate rights of reference to VUMC IND) from the completed VUMC study. If available, please provide an update of the VUMC study results. The VUMC study is important because it provides clinical data that can be subject to inspection and verification. We refer you to the July 1, 2014, meeting minutes.

Primary deficiency of the current submission (SDN 4 dated 10/7/14) is that there is no Statistical Analysis Plan (SAP) with which to conduct your review and analysis of the literature. We recommend that you chose an indication, design a SAP to capture your chosen endpoints (see discussion below) that will support that indication, and then prospectively perform the literature search and analysis. If not performed in a prospective fashion, the information obtained from your analyses would be exploratory in nature only.

The SAP should prespecify endpoints, performance criteria, the truth standard, and the methodology and definition of meaningful changes in patient management. With respect to the literature review protocol, we recommend that you:

- Prospectively perform your literature search and review *after* you have designed and written your statistical analysis plan.

- **Modify your adverse event toxicity scale** (b) (4)

We recommend that you consider the following toxicity scale:

- **Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf>**
- **Modify your case report forms to capture changes in patient management found with the information made available from the Ga-68 DOTATATE scan.**

We recommend a primary efficacy endpoint of assessment of the test's performance. For assessment of the test's performance, we recommend measuring patient level disease detection ("sensitivity") using blinded readers and a specified standard of truth (histopathology or a composite of conventional imaging, clinical information and histopathology). Alternatively a "within patient sensitivity" would be acceptable if the standard of truth (SOT) is available on a lesion by lesion basis. Demonstrating statistically significant superiority or non-inferiority in relation to a comparator (111-In-octreotide) or superiority over a pre-defined threshold would be acceptable.

We do not object to a primary efficacy endpoint involving changes in patient management and consider such an endpoint to be important in establishing the test's clinical utility. However based on the information you have provided, this endpoint might be difficult to achieve. Therefore, we recommend using this endpoint for a secondary analysis and designating the test's performance as the primary analysis.

We are particularly concerned about false positive detections and recommend measuring "specificity" as a co-primary endpoint. Enrolling patients with a suspected NET and a negative SOT would contribute to the patient-level "specificity population". Measuring lesion-level false detection rate would also be acceptable. Here again we recommend a pre-specified comparison to 111-Inoctreotide or to a threshold.

As for the "patient management" endpoint, we recommend evaluating a change in management prospectively for the VUMC trial (and in the articles if possible) in the following fashion:

- Octreoscan (or comparator(s) of your choice) results 'a' leading to patient management decision 'b'
- Dotatate scan results 'c' leading to patient management decision 'd'
- Comparative assessment between "d" and "b"

- **Please note that your protocol should provide details for the methodology used in your study to make the clinical management determinations in order to minimize bias. For example, you should describe:**
 - **Who will independently/blinded read the comparator scan**
 - **Who will independently/blinded make the management decision using the results of the comparator scan**
 - **Who will independently/blinded read the Dotatate scan**
 - **The information that will be made available to make these clinical decisions**
 - **Who will independently/blinded make the management decision using the results of the Dotatate scan**
 - **A definition of ‘change in patient management’**
 - **Randomization and blinding of images**
 - **Design of a case report form to capture these data**

Specific Statistical Comments:

We strongly recommend you submit a statistical analysis plan (SAP) with pre-specified analysis approaches before conducting the systematic review and meta-analysis. Please clearly provide the following information in the SAP.

- 1. Specify the clinically well-defined patient population, standard of truth, and the measures taken (in the studies) to minimize bias in the image interpretation such as prospective design, and blinded readers.**
- 2. Specify the endpoints (primary and secondary), the statistical approaches, and how will you collect the data to support the primary and other analyses.**
- 3. Provide a clear summary table with the definitions of sensitivity and specificity for the studies in the review articles.**
- 4. Provide the details of the forest plots and the hierarchical summary receiver operator curves, and the other methods for heterogeneity.**
- 5. Clarify the analytical approach in its entirety for comparing the two imaging modalities (68GA-DATATE vs. 111In-octreotide) for either superiority or non-inferiority. In testing non-inferiority, margin must be pre-specified and justified. If Hierarchical SROC will be used, please provide the complete details.**
- 6. Pre-specify the response variables, and the independent variables for fixed effect and random effect included in the generalized linear mixed models.**
- 7. Sensitivity analyses should be conducted for different missing data approaches.**
- 8. If the doses are variable in different studies, please consider it in the efficacy and safety evaluations.**

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies 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 PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP 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 pdit@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

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.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 [CDER/CBER Position on Use of SI Units for Lab Tests \(http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm\)](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In

your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

| List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature | |
|--|--|
| Source of information (e.g., published literature, name of listed drug) | Information Provided (e.g., specific sections of the 505(b)(2) application or labeling) |
| <i>1. Example: Published literature</i> | <i>Nonclinical toxicology</i> |
| <i>2. Example: NDA XXXXXX “TRADENAME”</i> | <i>Previous finding of effectiveness for indication X</i> |
| <i>3. Example: NDA YYYYYY “TRADENAME”</i> | <i>Previous finding of safety for Carcinogenicity, labeling section XXX</i> |

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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/s/

MODUPE O FAGBAMI
11/17/2014

LIBERO L MARZELLA
11/17/2014



PIND 122818

MEETING MINUTES

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Executive Director
350 5th Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ⁶⁸Ga-DOTA⁰-Tyr³-Octreotate.

We also refer to the meeting between representatives of your firm and the FDA on July 1, 2014. The purpose of the meeting was to discuss the requirements for an IND submission to conduct a confirmatory bridging study.

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, please don't hesitate to contact me at (301) 796-1994.

Sincerely,

{See appended electronic signature page}

Sharon Thomas, BS, RHIT, CCRP
Project Management Staff
Division of Medical Imaging Products
Office of Drug Evaluation IV
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: B
Meeting Category: Pre-IND

Meeting Date and Time: July 1, 2014, 11:00 am -12:00 pm EST
Meeting Location: White Oak Bldg. 22, Conference Room 1315

Application Number: PIND 122818
Product Name: ^{68}Ga -DOTA⁰-Tyr³-Octreotate
Indication: Diagnostic for [REDACTED] (b) (4)
neuroendocrine tumors (b) (4) NETs).

Sponsor/Applicant Name: Advanced Accelerator Applications USA, Inc. (AAA)

FDA ATTENDEES

Division of Medical Imaging Products (DMIP)

Libero Marzella, M.D., Ph.D., Division Director, DMIP
Alex Gorovets, M.D., Deputy Director (acting), DMIP
Jagjit Grewal, M.P.H, Associate Director for Regulatory Affairs, ODE IV
Cynthia Welsh, M.D., Medical Officer, DMIP
Eldon Leutzinger, Ph.D., CMC Lead, ONDQA
Sunny Awe Ph.D., Non Clinical Reviewer, DMIP
Christy John, Ph.D., Clinical Pharmacologist, OCP (attempted to join by telephone)
Stephen E. Langille, Ph.D. Microbiology Reviewer, OPS (attempted to join by telephone)
Sharon Thomas, B.Sc., Regulatory Project Manager, DMIP

SPONSOR ATTENDEES

Advanced Accelerator Applications

Clementina Brambati, PharmD, Project Manager (by telephone)
Stefano Buono, PhD, Chairman & CEO
Daniela Chicco, PhD, R&D Pre-Clinical Manager (by telephone)
Jack Erion, PhD, CEO
Lorenza Fugazza, MChem, R&D Team Leader Imaging (by telephone)
Claude Hariton, PhD, DSc, Head of Clinical Development
Maurizio Franco Mariani, MD, PhD, D.A.B.T. VP Head Research & BD (by telephone)
Victor Paulus, PhD, Head Regulatory Affairs, North America
Maribel Lopera Sierra, MD, Chief Medical Officer
Michael Zhang, MD, Clinical Project Manager

SNMMI I Vanderbilt University Medical Center

(b) (4)

Ronald C. Walker, MD, FACNM, F ACR, Professor of Clinical Radiology & Radiological Sciences, Vanderbilt University Medical Center

Eric H. Liu, MD, Asst. Professor of Surgical Oncology, Vanderbilt University Medical Center

Jeffrey Clanton, MS, RPh, Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center

1.0 BACKGROUND

On May 15, 2014, the Sponsor requested a pre-IND meeting to discuss the requirements for an IND submission to conduct a confirmatory bridging study for ⁶⁸Ga-DOTA⁰-Tyr³-Octreotate.

On June 26, 2014, FDA provided preliminary comments to Sponsor's questions posed in their meeting briefing package dated May 30, 2014. The Sponsor responded via email on June 30, 2014, indicating the questions/responses requiring further discussion at the meeting. The original questions provided by the Sponsor are presented in italics, followed by FDA's preliminary responses in bold text. The Discussion points are shown in *blue italics* below.

2.0 DISCUSSION

A. CMC

Sponsor's Question A.1

The Sponsor has developed a GMP kit for the preparation of the Drug Product, ⁶⁸Ga-DOTA⁰-Tyr³-Octreotate in a radiopharmacy. The Drug Product is prepared by combining a lyophilized peptide drug precursor with buffer, and the eluate from a ⁶⁸Ge/⁶⁸Ga generator. This approach provides a ready to inject solution that meets pre-defined specifications. There is a standardized reconstitution protocol using the eluate from different ⁶⁸Ge/⁶⁸Ga generators, and the Drug Product does not require intermediate purification steps.

Does the Agency agree with this approach?

FDA RESPONSE:

A partial yes. Conceptually, the approach is acceptable. However, we are concerned about the brevity of testing in release of the kit vials reconstituted with ⁶⁸Ga(III) generator eluate, as well your method for radiochemical purity (RCP) in the radiopharmacy. We have the following comments:

- 1. There is no appearance test (visual) for color and particulate matter. Yet, you are apparently presuming that this is adequately covered by the test performed in release of the manufactured "cold" kits. That presumption does not rule out the**

chance event that one vial out of a batch could be compromised, either intrinsically, or as a result of the reconstitution procedure. You need to refer to standard practices for all “parenteral” radiopharmaceuticals and to USP <823> for PET manufacture.

- 2. We are concerned about use of the less rigorous ITLC method for RCP, as performed in the radiopharmacy. We are expecting that the ITLC method for RCP will have been demonstrated to give results reasonably equivalent to the more rigorous RP-HPLC method (Table 4) used in releasing the cold kits, and the appropriate data needs to be provided in the IND.**
- 3. We did not see your “standardized reconstitution protocol” in the briefing package. We are expecting to see that protocol in the forthcoming IND. Also, it is not clear whether this protocol will change with the type of ⁶⁸Ge/⁶⁸Ga generator used. If it does change, you need to describe the change, and verify that it has no impact on the final reconstituted product.**

AAA’s Response to Question A.1 (per June 30, 2014 e-mail):

The response provided in the CMC section are overall quite clear and do not appear to require further clarification with the exception of:

- a. Question A.1, FDA part (2). We would like to further discuss the suitability of ITL versus other release test options for determination of radiolabeling efficiency, and what would be required in the IND to meet FDA concerns with this test.*
- b. Question A.3, Generator issues: We would like to obtain further clarifications – for the IND is it necessary for the generator to have a US DMF or is other documentation acceptable (e.g., Letter of Authorization from the manufacturer, Certificate of Analysis). For the IND/NDA is it acceptable to use the manufacturer’s Certificate of Analysis.*

DISCUSSION:

- a. FDA did not object to the sponsor’s proposal on the kit-based approach developing the imaging product. FDA emphasized the importance of manufacturing under GMP and appropriate use of ITLC in the radio pharmacy. FDA encouraged sponsor to provide a more robust identity method used at time of kit release to verify the results obtained in the radio-pharmacy. FDA noted the suitability of ITLC and demonstration of HPLC to confirm the correlation between the two methods. FDA suggested once correlation is established, via batch testing, the HPLC need only be performed for a limited period or number of batches. FDA referred the sponsor to the USP Chapter 823 and GMP regulations of Title 21 part 212. FDA acknowledged the sponsor’s*

(b) (4)

DA encouraged the sponsor to work with the manufacturer to finalize the DMFs.

- b. *It was agreed that the sponsor will provide a COA, information on the breakthrough, in elution and generator maintenance in the IND. FDA also requested standardized reconstitution procedure and the adapted procedure) with the IND.*

Sponsor's Question A.2

Does the Agency find the selection of the components for the proposed formulation acceptable from a safety perspective for a Radiolabelled Imaging Product?

FDA RESPONSE:

Yes.

Sponsor's Question A.3

(b) (4)

(b) (4)

FDA RESPONSE:

Yes, but we expect that you will provide in the forthcoming IND data demonstrating that the use of the Eckert & Ziegler, will afford final drug product meeting the release specifications in Table 4.

but will need to include a Letter of Authorization to refer to the DMF for the appropriate CMC information.

Microbiology Response:

Provide a brief description of the manufacturing environment and manufacturing process for the kit lyophilized formulation and kit buffer. Also provide a commitment to use a new

.

Sponsor's Question A.4

(b) (4)

Does the Agency consider this approach acceptable for the proposed confirmatory bridging clinical study?

FDA RESPONSE:

Yes.

Sponsor's Question A.5

The specifications defined for the proposed product formulation are in accordance with relevant guidelines for radiopharmaceuticals in clinical development in the EU (Verbruggen et al. 2008). Moreover, the proposed specifications are equal to or more stringent than those indicated in the Monograph "Gallium (68Ga) Edotreotide Injection" (PA/PH/Exp. 14/T (07) 12 ANP) (68Ga-DOTATOC), used as a reference, or described in the 2010 EANM Guideline

Does the Agency agree with this approach for setting the characteristics and specifications of the proposed Investigational New Drug?

FDA RESPONSE:

Yes.

Microbiology Response:

USP Chapter <85> states that the endotoxin limit for radiopharmaceutical products is 175 EU/dose. The proposed endotoxin limit for the kit lyophilized formulation, and the kit buffer are (b)(4) EU/vial. Thus the combined endotoxin limit for the lyophilized formulation and buffer is (b)(4) EU/dose without taking into account the endotoxin load conferred by the generator eluate. The endotoxin limit for the lyophilized formulation and buffer should be reduced to levels that will ensure that the total endotoxin load per dose of product, including the endotoxin load conferred by the generator eluate, does not exceed 175 EU/dose.

B. Non-clinical

Sponsor's Question B.1

Does the Agency agree that the available preclinical toxicological package fulfils the requirements necessary for carrying out the proposed study using the GMP kit for the preparation of 68Ga-DOTA0-Tyr3-Octreotate?

FDA RESPONSE:

FDA agrees that the available preclinical toxicological package fulfils the requirements necessary for carrying out the proposed study using the GMP kit for the preparation of 68Gaa-DOTA0-Tyr3-Octreotate.

C. Clinical

Sponsor's Question C.1

68Ga-DOTA⁰-Tyr³-Octreotate is widely used in clinical practice (in Europe) as a diagnostic agent in patients with sstr2-expressing NETs. A vast range of relevant literature data is available, as well as the data generated in the Phase I/II trial conducted at the Vanderbilt University Medical Center. It is the Sponsor's opinion that this information combined with a single Bridging Study to confirm safety, and tolerability in 30 patients for the proposed orphan indication is applicable and adequate to complete the clinical development of the Drug Product kit.

Does the Agency agree?

FDA RESPONSE:

In general, for your IND and eventual NDA, evidence of safety and efficacy may be based on literature with supportive data supplied by the already completed VUMC study.

Systematic review of literature:

We encourage you to perform a systematic review and summarize the literature about the clinical use (dosimetry, generator used, safety and efficacy) of Ga69 DOTATATE, consider a meta-analysis if appropriate, and submit that information in support of your IND and eventual NDA.

We recommend that you develop a protocol for conducting a systematic review of the literature. You will need to establish criteria for study quality based on factors such as prospective design, endpoints, and analysis plan, well defined truth/reference standard or comparator, minimum numbers of study patients, clinically well-defined patient population (including the pediatric population if applicable), demographic information, information on imaging drug including dosage and generator utilized, image acquisition ideally focusing on current comparable imaging technology (e.g. SPECT, PET; SPECT/CT, PET/CT), accounting for missing data, adequate study conduct including minimization of bias in the image interpretation. Please include an analysis on information related to the limitations of use of your product. For example: false positive results higher in x population such as inflammatory conditions; false negative results higher in y population such as high grade NET.

We recommend that you limit your review to diagnostic studies and avoid studies that assess patient prognosis, likelihood of response, or actual response to treatment.

If the literature based data are insufficient we recommend conducting a clinical trial in a clinically relevant patient population. Examples include:

- **Patients who underwent curative primary resection and are imaged to assess adequacy of resection or for surveillance**

- **Patients who are undergoing evaluation of clinical recurrence and in whom other imaging modalities are negative**
- **Patients who are scheduled for surgery and are undergoing primary staging; the study would include lesion mapping and discordant imaging results would be adjudicated using histopathology; the primary endpoint might be sensitivity and specificity; meaningful changes in staging could be captured in the study.**

The sample size of such a study or studies would depend on the study design, importance of endpoint and Statistical tests. We refer you to FDA “Guidance for Industry, Developing Medical Imaging Drug and Biological Products, Part 3: Design, Analysis, and Interpretation of Clinical Studies”, June 2004.

AAA’s Response to Question C.1 (per June 30, 2014 e-mail):

a- Nature and design of the prospective meta-analysis of Literature data: Regarding the extent of the systematic review and meta-analysis, we would like to confirm the inclusion in the analysis of related products, e.g. 68Ga-DOT ATOC and 68Ga- DOT ANOC. These 68Ga-labelled somatostatin analogs have the same indication, same clinical use, and same mechanism of action as 68Ga-DOT A TATE.

DISCUSSION:

a- FDA explained the sponsor’s proposal is acceptable in theory, however stated the analogs of DOTATATE are separate entities. FDA agreed to review a prospective protocol based on a pooled analysis of individual subjects. FDA proposed a systematic literature review as a two-step process by first categorizing studies then conducting an evaluation of the studies. FDA encouraged the sponsor to submit a prospective plan/protocol for selection and analysis of study data prior to the selection of studies.

AAA’s Response to Question C1. (per June 30, 2014 e-mail):

b- Clinical data from VUMC and strategy for performing bridging study: We would like to confirm with the Agency that the detailed information from the VUMC study as well as their overall clinical experience of 68Ga-DOT AT ATE will also be included in the IND to support the proposal for a bridging clinical trial.

DISCUSSION:

b- It was agreed that the sponsor will submit detailed information from the VUMC study as well as the overall clinical experience of 68Ga-DOTATATE in the IND submission. The Sponsor agreed to provide a LOA or data use agreement from VUMC. With regards to the IND, FDA discussed the expanded access program, however questioned the relevance of the proposed bridging study in the light of the data possibly available through the systematic review of literature. It was agreed that a clinical trial might not be necessary.

AAA's Response to Question C1. (per June 30, 2014 e-mail):

c- Clinical Pharmacology: We would like to confirm that the required information can be derived from data already available for other ⁶⁸Ga-DOTATATE pre-clinical and clinical studies, and obtain clarifications regarding the intrinsic or extrinsic factors which should be considered.

DISCUSSION:

c- Clinical Pharmacology: In a post meeting note on July 2, 2014, FDA provided the following comments to the sponsor via email:

“Yes, you can use the literature data to derive information that is available for Ga-68-DOTATATE clinical studies. By extrinsic factors we mean possibility of drug interaction of Ga-68-DOTATATE with concomitantly administered drugs. By intrinsic factors we mean the dosing paradigm in special population such as renal impaired patients of hepatic impaired patients.”

Sponsor's Question C.2

Does the Agency agree with the proposed Drug Product dosage of administered radioactivity for the proposed clinical Bridging Study?

FDA RESPONSE:

See our response to question C1.

Your proposed dose of 2 MBq/kg [REDACTED] ^{(b) (4)} appears reasonable. However, the adequacy of data to support this dose, and that lower doses are likely to be less effective, will be a review issue (see FDA ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS).

Sponsor's Question C.3

Does the agency agree with the proposed patient population in the confirmatory Bridging Study?

FDA RESPONSE:

See our response to question C1.

Sponsor's Question C.4

Does the Agency agree with the approach of performing a single confirmatory Bridging Study to determine the safety and tolerability of kit prepared ⁶⁸Ga-DOTA⁰-Tyr³-Octreotate in patients with proven [REDACTED] ^{(b) (4)} NETs?

FDA RESPONSE:

See our response to question C1.

Sponsor's Question C.5

Does the Agency agree with the Sponsor's choice of the endpoints in the study and the study sample size?

FDA RESPONSE:

See our response to question C1.

Sponsor's Question C.6

Does the agency agree with the approach of performing a single confirmatory bridging study in addition to literature data, as well as the results from the Phase I/II clinical study conducted at Vanderbilt University MC to support the Market Authorization of the Drug Product kit?

FDA RESPONSE:

See our response to question C1.

FDA ADDITIONAL COMMENTS

CLINICAL:

Regarding general drug development programs, we refer you to the following FDA Guidance Documents:

- *Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*
<http://www.fda.gov/downloads/Drugs/Guidances/ucm078749.pdf>
- *Guidance for Industry Developing Medical Imaging Drug and Biological Products Part 1: Conducting Safety Assessments*
<http://www.fda.gov/downloads/Drugs/Guidances/ucm071600.pdf>
- *Guidance for Industry Developing Medical Imaging Drug and Biological Products Part 2: Clinical Indications*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071603.pdf>
- *Guidance for Industry Developing Medical Imaging Drug and Biological Products Part 3: Design, Analysis, and Interpretation of Clinical Studies*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071604.pdf>

- *Guidance for Industry Applications Covered by Section 505(b)(2)*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079345.pdf>
- *Guidance PET Drug Applications — Content and Format for NDAs and ANDAs*
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078738.pdf>
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070107.pdf>

CLINICAL PHARMACOLOGY:

These comments are most commonly conveyed to sponsors at the pre-IND or initial IND stage of drug development.

1. We recommend that you explore doses and timing of imaging to determine an optimal dose, imaging window, and imaging parameters.
2. We recommend that your drug development include A) learning the optimal exposure for the general patient population, and B) learning how intrinsic and extrinsic factors alter exposure for specific patient populations. This allows rational dose adjustment for patients that have varied intrinsic or extrinsic factors. While we are open to considering justifications for not acquiring this information, low mass dose, in of itself, does not seem to be a rationale.
3. FDA expectations for the performance of the analytical methods used for blood drug concentration determination can be found in the May, 2001 *Guidance Bioanalytical Method Validation* located at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>
4. FDA recommends the following items be determined with a timing that allows FDA input into the need for, and design of, subsequent *in vivo* clinical studies to be included in the NDA:
 - A. the identity of any major metabolites of and the activities (efficacy-related and toxicity-related) of such metabolites,

B. the means by which ⁶⁸Ga-DOTA⁰-Tyr³-Octreotate and any major metabolites are eliminated and excreted,

C. the ability of ⁶⁸Ga-DOTA⁰-Tyr³-Octreotate and any major metabolites to act as substrates for CYP enzymes, and

D. the pharmacokinetics of ⁶⁸Ga-DOTA⁰-Tyr³-Octreotate and any major metabolites.

This information will be used to determine the need for, and the design of, drug interaction studies and studies in patients with hepatic and/or renal impairment.

3.0 ISSUES REQUIRING FURTHER DISCUSSION:

None

4.0 ACTION ITEMS:

The Sponsor to submit the IND when ready.

5.0 ATTACHMENT:

505(b)(2) Regulatory Pathway Document

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

We encourage you to identify each section of your proposed 505(b)(2) application that relies on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (including proprietary name if applicable) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

| List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature | |
|---|--|
| Source of information (e.g., published literature, name of listed drug) | Information Provided (e.g., specific sections of the 505(b)(2) application or labeling) |
| <i>1. Example: Published literature</i> | <i>Nonclinical toxicology</i> |

| | |
|--|--|
| | |
| | |
| | |

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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/s/

SHARON P THOMAS
07/29/2014

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 208547

LATE-CYCLE MEETING MINUTES

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head, Regulatory Affairs
350 Fifth Avenue, Floor 69, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) dated July 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on January 28, 2016.

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

If you have any questions, call Modupe Fagbami, Regulatory Project Manager at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Alexander Gorovets, M.D. (CDTL)
Deputy Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: January 28, 2016, at 1:00 pm
Meeting Location: WO, Building 22, Room 1415

Application Number: NDA 208547
Product Name: (b) (4) (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection). New Proprietary name: NETspot (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection).

Applicant Name: Advanced Accelerator Applications USA, Inc. (AAA)

Meeting Chair: Alex Gorovets, M.D., Deputy Director, DMIP (CDTL)
Meeting Recorder: Modupe Fagbami, Regulatory Project Manager, DMIP

FDA ATTENDEES

Libero Marzella, M.D., Ph.D., Director, DMIP
Alex Gorovets, M.D., Deputy Director, DMIP (CDTL)
Eric Duffy, Ph.D., Division Director, OPQ/ONDP/DNDPII
Nushin Todd, M.D., Associate Director, Labeling, DMIP
Cynthia Welsh, M.D., Medical Officer, DMIP
Danae Christodoulou, Ph.D., CMC Branch Chief, OPQ/ONDP/DNDPII/NDPBVI
Eldon Leutzinger, Ph.D., CMC Team Leader, OPQ/ONDP/DNDPII/NDPBVI
John Amartei, Ph.D., CMC Reviewer, OPQ/ONDP/DNDPII/NDPBVI
Martin Haber, Ph.D., CMC Reviewer, OPQ/ONDP/DNDPII/NDPBVI
Adebayo Lanionu, Ph.D., Pharmacology and Toxicology Supervisor, DMIP
Ronald Honchel, Ph.D., Pharmacology and Toxicology Reviewer, DMIP
Gene Williams, Ph.D., Clinical Pharmacology Team Leader, CDER/OTS/OCP/DCPV
Christy John, Ph.D., Clinical Pharmacology Reviewer, CDER/OTS/OCP/DCPV
Jyoti Zalkikar, Ph.D., Biostatistics Reviewer, CDER/OTS/OB/DBV
Satish Misra, Ph.D., Biostatistics Reviewer, CDER/OTS/OB/DBV
Jagjit Grewal, Associate Director, Regulatory Affairs, ODEIV
Helen Ngai, Ph.D., Microbiology Reviewer, OPQ/OPF/DMA/BI
Tien-Mien Chen, Ph.D., Acting Biopharmaceutics Team Leader, OPQ/ONDP/DB/BBII
Vidula Kolhatkar, Ph.D. Biopharmaceutics Reviewer, OPQ/ONDP/DB/BBII
Henry Startzman, M.D., Supervisory Medical Officer, OMPT/OSMP/OOPD
Michele Rutledge, PharmD., Safety Evaluator, OSE/DMEPA
Modupe Fagbami, Regulatory Project Manager, DMIP

EASTERN RESEARCH GROUP ATTENDEE

Marc Goldstein, Independent Assessor, Eastern Research Group

APPLICANT ATTENDEES

Jack Erion, Ph.D., Vice President, AAA
Claude Hariton, Ph.D., Head of Clinical Development, AAA
Maurizio Mariani, Ph.D., M.D., Head of Nonclinical Research, AAA
Victor Paulus, Ph.D., Head, Regulatory Affairs, AAA
Maribel Sierra, M.D., Chief Medical Officer, AAA
Michael Zhang, M.D., Clinical Project Manager, AAA

(b) (4)
Ronald C. Walker, M.D., F.A.C.N.M., F.A.C.R., Professor of Clinical Radiology & Radiological Sciences, Vanderbilt University Medical Center

Jeff Clanton, D.Ph., Director of Radiopharmacy Services, Vanderbilt University Medical Center

BACKGROUND

NDA 208547 was submitted on July 1, 2015, for (b) (4) (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection). New Proprietary name: NETspot (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection).

Proposed Indication: Diagnostic for (b) (4) neuroendocrine tumors (b) (4) NETs)

PDUFA Goal Date: March 1, 2016

FDA issued a Background Package in preparation for this meeting on January 15, 2016.

DISCUSSION

1. Introductory Comments

Modupe Fagbami welcomed the Applicants and the FDA attendees to the Late Cycle meeting for NDA 208547 for NETspot (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection) that is proposed as a diagnostic for (b) (4) neuroendocrine tumors.

The RPM stated that the purpose of the Late Cycle meeting is to share and discuss information with the Applicant on unresolved deficiencies identified during the review of NDA 208547, and to plan for the remainder of the review cycle. She said that the meeting is not a decisional meeting but outstanding responses to the Agency's information requests and Discipline Review letter will be discussed and consider whether their submission may be considered a major amendment triggering an extension of the PDUFA goal date, if accepted for review during the current review cycle.

The CDTL added that The Division of Medical Imaging Product is sharing and discussing the issues raised in the Discipline Review Letter to promote a collaborative and successful discussion at this meeting.

2. Discussion of Substantive Review Issues

Clinical:

Late Cycle Meeting Agenda item 2a

i.

(b) (4)
However, the data may support your drug's potential utility in aiding the localization of tumors in patients with neuroendocrine tumors (NETs).

(b) (4)
the intended patient population to adults and children with NETs.

You may consider submitting updated labeling with a revised indication such as: "A kit for the preparation of ^{68}Ga -DOTATATE indicated for positron emission tomography (PET) imaging, as an adjunct to other diagnostic tests, for localization of neuroendocrine tumors (NETs)." Alternatively, you may provide scientific justification in support of your initial proposed indication.

- ii. Please note that a change to the indication statement, as noted above, may have implications regarding your orphan designation status and orphan drug exclusivity. You should contact the Office of Orphan Drug Products for further advice and to discuss the possibility of amending your orphan drug designation.
- iii. We have identified a number of deficiencies in the format and content of labeling and will provide you with the proposed revisions shortly.

Meeting Discussion:

The Applicant agreed with the Division and OOPD and acknowledge that NETspot will not be used as a primary diagnostic tool but only to confirm the presence and location NETS as an adjunct to other diagnostic tests.

CMC:

Late Cycle Meeting Agenda item 2b

- i. We remind you of your agreement to provide a translated version of the executed batch record. You have provided the executed batch records for the manufacture of Vial 1 (ct002-13002-v1, ct002-13003-v1, ct002-14001-v1), vial 2(ct0031 14001-v2, ct0031 14002-v2, ct003114003-v2) and cartridge in Italian. On 10/09/15, 10/16/2015 and 11/24/2015 we requested all the executed batch records and in process test results in

- English. You provided the English translation of the unfilled master batch record. We informed you on 12/7/2015 that we require at least one executed batch record for vial 1, vial 2 and Cartridge including the notes present in the Italian version translated into English. You agreed to provide the translated version of the executed batch record in two weeks. The executed batch record for the next two batches will be provided after the post action date.
- ii. On 10/16/2015 we requested three validation batches of [68Ga]-DOTATATE produced from the kits with batch analysis data, COA, Radio/UV HPLC chromatograms and quantitative levels of (b) (4) present in the final drug product. You provided the study report on 12/07/2015. The report is currently under review.
 - iii. We remind you of your agreement during the TCON on 12/07/2015 to provide data that validates the ITLC method against the HPLC method to determine the suitability of the ITLC method for evaluation of the radiolabeling efficiency.
 - iv. The fill volume limit provided for vial 2 in Table 1 (In process tests and corresponding limit) is (b) (4) mL which is not acceptable. Revise the fill volume limit as not less than 1 ml as per USP <1>. Also, the fill volume range must be included in the in process test table for vial 2 as per USP <1151>.

Meeting Discussion:

Applicant promised to provide response to the pending translated version of the executed batch record based on the timeline that they provided prior to the meeting or if possible expedite the submission.

Agency informed the Applicant that the study report on the validation batches of December 7, 2015, is under review.

Microbiology:

Late Cycle Meeting Agenda item 2c

The questions address the sterility assurance of the final drug product supported by the manufacturing process. The responses received thus far have not been sufficient to demonstrate if the process has been validated and/or reproducible.

Meeting Discussion:

Applicant acknowledged the January 26, 2016 letter that indicates that responses to Microbiology comments will be sent by mid-February 2016.

Biopharmaceutics:

Late Cycle Meeting Agenda item 2d

Missing osmolality values (measured and/or calculated) for the product utilized in the VUMC study to allow for adequate evaluation of your biowaiver request.

Meeting Discussion:

The items listed have been resolved by the Applicant's email response of January 19, 2016.

3. Information Requests

Late Cycle Meeting Agenda item 3a

Biopharmaceutics

Provide osmolality values (measured and/or calculated) for the product utilized in the VUMC study to allow for evaluation of your biowaiver request. Include rationale that the difference in osmolality values, if any, between the clinically tested and the to-be-marketed formulations, will not affect the pharmacokinetic (PK) performance and/or clinical outcome of your proposed drug product.

Meeting Discussion:

The items listed have been resolved by the Applicant's submission of January 19, 2016.

4. Major Labeling Issues

Reference item 2 a(iii)

We have identified a number of deficiencies in the format and content of labeling and will provide you with the proposed revisions shortly.

Meeting Discussion:

The review of the labeling is still on-going particularly the Dosage Form and Clinical Studies sections

5. Review Plans

Discussion:

The Division informed the Applicant that their submission in response to the Discipline Review letter will directly influence the review timeline which may lead to a major amendment and shift the PDUFA due date because of the various review levels that cannot be skipped.

The Applicant understood this fact and promised to if possible adjust their prior response plans to expedite the submissions of their responses.

The Applicant stated that the Discipline Review Letter are being addressed and will be submitted to the Agency on an item by item basis as they complete the responses.

6. Wrap-up and Action Items

Discussion:

The Division Director stated that the efforts of the Applicant and the review team are appreciated and the Agency will work together with the Applicant.

Post Meeting Note:

The PDUFA due date of March 1, 2016, was extended by 3 months to June 1, 2016, in response to the Applicant's February 12, 2016, submission.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

ALEXANDER GOROVETS
02/25/2016



NDA 208547

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head, Regulatory Affairs
350 Fifth Avenue, Floor 69, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [REDACTED] ^{(b) (4)} (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection).

We also refer to the Late-Cycle Meeting (LCM) scheduled for January 28, 2016. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Modupe Fagbami, Regulatory Project Manager, at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Liberio Marzella, MD., Ph.D.
Director,
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: January 28, 2016 at 1:00 pm
Meeting Location: WO, Building 22, Room 1415

Application Number: NDA 208547
Product Name: NETspot (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection
Indication: Diagnostic for [REDACTED] (b) (4)
neuroendocrine tumors (b) (4) NETs)
Applicant Name: Advanced Accelerator Applications (AAA)

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

In addition to the contents of this background document, please refer to the Discipline Review letter already provided to you on December 11, 2015:

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Clinical:

Please refer our Discipline Review letter of December 11, 2015.

Chemistry, Manufacturing and Controls (CMC):

Please refer our Discipline Review letter of December 11, 2015.

Microbiology

Microbiology questions concerning DMF (b) (4) container closure integrity testing validation studies, environmental monitoring, validation of the sterilization and depyrogenation process for equipment and container closure system components, media fill simulations, endotoxins testing and sterility test validation studies were issued in the December 11, 2015 discipline review letter.

Biopharmaceutics

We acknowledge your osmolality measurement report for the proposed product. You should also provide osmolality values (measured and/or calculated) for the product utilized in the VUMC study to allow for evaluation of your biowaiver request. In addition, include rationale that the difference in osmolality values, if any, between the clinically tested and the to-be-marketed formulations.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments 5 minutes (Modupe Fagbami, Regulatory Project Manager; Alexander Gorovets, M.D., Cross Discipline Team Lead)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues –35 minutes

Each issue will be introduced by FDA and followed by a discussion.

a. Clinical:

- i. (b) (4)
However, the data may support your drug's potential utility in aiding the localization of tumors in patients with neuroendocrine tumors (NETs).

(b) (4)
[REDACTED]
[REDACTED] the intended patient population to adults and children with NETs.

You may consider submitting updated labeling with a revised indication such as:

“A kit for the preparation of ^{68}Ga -DOTATATE indicated for positron emission tomography (PET) imaging, as an adjunct to other diagnostic tests, for localization of neuroendocrine tumors (NETs).”

Alternatively, you may provide scientific justification in support of your initial proposed indication.

- ii. Please note that a change to the indication statement, as noted above, may have implications regarding your orphan designation status and orphan drug exclusivity. You should contact the Office of Orphan Drug Products for further advice and to discuss the possibility of amending your orphan drug designation.
- iii. We have identified a number of deficiencies in the format and content of labeling and will provide you with the proposed revisions shortly.

b. Chemistry, Manufacturing and Controls (CMC):

- i. We remind you of your agreement to provide a translated version of the executed batch record. You have provided the executed batch records for the manufacture of Vial 1 (ct002-13002-v1, ct002-13003-v1, ct002-14001-v1), vial 2(ct0031 14001-v2, ct0031 14002-v2, ct003114003-v2) and cartridge in Italian. On 10/09/15, 10/16/2015 and 11/24/2015 we requested all the executed batch records and in process test results in English. You provided the English translation of the unfilled master batch record. We informed you on 12/7/2015 that we require at least one executed batch record for vial 1, vial 2 and Cartridge including the notes present in the Italian version translated into English. You agreed to provide the translated version of the executed batch record in two weeks. The executed batch record for the next two batches will be provided after the post action date.
- ii. On 10/16/2015 we requested three validation batches of ^{68}Ga -DOTATATE produced from the kits with batch analysis data, COA, Radio/UV HPLC chromatograms and quantitative levels of [REDACTED] (b) (4) present in the final drug product. You provided the study report on 12/07/2015. The report is currently under review.

- iii. We remind you of your agreement during the TCON on 12/07/2015 to provide data that validates the ITLC method against the HPLC method to determine the suitability of the ITLC method for evaluation of the radiolabeling efficiency.
- iv. The fill volume limit provided for vial 2 in Table 1 (In process tests and corresponding limit) is ^{(b) (4)} mL which is not acceptable. Revise the fill volume limit as not less than 1 ml as per USP <1>. Also, the fill volume range must be included in the in process test table for vial 2 as per USP <1151>.

c. Microbiology

The questions address the sterility assurance of the final drug product supported by the manufacturing process. The responses received thus far have not been sufficient to demonstrate if the process has been validated and/or reproducible.

d. Biopharmaceutics

Missing osmolality values (measured and/or calculated) for the product utilized in the VUMC study to allow for adequate evaluation of your biowaiver request.

3. Information Requests – 10 minutes

a. Biopharmaceutics

Provide osmolality values (measured and/or calculated) for the product utilized in the VUMC study to allow for evaluation of your biowaiver request. Include rationale that the difference in osmolality values, if any, between the clinically tested and the to-be-marketed formulations, will not affect the pharmacokinetic (PK) performance and/or clinical outcome of your proposed drug product.

- 4. Major labeling issues –10 minutes
- 5. Review Plans – 5 minutes
- 6. Wrap-up and Action Items – 10 minutes

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/s/

ALEXANDER GOROVETS
01/15/2016