

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208325Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 208325

SUPPL #

HFD # 510

Trade Name Parsabiv

Generic Name etelcalcetide injection

Applicant Name KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen, Inc.

Approval Date, If Known February 7, 2017

### 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

NME-original

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.

n/a

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:

n/a

c) Did the applicant request exclusivity?

YES  NO

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

5-years

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?

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

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #

YES

!  
!

! NO

! Explain:

Investigation #2

IND #

YES

!  
!

! NO

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

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:

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Name of person completing form: Meghna M. Jairath, Pharm.D.  
Title: Regulatory Project Manager  
Date: February 7, 2017

Name of Division Director signing form: Jean-Marc Guettier  
Title: Division Director

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MEGHNA M JAIRATH  
02/07/2017

JEAN-MARC P GUETTIER  
02/08/2017

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 208325 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Parsabiv Established/Proper Name: etelcalcetide injection Dosage Form: 2.5 mg/0.5mL, 5mg/mL, and 10 mg/2mL		Applicant: KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen Inc. Agent for Applicant (if applicable):
RPM: Meghna M. Jairath		Division: Metabolism and Endocrinology Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input 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)		<b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b> <ul style="list-style-type: none"> <li><input type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i></li> </ul> </li> </ul> Date of check: <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"> <li>Proposed action</li> <li>User Fee Goal Date is <u>February 9, 2017</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input type="checkbox"/> None   CR-8/24/16
❖ 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> 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): Type 2 Resubmission  
 (*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 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 checked="" 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 checked="" type="checkbox"/> None <input 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.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ 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(s) and date(s) Approval- 2/7/17 CR-8/24/16
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included Final label in AP letter which is pending
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<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"> <li>Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input type="checkbox"/> Included n/a
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included n/a
❖ Labels <b>(full color carton and immediate-container labels)</b> <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included Final Carton and Container labels included in AP letter-2/7/17
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>Review(s) <i>(indicate date(s))</i></li> </ul>	Acceptable:1/3/17; 11/18/15 Reviews: 1/3/17; 11/16/15
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: 11/5/15 DMEPA: 1/5/17; 8/23/16; 7/19/16; 5/20/16 DMPP/PLT (DRISK): 5/5/16 OPDP: 1/13/17; 8/18/16 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: maternal health-7/27/16 ARIA sufficiency Template-8/22/16
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	11/6/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Completed <b>(Do not include) pending</b>

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

❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP           <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<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"> <li>• Date reviewed by PeRC <u>6/15/16 (PERC meeting)</u>            If PeRC review not necessary, explain: _____</li> </ul>	For the resubmission, the application did not have to go through another PERC review.
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• 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>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></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 Master File letters; do not include previous action letters, as these are located elsewhere in package</i> )	1/27/17; 1/23/17; 1/17/17; 1/13/17; 1/6/17; 12/19/16; 12/16/16; 8/24/16 (2); 8/23/16 (2); 8/17/16 (2); 8/9/16 (2); 8/4/16; 8/3/16; 7/29/16, 7/26/16 (4); 7/13/16; 7/6/16 (2); 6/20/16; 5/25/16; 5/13/16; 5/5/16 (2); 4/26/16; 1/21/16; 1/8/16; 1/4/16; 11/6/15; 10/14/15; 9/3/15
❖ 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)	n/a
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 5/13/15</li> </ul>	mtg cancelled-5/8/15
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>) 7/9/12</li> </ul>	mtg 7/9/12
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>) 2/8/16</li> </ul>	mtg 2/3/16 (Midcycle communication)
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>) 6/1/16</li> </ul>	<input type="checkbox"/> mtg cancelled 5/27/16 (LC background package)
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	12/17/12 CMC EOP2 mtg

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	2/7/17; 8/24/16
Division Director Summary Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	2/3/17; 8/24/16
PMR/PMC Development Templates ( <i>indicate total number</i> )	2/8/17; 9/8/16; 8/22/16; 4 PMRs
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) ( <i>indicate date for each review</i> )	1/30/17; 8/19/16; 10/22/15
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None n/a
❖ 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 ( <i>indicate date of review/memo</i> )	8/19/16 (pgs. 168-170)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> ) <sup>5</sup>	Immunogenicity-4/8/16 QT-IRT-1/4/16
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management • REMS Documents and REMS Supporting Document ( <i>indicate date(s) of submission(s)</i> ) • REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> ) • Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> ); 9/12/16; 8/2/16; 5/9/16 (2); 4/21/16; 4/4/16 (3)	<input type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	1/27/17; 8/18/16 (filing); 4/28/16

<sup>5</sup> For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	5/5/16; 10/19/15
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 8/22/16
• 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>	7/13/16; 4/27/16; 10/5/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	3/8/16
❖ ECAC/CAC report/memo of meeting	3/3/16 Included in P/T review, page101
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews <sup>6</sup>	
• Tertiary review <i>(indicate date for each review)</i>	<input type="checkbox"/> None n/a
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input type="checkbox"/> None n/a
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	1/4/17; 8/4/16; 4/25/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	1/4/17
<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 (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation <b>before issuing approval letter</b> ) <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: n/a <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

<sup>6</sup> Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes n/a <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done n/a
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done n/a ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<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 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 checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

**From:** [Jairath, Meghna](#)  
**To:** [Sholter, Juliana \(juliana@amgen.com\)](mailto:juliana@amgen.com)  
**Subject:** RE: PI NDA 208325 vs3  
**Date:** Thursday, January 26, 2017 3:17:15 PM  
**Attachments:** [Draft Parsabiv USPI FDA rsp to Amgen vs3.doc](#)  
**Importance:** High

---

Hello,

I am sending you the PI for your review.

Please acknowledge the receipt of this email and respond by, January 27, 2017.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
01/27/2017

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

**From:** [Jairath, Meghna](#)  
**To:** [Sholter, Juliana \(juliana@amgen.com\)](mailto:juliana@amgen.com)  
**Subject:** PI NDA 208325 vs2  
**Date:** Monday, January 23, 2017 8:17:38 AM  
**Attachments:** [FDA rsp PI vs 2 NDA 208325.doc](#)

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Hello,

I am sending you the PI for your review.

Please acknowledge the receipt of this email and respond by, January 24, 2017.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
01/23/2017

**From:** [Jairath, Meghna](#)  
**To:** [Sholter, Juliana \(juliana@amgen.com\)](mailto:Sholter_Juliana@amgen.com)  
**Subject:** PI NDA 208325 version 1  
**Date:** Friday, January 13, 2017 5:54:23 PM  
**Attachments:** [Information request Amgen labelling RevA.DOC](#)  
[FDA to sponsor 1\\_13\\_17\\_NDA 208325 vs 1.doc](#)

---

Hello,

I am sending you the PI for your review. Also, there is an attached explanation to the changes made in table 3. Please do not submit anything to the NDA until we have agreed upon a final label.

Please acknowledge the receipt of this email and respond by EOB, January 17, 2017.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
01/17/2017

**From:** [Sholter, Juliana](#)  
**To:** [Jairath, Meghna](#)  
**Subject:** RE: NDA 208325 Type 1 resubmission  
**Date:** Friday, January 13, 2017 12:22:24 PM

---

Hi Meghna,

The team has reviewed the updated PMR-PMC list and we are in agreement with the list as it currently reads.

Kind regards,

**Juliana**  
202.585.9693 (office); [REDACTED] (b) (6) (mobile) | [juliana.sholter@amgen.com](mailto:juliana.sholter@amgen.com)

---

**From:** Jairath, Meghna [mailto:[Meghna.Jairath@fda.hhs.gov](mailto:Meghna.Jairath@fda.hhs.gov)]  
**Sent:** Friday, January 06, 2017 3:52 PM  
**To:** Sholter, Juliana <[juliana@amgen.com](mailto:juliana@amgen.com)>  
**Subject:** RE: NDA 208325 Type 1 resubmission

Thx  
You too!

---

**From:** Sholter, Juliana [mailto:[juliana@amgen.com](mailto:juliana@amgen.com)]  
**Sent:** Friday, January 06, 2017 3:49 PM  
**To:** Jairath, Meghna  
**Subject:** RE: NDA 208325 Type 1 resubmission

Thanks, Meghna. I will provide a response/confirmation by next Friday, 13 January 2017.

Have a great weekend!

**Juliana**  
202.585.9693 (office); [REDACTED] (b) (6) (mobile) | [juliana.sholter@amgen.com](mailto:juliana.sholter@amgen.com)

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**From:** Jairath, Meghna [mailto:[Meghna.Jairath@fda.hhs.gov](mailto:Meghna.Jairath@fda.hhs.gov)]  
**Sent:** Friday, January 06, 2017 3:27 PM  
**To:** Sholter, Juliana <[juliana@amgen.com](mailto:juliana@amgen.com)>  
**Subject:** NDA 208325 Type 1 resubmission  
**Importance:** High

Hello,  
I am attaching an updated PMR-PMC list.  
Please review the document and let us know if you agree by, January 13, 2017.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
01/13/2017

**From:** [Jairath, Meghna](#)  
**To:** [Sholter, Juliana \(juliana@amgen.com\)](mailto:Sholter_Juliana@amgen.com)  
**Subject:** NDA 208325 Type 1 resubmission  
**Date:** Friday, January 06, 2017 3:26:57 PM  
**Attachments:** [Parsabiv PMR-PMC list for applicant.doc](#)  
**Importance:** High

---

Hello,

I am attaching an updated PMR-PMC list.

Please review the document and let us know if you agree by, January 13, 2017.

Thanks,  
Meghna

**PMR/PMC list for NDA 208325  
PARSABIV (etelcalcetide), injection**

While review of your application continues, we are sending you a draft list of PMRs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest.

Please submit by email a copy of the PMR studies/trials to us with milestone dates, which include **Final Protocol Submission, Study Completion and Final Report Submission**, as applicable.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date. The draft milestone dates proposed below are based on the timelines that were negotiated with you during the previous review cycle for this application.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA; you should plan on submitting your initial draft protocol at least 6 months prior to this date.

**Postmarketing Requirements**

- 1) Conduct a pharmacokinetic/pharmacodynamics (PK/PD) modeling study evaluating Parsabiv (etelcalcetide) injection in adults with secondary hyperparathyroidism receiving hemodialysis to determine a safe starting dose in children.

Trial Completion:	February 2017
Final Report Submission:	May 2017

- 2) Conduct a 26-week Phase 3, randomized, multiple-dose titration safety and PK study evaluating Parsabiv (etelcalcetide) injection with a comparator control arm in patients aged 2 to (b)(4) years (Part 1), and subjects aged 1 month to 2 years (Part 2), both with secondary hyperparathyroidism receiving hemodialysis.

Final Protocol Submission:	May 2018
Trial Completion:	January 2023
Final Report Submission:	June 2023

- 3) Conduct a comparative pharmacokinetic/pharmacodynamics (PK/PD) modeling study evaluating Parsabiv (etelcalcetide) injection in adult and pediatric subjects with secondary hyperparathyroidism receiving maintenance hemodialysis.

Trial Completion:	September 2023
Final Report Submission:	December 2023

- 4) Conduct a hypothesis-testing observational study to provide data regarding the potential association between Parsabiv (etelcalcetide) and fatal and non-fatal gastrointestinal bleeding. The study should have a comparator group, be powered to detect the outcomes of interest, with justification for the proposed detectable differences in incidence rates. Special attention should be given to complete data availability in dialysis patients with secondary hyperparathyroidism above and below the age of 65 years, the ability to ascertain cause of death in a timely manner, and a statistical consideration of competing risks. Secondary analyses should aim to quantify the exposure-risk window, including periods after exposure discontinuation. The choice of study design, data source(s), and sample size should be supported by a feasibility analysis submitted to and reviewed by FDA prior to protocol finalization.

Feasibility Analysis:	July 2017
Final Protocol Submission:	December 2017
Interim Report Submissions:	May 2018
	May 2019
	May 2020
Study Completion:	June 2020
Final Report Submission:	December 2020

### Additional Information

We would also like to remind you of our intention to include the following request in the action letter for this product, if approved:

We request that for a period of 2 years, you submit all cases of gastrointestinal ulceration and bleeding events reported with Parsabiv (etelcalcetide) injection as 15-day alert reports, and that you provide detailed analyses of gastrointestinal ulceration and bleeding events reported from clinical study and post-marketing reports of gastrointestinal bleeding events as adverse events of special interest in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should show cumulative data relative to the date of approval of Parsabiv (etelcalcetide) injection as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of gastrointestinal bleeding events reported with Parsabiv (etelcalcetide) injection should also be provided in the periodic safety report.

Please note that if your product is approved and you wish to submit the periodic safety report in the ICH E2C PBRER format, you will need to submit a formal waiver request to CDER's Office of Surveillance and Epidemiology to submit PBRERs instead of PADERs. Prior to approval, you may submit a proposal for data lock dates and frequency of reporting order to obtain preliminary feedback. You should ensure that your proposal does not result in any gaps in reporting.

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/s/  
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MEGHNA M JAIRATH  
01/06/2017



NDA 208325

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

KAI Pharmaceuticals, Inc.  
A wholly owned subsidiary of Amgen, Inc.  
One Amgen Center Drive  
Mail Stop: 17-2-A  
Thousand Oaks, CA 91320-1799

ATTENTION:           Juliana Sholter, MS, RAC  
                                  Manager, Regulatory Affairs

Dear Ms. Sholter:

Please refer to your New Drug Application (NDA) dated and received December 9, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Etelcalcetide Injection, 2.5 mg/0.5 mL, 5 mg/mL, and 10 mg/2 mL.

We also refer to your correspondence, dated and received December 9, 2016, requesting review of your proposed proprietary name, Parsabiv.

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

If any of the proposed product characteristics as stated in your December 9, 2016 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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 Deveonne Hamilton-Stokes, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2253. For any other information regarding this application, contact Meghna Jairath, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4267.

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/  
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DANIELLE M HARRIS on behalf of TODD D BRIDGES  
01/03/2017

**From:** [Jairath, Meghna](#)  
**To:** [Batra, Monica \(mbatra@amgen.com\)](#)  
**Cc:** [Sholter, Juliana \(juliana@amgen.com\)](#)  
**Subject:** NDA 208325 Parsabiv  
**Date:** Monday, December 19, 2016 3:53:57 PM  
**Importance:** High

---

**IR**  
**NDA 208325**

Hello,

Please submit the following request listed below by **December 21, 2016**.

*You have changed the proposed USPI with respect to the number of cases of fatal upper GI bleed (3 cases in the original USPI vs. 2 cases in the current USPI) based on a re-analysis suggesting that patient 0517-1547 (Case USACT2012058566) had a lower GI bleed rather than an upper GI bleed as initially classified. Please provide a full autopsy report for Subject 0517-1547 (Case USACT2012058566).*

You can submit a courtesy copy of the response to me via email but an official copy should be submitted to the IND.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
12/19/2016



NDA 208325

**ACKNOWLEDGE -  
CLASS 1 COMPLETE RESPONSE**

KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen, Inc.  
Attention: Juliana Sholter, MS, RAC  
Manager, Regulatory Affairs  
One Amgen Center Drive; Mail Stop: 17-2-A  
Thousand Oaks, CA 91320-1799

Dear Ms. Sholter:

We acknowledge receipt on December 9, 2016, of your December 9, 2016, resubmission to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for etelcalcetide injection.

We consider this resubmission a complete, class 1 response to our action letter. Therefore, the user fee goal date is **February 9, 2017**.

If you have any questions, call me, at (301) 796-4267.

Sincerely,

*{See appended electronic signature page}*

Meghna M. Jairath, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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MEGHNA M JAIRATH  
12/16/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer](#)  
**Subject:** NDA 208325 PI version 6  
**Date:** Wednesday, August 24, 2016 10:42:53 AM  
**Attachments:** [Draft Parsabiv USPI FDA rsp to Amgen Vs.6.doc](#)  
**Importance:** High

---

Hello,

I am sending you the PI for your review. The active comparator trial data is deleted from the USPI and this will be the final version from FDA. Please provide a statement of agreement or non-agreement to final labeling in one hour, 11:40 am EST today. We will be moving forward with the action.

Please acknowledge the receipt of this email.

Thanks,  
Meghna

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immediately following this page

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MEGHNA M JAIRATH  
08/24/2016

**From:** [Steinbock, Jennifer](#)  
**To:** [Jairath, Meghna](#)  
**Subject:** RE: NDA 208325 PI version 6  
**Date:** Wednesday, August 24, 2016 11:47:13 AM

---

Hi Meghna,

I confirm that Amgen is not in agreement with [REDACTED] (b) (4)

Thanks,

*Jen*

---

**From:** Jairath, Meghna [mailto:Meghna.Jairath@fda.hhs.gov]  
**Sent:** Wednesday, August 24, 2016 7:43 AM  
**To:** Steinbock, Jennifer  
**Subject:** NDA 208325 PI version 6  
**Importance:** High

Hello,

I am sending you the PI for your review. [REDACTED] (b) (4) is deleted from the USPI and this will be the final version from FDA. Please provide a statement of agreement or non-agreement to final labeling in one hour, 11:40 am EST today. We will be moving forward with the action.

Please acknowledge the receipt of this email.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
08/24/2016

8/23/16

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer](#)  
**Subject:** NDA 208325 PI version 5  
**Date:** Tuesday, August 23, 2016 6:23:28 PM  
**Attachments:** [Draft clean version Parsabiv USPI FDA rsp to Amgen Vs. 5.doc](#)  
[Draft TC Parsabiv USPI FDA rsp to Amgen rsp vs 5.doc](#)  
**Importance:** High

---

Hello,

I am sending you the PI for your review. I attached a tracked changes and clean version of the USPI. Please do not submit anything to the NDA until we have agreed upon a final label.

Please acknowledge the receipt of this email. Please respond by EOB today if possible, August 23, 2016.

Thanks,  
Meghna

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Reference ID: 3976415

Reference ID: 4057401

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MEGHNA M JAIRATH  
08/23/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** NDA 208325 PI version 4  
**Date:** Friday, August 19, 2016 9:47:47 AM  
**Attachments:** [NDA 208325 FDA rspn to Amgen V4 8 19 16.doc](#)

---

Hello,

I am sending you the PI for your review. Please address residual comments. We consider this to be a near final version of the full PI. Please tell edit the highlights and TOC to make consistent with the full PI. Please do not submit anything to the NDA until we have agreed upon a label.

Please acknowledge the receipt of this email. Please respond by EOB today, August 19, 2016.

Thanks,  
Meghna

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MEGHNA M JAIRATH  
08/23/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** NDA 208325 PMR  
**Date:** Friday, August 12, 2016 11:08:59 AM  
**Attachments:** [Parsabiv PMR-PMC list for applicant 8-12-2016 FDA Response.doc](#)

---

Hello,

I am attaching an updated PMR-PMC list. We do concur with the proposed dates but have made some minor changes. Please review the document and let us know if you agree by today, August 12, 2016.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
08/17/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** Third round PI FDA rspn to Amgen NDA 208325  
**Date:** Friday, August 12, 2016 10:44:50 AM  
**Attachments:** [Draft Parsabiv USPI - FDA rsp version 3 to Amgen 8-12-2016.doc](#)  
**Importance:** High

---

Hello,  
Here is the PI with our comments. Please respond by Monday, August 15, 2016.

Thanks,  
Meghna

**PMR list for NDA 208325  
PARSABIV (etelcalcetide) injection**

While review of your application continues, we are sending you a draft list of PMRs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest.

Please submit by email a copy of the PMR studies/trials to us with milestone dates, which include **Final Protocol Submission, Study Completion** and **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA; you should plan on submitting your initial draft protocol at least 6 months prior to this date.

**Postmarketing Requirements**

- 1) Conduct a pharmacokinetic/pharmacodynamics (PK/PD) modeling study evaluating Parsabiv (etelcalcetide) injection in adults with secondary hyperparathyroidism receiving hemodialysis to determine a safe starting dose in children.

Study Completion: February 2017  
Final Report Submission: May 2017

- 2) Conduct a 26-week Phase 3, randomized, multiple-dose titration safety and PK study evaluating Parsabiv (etelcalcetide) injection with a comparator control arm in patients aged 2 to <sup>(b) (4)</sup> years (Part 1), and subjects aged 1 month to 2 years (Part 2), both with secondary hyperparathyroidism receiving hemodialysis.

Final Protocol Submission: May 2018  
Study Completion: January 2023  
Final Report Submission: June 2023

- 3) Conduct a comparative pharmacokinetic/pharmacodynamics (PK/PD) modeling study evaluating Parsabiv (etelcalcetide) injection in adult and pediatric subjects with secondary hyperparathyroidism receiving maintenance hemodialysis.

Study Completion: September 2023  
Final Report Submission: December 2023

- 4) Conduct a hypothesis-testing observational study to provide data regarding the potential association between Parsabiv (etelcalcetide) and fatal and non-fatal gastrointestinal bleeding. The study should have a comparator group, be powered to detect the outcomes of interest, with justification for the proposed detectable differences in incidence rates. Special attention should be given to complete data availability in dialysis patients with secondary hyperparathyroidism above and below the age of 65 years, the ability to ascertain cause of death in a timely manner, and a statistical consideration of competing risks. Secondary analyses should aim to quantify the exposure-risk window, including periods after exposure discontinuation. The choice of study design, data source(s), and sample size should be supported by a feasibility analysis submitted to and reviewed by FDA prior to protocol finalization.

Feasibility Analysis:	January 2017
Final Protocol Submission:	June 2017
Interim Reports:	<del>Annually, starting</del> November 2017
	November 2018
	November 2019
Study Completion:	December 2019
Final Report Submission:	June 2020

### **Additional Information**

We would also like to inform you of our intention to include the following request in the action letter for this product, if approved:

We request that for a period of two years, you submit all cases of gastrointestinal ulceration and bleeding events reported with Parsabiv (etelcalcetide) injection as 15-day alert reports, and that you provide detailed analyses of gastrointestinal ulceration and bleeding events reported from clinical study and post-marketing reports of gastrointestinal bleeding events as adverse events of special interest in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should show cumulative data relative to the date of approval of Parsabiv (etelcalcetide) injection as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of gastrointestinal bleeding events reported with Parsabiv (etelcalcetide) injection should also be provided in the periodic safety report.

Please note that if your product is approved and you wish to submit the periodic safety report in the ICH E2C PBRER format, you will need to submit a formal waiver request to CDER's Office of Surveillance and Epidemiology to submit PBRERs instead of PADERs. Prior to approval, you may submit a proposal for data lock dates and frequency of reporting order to obtain preliminary feedback. You should ensure that your proposal does not result in any gaps in reporting.

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/s/  
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MEGHNA M JAIRATH  
08/17/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** IR NDA 208325 Etecalcetide  
**Date:** Tuesday, August 09, 2016 1:16:41 PM  
**Importance:** High

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**IR**  
**NDA 208325**

Hello,

We have the following comment below in regards with your carton and container labels. Please respond by tomorrow, August 10, 2016.

*Provide total subjects exposure (total number of subjects and subjects-years) to **any** comparator drug(s) (placebo **AND** cinacalcet) received in Phase 2/3 studies (Studies 20120229, 20120230, (b) (4) 20120330, 20120331, 20120334, 20120359, 20120231 and 20130213); Safety Analysis set. Provide the data in tabular format similar to the Table 1-2 in Integrated summary of Safety (5.3.5.3) , page 180.*

Please acknowledge the receipt of this email. You can send a response via email but submit an official response to the NDA.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
08/09/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** NDA 208325 PMR  
**Date:** Tuesday, August 09, 2016 1:01:26 PM  
**Attachments:** [Parsabiv PMR-PMC list for applicant 8-9-2016 DMEP.doc](#)  
**Importance:** High

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Hello,  
Please review the PMR document attached and submit your comments by EOB, Thursday, August 11, 2016.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
08/09/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** IR NDA 208325  
**Date:** Thursday, August 04, 2016 10:06:45 AM  
**Importance:** High

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Hello,

We refer to your email dated August 3, 2016, requesting clarification regarding what analysis triggered the inclusion of the new warning for Upper GI bleed in the package insert and the request for the PMR on GI bleeding. Please see our analysis below.

1. Two fatal cases were reported in Phase 3 placebo-controlled studies (20120229 & 20120230):
  - case 22965007001; occurred two weeks after starting treatment and was formally listed as death of unknown cause
  - case 23066026008; occurred about (b) (6) weeks after drug discontinuation on week 17 of the study
2. One fatal case was reported in Phase 2b open label extension study 20120331
  - case 0517-1547; occurred 10 days after drug discontinuation on Study Day 33

Thanks,  
Meghna

---

**From:** Steinbock, Jennifer [<mailto:jsteinbo@amgen.com>]  
**Sent:** Wednesday, August 03, 2016 10:24 AM  
**To:** Jairath, Meghna  
**Subject:** RE: NDA 208325 round two PI

Dear Meghna,

We would like to request clarification regarding what analysis triggered the inclusion of the new warning for Upper GI bleed in the USPI and the request for the PMR on GI bleeding. If a reply can be provided today or early tomorrow, this will help us develop the responses to both documents. If there is a specific case that FDA is concerned about, please let us know that as well.

Many thanks,

*Jen*

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/s/  
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MEGHNA M JAIRATH  
08/04/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** NDA 208325 round two PI  
**Date:** Tuesday, August 02, 2016 5:05:46 PM  
**Attachments:** [NDA 208325 PI version 2 to sponsor.doc](#)  
**Importance:** High

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Hello,  
Sending you round two of the PI. Please by Friday, August 5, 2016.

Please respond in the comment bubble if you agree or disagree with your comments.

Do not submit anything to the NDA until we have agree upon a final label.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
08/03/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** NDA 208325 PMR  
**Date:** Friday, July 29, 2016 3:28:40 PM  
**Attachments:** [Parsabiv PMR-PMC list for applicant 7-29-16.doc](#)

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Hello,

Please review the PMR document attached and submit your comments by EOB, Thursday, August 4, 2016.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
07/29/2016

From: [Jairath Meghna](#)  
 To: [Steinbock Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
 Subject: IR NDA 208325  
 Date: Friday, July 15, 2016 6:52:29 PM

IR  
 NDA 208325  
 Hello,

We have the following comments which need a written response. Please respond by EOB, July 20, 2016.

1. Provide the number and percent of patients from the study 20120360 who continued in the extension study(s). Provide the ID number of these studies.
2. For patients enrolled in placebo controlled studies 20120229 and 20120230 only (509 patients in study 20120229 and 514 patients in study 20120230) and completed 6 month of treatment in pivotal studies and/or continued in the extension studies: provide the total number and percent of patients who had duration of treatment with etelcalcetide  $\geq 6$  months, and  $\geq 12$  months. Provide the same information for the patients enrolled in the study 20120360.
3. Provide the analysis of the number and percentage of patients with at least one iPTH value  $< 100$  pg/ml during 6-month treatment in each treatment group in studies 20120229, 20120230 and studies 20120229 and 20120260. Provide how many patients with decreased iPTH values  $< 100$  pg/ml required dose suspension. Provide such analysis of pooled data from studies 20120229 and 20120230 and separate analysis of data from study 20120360.

Provide the individual results (patient-level) for the patients who had at least one iPTH level  $< 100$  pg/ml in the following table format:

Study	Patient ID	Study Visit at which iPTH level $< 100$ pg/ml was identified					Subsequent visit			Study visit at which iPTH level increased to $> 100$ pg/ml		
		iPTH level, pg/ml	Visit, n (days)	Drug group	Dose, mg	Calcium level, mg/dl	iPTH level, pg/ml	Visit, n (days)	Drug Dose, mg	iPTH level, pg/ml	Visit, n (days)	Drug Dose, mg

Please acknowledge the receipt of this email. You can provide me a response via email but submit an official response to the NDA.

Thanks,  
 Meghna

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/s/  
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MEGHNA M JAIRATH  
07/26/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** FW: IR NDA 208325 Etelcalcetide  
**Date:** Tuesday, July 19, 2016 1:41:49 PM

---

Hello,  
Please see our responses in red below.

Thanks,  
Meghna

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**From:** Steinbock, Jennifer [<mailto:jsteinbo@amgen.com>]  
**Sent:** Friday, July 15, 2016 4:06 PM  
**To:** Jairath, Meghna  
**Subject:** RE: IR NDA 208325 Etelcalcetide

Dear Meghna,

With regards to Question 2, we plan to replicate the key elements of the IXRS algorithm to answer this question as that would be faster than updating and running the IXRS algorithm (which has been archived by the vendor). As time is needed for programming, validation, analysis, and drafting the response, we respectfully request an extension of the response deadline to Wednesday July 20th. **FDA response-This as acceptable.**

Regarding “Additional Question 1”, Amgen respectfully asks that FDA reconsider the request to repeat the noninferiority and superiority analyses excluding patients who had an increase in calcium supplements or vitamin D dose. As part of their mechanism of action, calcimimetics lower serum calcium and as such may necessitate subjects to undergo increases in calcium supplements or vitamin D sterol doses. Changes in these concomitant medications are expected and may have additional effects in reducing PTH. As noted in the response to question 3 from the mid-cycle information request, there was a similar proportion of subjects in the etelcalcetide and cinacalcet arms with a dose increase in calcium supplements (40.0% [n = 136] AMG 416, 39.7% [n = 136] cinacalcet). As noted in the response to question 2 from the mid-cycle information request, 36.8% of subjects in the etelcalcetide arm (n = 125) and 30.6% of subjects in the cinacalcet arm (n = 105) had an increase in vitamin D sterols during the study. In total, 231 subjects in the AMG 416 group (62.6%) and 183 subjects (53.4%) in the cinacalcet group had an increase in either vitamin D or calcium supplements during the study. Given this large percentage of subjects who had increases in calcium supplements or vitamin D, repeating the noninferiority and superiority analyses excluding subjects with either an increase in calcium supplements or vitamin D sterol dose would be statistically flawed for the following reasons:

Firstly, this would introduce bias into the analysis from two aspects:

- a) Calcium supplement or vitamin D sterol dose increase on-study is a post randomization variable. Limiting the analysis to the subset of subjects who did not have an increase in calcium supplements or vitamin D sterol dose will violate the original randomization that was stratified based on key baseline variables of baseline PTH levels and region.

Furthermore, it is not advisable to adjust the main analyses for variables measured after randomization because they may be affected by the treatments, per the ICH E9 guidance.

b) Serum calcium reductions in subjects with sHPT treated with a calcimimetic is an indirect indicator of efficacy as calcimimetics lower PTH which is followed by a reduction in serum calcium. As bone turnover is reduced by calcimimetics, less calcium is released from the bone and more calcium is taken up by the bone. Consequently limiting the analysis to subjects who did not have an increase in calcium supplement or vitamin D sterol dose (in response to reductions in serum calcium) biases the data to subjects who may be less likely to have an effective PTH reduction.

Secondly, the proposed analysis will have insufficient power for the statistical test of non-inferiority or superiority and render the results inconclusive, because by excluding subjects with no increase in calcium supplements and vitamin D sterol dose, the majority of the subjects (62.6% AMG 416 and 53.4% cinacalcet) would be removed from the analysis. The resulting sample size would be 127 subjects in the AMG 416 group and 160 subjects in the cinacalcet group.

Despite these concerns, Amgen has performed a descriptive analysis for the subgroup of subjects with no vitamin D sterol increase during the study. Statistical testing of non-inferiority and superiority has not been performed for the reasons outlined above. In this subgroup of subjects, there were numerically more subjects in the etelcalcetide arm (62.3%  $\pm$  3.3%) than in the cinacalcet arm (52.9%  $\pm$  3.2%) that achieved the primary endpoint of >30% reduction in PTH from baseline during the efficacy assessment period.

FDA response-Descriptive statistics as acceptable.  
But you should include the percentages for >30% and >50% responders in pts with no increases in vitamin D supplements alone, no increases in Ca supplements alone and the combined group with neither an increase in vitamin D nor calcium supplements for study 20120360.

We look forward to your response.

Kind regards,

*Jen*

---

**From:** Jairath, Meghna [<mailto:Meghna.Jairath@fda.hhs.gov>]  
**Sent:** Wednesday, July 13, 2016 12:56 PM  
**To:** Steinbock, Jennifer  
**Subject:** RE: IR NDA 208325 Etelcalcetide

thx

---

**From:** Steinbock, Jennifer [<mailto:jsteinbo@amgen.com>]  
**Sent:** Wednesday, July 13, 2016 3:54 PM  
**To:** Jairath, Meghna  
**Subject:** RE: IR NDA 208325 Etelcalcetide

Hi Meghna,

I confirm receipt. I will discuss with the team and get back to you.

Kind regards,

*Jen*

---

**From:** Jairath, Meghna [<mailto:Meghna.Jairath@fda.hhs.gov>]

**Sent:** Wednesday, July 13, 2016 11:37 AM

**To:** Steinbock, Jennifer

**Subject:** IR NDA 208325 Etelcalcetide

**Importance:** High

**IR  
NDA 208325**

Hello,

We refer to your submission dated July 12, 2016, containing a response to our email correspondence dated June 30, 2016.

We have the following comments which need a written response. Please respond by EOB, July 18, 2016.

1. We note that in In Table 160630-5.4., there were substantially more subjects with the Dosing decision: "Maintain" listed as "Other" in the cinacalcet group compared to the etelcalcetide group during the potential dose titration visits at weeks 13 and 17 i.e. 33 (19.2%) vs. 11 (7.2%) and 25 (15.2%) vs. 7 (4.9%), respectively. Can you clarify specifically what the reasons were that lead to the designation of "Other" as the reason for maintaining the dose at these two visits? Were the reasons different for the different treatment groups?
  - a. We also note that the reason "Other" was also more common in the cinacalcet group as a reason to Maintain Dosing at the earlier visits at Weeks 5 and 9 and as a reason to Suspend Dosing at all of the visits (weeks 5, 9, 13 and 17). Were the reasons labeled as "Other" for maintaining the dose at the earlier visits the same as the reasons observed during the Week 13 and 17 visits? Were the reasons different for the different treatment groups?
  - b. Also were the reasons labeled as "Other" similar for subjects for whom the dose was suspended and those for whom the dose was maintained between the treatment groups?
2. We are concerned that a higher percentage of subjects in the cinacalcet group continued to have a dosing decision of "Increase" at the Week 17 visit 49 (19.1%) vs.

19 (9.9%). Can you run the IXRS dosing algorithm on week 20 data to determine what the dosing decisions would have been for the two treatment groups if there was an option for another dose increase at week 21?

Additional Question:

1. Given that lower serum calcium levels were observed in the etelcalcetide group in study 20120360 compared to the cinacalcet group we are concerned that use of calcium and vitamin D supplements may have been greater in the etelcalcetide group and have contributed to the greater efficacy seen in the etelcalcetide group. We ask that you repeat the noninferiority and superiority analyses excluding patients who had either an increase in calcium supplements or an increase in vitamin D dose during the trial to determine the difference in efficacy due only to treatment with the calcium sensing receptor agonists.

-

Please acknowledge the receipt of this email. You can provide me a response via email but submit an official response to the NDA.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
07/26/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** IR NDA 208325 Etelcalcetide  
**Date:** Monday, July 25, 2016 2:12:12 PM

---

**IR  
NDA 208325**

Hello,

We refer to your submissions dated July 13, 2016, containing a response to our email correspondence dated June 30, 2016.

We have the following comments which need a written response. Please respond by EOB, July 27, 2016.

1. With regards to your response to the July 13, 2016 information request Question 2. Your data from Table 1 shows that there are still a larger number of patients that might have benefited from a dose increase in the cinacalcet group compared to the etelcalcetide group using your prediction for dose increase at week 21 i.e. 29 vs. 7. While it is not known if the dose increase would have made more of the cinacalcet treated patients responders, we note that the difference in 30% responders in study 20120360 was only 232-198=34 patients so it is possible that the number of subjects still with a potential for dose increase in the cinacalcet group might have affected the statistical significance of the data. We disagree that data from other trials with longer titration periods can be used to prove that there would be no more responders in this study with further titration given differences between trials in study populations, study design, etc. We ask that you clarify again from the study 20120360 data why you are so certain that there would be no increase in responders in the cinacalcet group if the titration had continued beyond week 17. Is it possible that tolerability was more of a problem in the cinacalcet group which delayed dose titration in this group and eventually with enough time the dose could have been increased high enough to increase the final number of responders so that there would have been no difference in efficacy between treatment groups?
2. With regards to your response to the July 13, 2016 information request Question 1. You mention "A manual review of the clinical database confirmed that all subjects identified in the "other" group category for dosing decision of "suspend" in Table 160630-5.4.1 had two consecutive PTH < 100 pg/mL prior to those titration visits." We wonder why weren't "Two consecutive PTH < 100 pg/mL" or "more than one reason" chosen as the reason for these dosing decisions as these seem like more appropriate options than the category "other" which was chosen? We are seeking more clarity about why the category "other" might be chosen instead of what appear to be reasonable alternatives. Did clinical investigator input go into designating the final decision category of "other"?

Please acknowledge the receipt of this email. You can a response via email but submit an official response to the NDA.

Thanks,

Meghna

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MEGHNA M JAIRATH  
07/26/2016

7/26/16

**From:** [Jairath, Meghna](#)  
**To:** [Batra, Monica](#)  
**Cc:** [Tokushige, Wade](#); [Steinbock, Jennifer](#)  
**Subject:** IR NDA 208325 Etelcalcetide  
**Date:** Monday, July 25, 2016 2:48:38 PM

---

**IR**  
**NDA 208325**

Hello,

We have the following comment below in regards with your carton and container labels.  
Please respond by EOB, July 27, 2016.

*We continue to recommend that*

(b) (4)

(b) (4)

Please acknowledge the receipt of this email. You can a response via email but submit an official response to the NDA.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
07/26/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer](#)  
**Subject:** IR NDA 208325 Etelcalcetide  
**Date:** Wednesday, July 13, 2016 2:36:50 PM  
**Importance:** High

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**IR  
NDA 208325**

Hello,

We refer to your submission dated July 12, 2016, containing a response to our email correspondence dated June 30, 2016.

We have the following comments which need a written response. Please respond by EOB, July 18, 2016.

1. We note that in In Table 160630-5.4., there were substantially more subjects with the Dosing decision: "Maintain" listed as "Other" in the cinacalcet group compared to the etelcalcetide group during the potential dose titration visits at weeks 13 and 17 i.e. 33 (19.2%) vs. 11 (7.2%) and 25 (15.2%) vs. 7 (4.9%), respectively. Can you clarify specifically what the reasons were that lead to the designation of "Other" as the reason for maintaining the dose at these two visits? Were the reasons different for the different treatment groups?
  - a. We also note that the reason "Other" was also more common in the cinacalcet group as a reason to Maintain Dosing at the earlier visits at Weeks 5 and 9 and as a reason to Suspend Dosing at all of the visits (weeks 5, 9, 13 and 17). Were the reasons labeled as "Other" for maintaining the dose at the earlier visits the same as the reasons observed during the Week 13 and 17 visits? Were the reasons different for the different treatment groups?
  - b. Also were the reasons labeled as "Other" similar for subjects for whom the dose was suspended and those for whom the dose was maintained between the treatment groups?
2. We are concerned that a higher percentage of subjects in the cinacalcet group continued to have a dosing decision of "Increase" at the Week 17 visit 49 (19.1%) vs. 19 (9.9%). Can you run the IXRS dosing algorithm on week 20 data to determine what the dosing decisions would have been for the two treatment groups if there was an option for another dose increase at week 21?

**Additional Question:**

1. Given that lower serum calcium levels were observed in the etelcalcetide group in study 20120360 compared to the cinacalcet group we are concerned that use of calcium and vitamin D supplements may have been greater in the etelcalcetide group and have contributed to the greater efficacy seen in the etelcalcetide group. We ask that you repeat the noninferiority and superiority analyses excluding patients who had either an increase in calcium supplements or an increase in vitamin D dose during the

trial to determine the difference in efficacy due only to treatment with the calcium sensing receptor agonists.

-

Please acknowledge the receipt of this email. You can provide me a response via email but submit an official response to the NDA.

Thanks,  
Meghna

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MEGHNA M JAIRATH  
07/13/2016

**From:** [Jairath, Meghna](#)  
**To:** [Batra, Monica](#)  
**Cc:** [Tokushige, Wade](#); [Steinbock, Jennifer](#)  
**Subject:** IR NDA 208325 Etelcalcetide  
**Date:** Monday, July 25, 2016 2:48:38 PM

---

**IR**  
**NDA 208325**

Hello,

We have the following comment below in regards with your carton and container labels.  
Please respond by EOB, July 27, 2016.

*We continue to recommend that*

(b) (4)

Please acknowledge the receipt of this email. You can a response via email but submit an official response to the NDA.

Thanks,  
Meghna

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MEGHNA M JAIRATH  
07/26/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** IR NDA 208325 Etelcalcetide  
**Date:** Thursday, June 30, 2016 11:47:06 AM  
**Importance:** High

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**IR**

**NDA 208325**

Hello,

Please provide a written response to our comments below by EOB, July 1, 2016.

1. We note that in study 20110360 more patients were titrated to higher doses in the etelcalcetide treatment group compared to cinacalcet when looking during the efficacy assessment period.

Provide the information as to why subjects in the different treatment groups did not have their dose increased during the initial 16 week dose titration phase (due to AEs (include type of AEs), efficacy (already reached iPTH < 300), physician discretion, etc.)?

2. We also request to provide additional analysis of dose ranges in each treatment group (cinacalcet and etelcalcetide) in the study 20120360. Include the following information:

a. Provide analysis of the daily doses in each treatment group in the study. Include the following information:

- average daily dose in each group (cinacalcet vs. etelcalcetide)
- average time from the beginning of the treatment required to achieve a stable dose in each group
- PTH level at the end of the study in each treatment group

b. Provide analysis of the doses in the nonresponders in each treatment group. Include the following information:

- average daily dose in each group (cinacalcet and etelcalcetide)
- subject distribution (n,%) across all dose levels of cinacalcet at the end of the study
- subject distribution (n,%) across all dose levels of etelcalcetide at the end of the study
- average time that elapsed from the beginning of the study to achieve the stable dose

c. Provide analysis of the doses in the responders in each treatment group. Include the

following information:

- average daily dose in each group (cinacalcet and etelcalcetide)
  - subject distribution (n,%) across all dose levels of cinacalcet at the end of the study
  - subject distribution (n,%) across all dose levels of etelcalcetide at the end of the study
  - average time that elapsed from the beginning of the study to achieve the stable dose
  - PTH level at the end of the study
3. Provide reasoning as to whether increased efficacy of cinacalcet would have been shown had the titration period been longer than 16 weeks.
  4. Provide information why subjects in the each treatment group did not have their dose increased during the initial 16 week dose titration phase (AEs including type of the AE, efficacy was achieved, physician discretion, etc.).
  5. Provide information as to why some subjects did not require any dose increase (in either treatment group) during the initial 16 week dose titration phase.

Please acknowledge receipt of the email. You can provide me a response via email but submit an official response to the NDA.

Thanks,

Meghna

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MEGHNA M JAIRATH  
07/06/2016

**From:** Jairath, Meghna  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:Steinbock, Jennifer (jsteinbo@amgen.com))  
**Bcc:** [Jairath, Meghna](mailto:Jairath, Meghna)  
**Subject:** FW: IR NDA 208325 Etelcalcetide  
**Date:** Friday, July 01, 2016 10:01:00 AM  
**Importance:** High

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Hello,  
Please see our responses in red and changes in blue below.  
Thanks,  
Meghna

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**From:** Steinbock, Jennifer [<mailto:jsteinbo@amgen.com>]  
**Sent:** Thursday, June 30, 2016 6:40 PM  
**To:** Jairath, Meghna  
**Subject:** FW: IR NDA 208325 Etelcalcetide

Dear Meghna,

I confirm receipt of this information request.

I discussed this request with the team and we have a couple points we would appreciate clarification on:

- Duplication of question
  - It appears that the same information is being requested in multiple areas of the information request (please see blue text below). Can FDA please clarify the distinction between these questions?
- Titration period
  - We noted that FDA refers to a 16 week dose titration phase in Study 20120360. We would like to clarify that the titration phase was 17 weeks (titration visits were at weeks 5, 9, 13, and 17). Please clarify if our response to the questions highlighted below in yellow should be based on 17 weeks instead of 16 weeks. **Yes, the information should be based on the end of titration period (17 weeks).**
- Stable dose
  - The protocol does not specify or define a concept of a stable dose. As this is a titratable drug, dose adjustments are always possible due to concomitant medications and changes to background medical therapy (eg., dialysate calcium). Can FDA clarify what is meant by stable dose, and what the expectation is for defining stable dose in our response to this information request? **The stable dose means end of titration period, i.e dose at the end of 17 weeks.**
- Timing of Response
  - We respectfully request additional time to respond to this information request, as a response by EOB July 1 is not considered to be feasible by the team. Though the company is closed next week, the team will be working on the response. We think that we may be able to provide a response by mid-next week for the portion of the request which asks for reasoning as to whether increased efficacy of cinacalcet

would have been shown had the titration period been longer. For the remaining portions of this request, we think we will more time but our estimate depends on FDA's response to our questions above. **Please submit all the information by Wednesday- Thursday of the next week.**

Many thanks for your consideration of these questions.

Kind regards,

*Jen*

---

**From:** Jairath, Meghna [<mailto:Meghna.Jairath@fda.hhs.gov>]

**Sent:** Thursday, June 30, 2016 8:47 AM

**To:** Steinbock, Jennifer

**Subject:** IR NDA 208325 Etelcalcetide

**Importance:** High

**IR  
NDA 208325**

Hello,

Please provide a written response to our comments below by EOB, July 1, 2016.

We note that in study 20110360 more patients were titrated to higher doses in the etelcalcetide treatment group compared to cinacalcet when looking during the efficacy assessment period.

Provide the information as to why subjects in the different treatment groups did not have their dose increased during the initial **16 week dose titration phase** (due to AEs (include type of AEs), efficacy (already reached iPTH < 300), physician discretion, etc.)?

We also request to provide additional analysis of dose ranges in each treatment group (cinacalcet and etelcalcetide) in the study 20120360. Include the following information:

Provide analysis of the daily doses in each treatment group in the study. Include the following information:

average daily dose in each group (cinacalcet vs. etelcalcetide)

average time from the beginning of the treatment required to achieve a stable dose in each group

PTH level at the end of the study in each treatment group

Provide analysis of the doses in the nonresponders in each treatment group. Include the following information:

average daily dose in each group (cinacalcet and etelcalcetide)

subject distribution (n,%) across all dose levels of cinacalcet at the end of the study

subject distribution (n,%) across all dose levels of etelcalcetide at the end of the study

average time that elapsed from the beginning of the study to achieve the stable dose

Provide analysis of the doses in the responders in each treatment group. Include the

following information:

average daily dose in each group (cinacalcet and etelcalcetide)

subject distribution (n,%) across all dose levels of cinacalcet at the end of the study

subject distribution (n,%) across all dose levels of etelcalcetide at the end of the study

average time that elapsed from the beginning of the study to achieve the stable dose

PTH level at the end of the study

Provide reasoning as to whether increased efficacy of cinacalcet would have been shown had the titration period been longer than 16 weeks.

(b) (4)

Please acknowledge receipt of the email. You can provide me a response via email but submit an official response to the NDA.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
07/06/2016

**PeRC Meeting Minutes  
June 15, 2016**

**PeRC Members Attending:**

Hari Cheryl Sachs (acting chair)

Meshaun Payne

Robert "Skip" Nelson

Shrikant Pagay

Wiley Chambers

Jackie Yancy

Adrienne Hornatko-Munoz

Maura O'Leary

Gil Burckart

Gerri Baer

Daiva Shetty

Kevin Krudys

John Alexander

Pat Dinndorf

Peter Starke ( (b) (4) Etelcalcetide, (b) (4)

Lisa Faulcon

**Agenda**

(b) (4)



11:10	NDA 208325	Etelcalcetide Injection (Partial Waiver/Deferral/Plan) with Agreed iPSP	DMEP	Meghna Jairath	For Secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis
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(b) (4)



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**Etelcalcetide Injection (Partial Waiver/Deferral/Plan) with Agreed iPSP**

- Indication: For Secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis
- PREA Trigger: new active ingredient, indications, dosage form, dosing regimen, route of administration.
- There is no change from the agreed iPSP which outlines a plan for a partial waiver in children ages birth to (b) (4) weeks because studies would be impossible or highly impracticable and a deferral in patients ages 1 month to 17 years until adult studies are completed.

- The division stated they are interested in assessing the risk of hypocalcemia and over-suppression of iPTH in this study population.
- *PeRC Recommendations:*
  - The PeRC agreed with the division to grant partial waiver in neonates and to the deferral in pediatrics 1 month of age to 17 years.
  - The PeRC recommends the division contact sponsor regarding the gap between initiating 2<sup>nd</sup> study and PK study and adjust timeline for study 3 accordingly.

(b) (4)

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JACQUILINE A YANCY  
07/05/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** IR NDA 208325  
**Date:** Thursday, June 16, 2016 6:21:30 PM  
**Importance:** High

---

**IR**  
**NDA 208325**

Hello,

Please provide a written response to our comments below by EOB, Monday, June 19, 2016.

Provide the analyses of the following adverse events that occurred in pooled data from the 6-month placebo controlled studies 20120229 & 20120230 only.

Provide the same analysis of these adverse events that occurred in the active controlled study 20120360 only.

1. Provide an analysis of all adverse events associated with **gastrointestinal (GI) bleeding** that occurred in the studies by Preferred Term (PT) and by incidence. Information should include both overall results and individual (patient- level) results.
  - a) For overall results:
    - the information should include but not limited to the total number of patients in the study, the total number of AEs associated with GI bleeding by treatment group, the total number of patients and the proportion of patients who developed GI bleeding by treatment group.
    - Calculate an event rate for all events of interest by treatment group. How does this correlate with the event rate expected from historical controls?
  - b) For individual (patient-level) results:
    - generate a table that includes the following information for all AEs (serious and nonserious):
      - patient ID, age
      - preferred term (PT) associated with GI bleeding
      - drug or placebo (active comparator for the analysis of the data in study 20120360)
      - dose at time of the event
      - duration of treatment to the onset of the adverse event (days)
      - severity of the event
      - concomitant medications at the time of the event, past medical history and/or other potential confounding variables
    - generate the same table that includes patient-level data for serious adverse events (SAEs) only associated with GI bleeding. Include the outcome of the events in this table
2. Provide an analysis of all adverse events associated with **upper GI erosions** (noninfectious gastritis, esophagitis, erosions, ulcers, etc.) that occurred in the studies by PT and by incidence. Information should include both overall results and individual (patient- level) results.
  - a) For overall results:

-the information should include but not limited to the total number of patients in the study, the total number of AEs associated with GI bleeding by treatment group, the total number of patients and the proportion of patients who developed GI bleeding by treatment group.

- Calculate an event rate for all events of interest by treatment group. How does this correlate with the event rate expected from historical controls?

b) For individual (patient-level) results:

-generate a table that includes the following information for all AEs (serious and nonserious):

patient ID, age

preferred term (PT) associated with GI bleeding

drug or placebo (active comparator for the analysis of the data in study

20120360)

dose at time of the event

duration of treatment to the onset of the adverse event (days)

severity of the event

whether the event was associated with GI bleeding

concomitant medications at the time of the event, past medical history and/or

other potential confounding variables

-generate the same table that includes patient-level data for serious adverse events (SAEs) only associated with GI bleeding. Include the outcome of the events in this table

Please acknowledge receipt of the email. You can provide me a response via email but submit an official response to NDA.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
06/20/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** IR NDA 208325  
**Date:** Wednesday, May 25, 2016 1:53:41 PM

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## Information Request

**NDA 208325**

**Drug Name: etelcalcetide injection**

**Proposed Indication: treat Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis**

**Applicant: KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc**

Hello,

Please submit a response to our comments below.

A. Container Label-Commercial

- i. For 2.5 mg/0.5 mL strength, remove the concentration statement “5 mg/mL” stated immediately under the established name of the product on the primary display panel of the label with 2.5 mg/0.5 mL, in accordance with USP General Chapter <1>, which states that for containers holding a volume of less than 1 mL, the strength per fraction of a mL should be the only expression of strength.
- ii. For 5 mg/mL strength, revise the “5 mg/1 mL” statement in the circle to “5 mg/mL” in accordance with USP General Chapter <1>, which states that strength per single mL should be expressed as mg/mL, not mg/1 mL.<sup>2</sup>
- iii. Revise the presentation of the product strength and concentration statements on the label for the 10 mg/2 mL product so that the total drug content (i.e., strength) is noted first with the concentration immediately following on the same line: 10 mg/2 mL (5 mg/mL). Currently, the strength and concentration statements are on different parts of the label which increases the risk of dosing errors if one assumes the concentration is the total drug content.
- iv. There is inadequate contrast between the established name and the colored background. Change the font color of the established name to a darker color (e.g., black) to improve readability of the established name against the colored background on each of the labels.
- v. Revise the font color of the proprietary name (purple) or revise the color scheme of the 10 mg strength (purple) so that either the strength or the proprietary name appears in its own unique color and the color does not overlap with any of the other colors utilized to highlight the product strengths. The use of the same purple color font for the proprietary name and one of the product’s strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors.

- vi. Revise the statement “for IV use only” to read “For intravenous use only”.
- vii. Decrease the prominence of the statement “Rx Only” as this information appears as prominent as other safety information listed on the label.
- viii. Consider revising the “2.5 mg/0.5 mL and “10 mg/2mL” statements on the images to “2.5 mg per 0.5 mL” and “10 mg per 2 mL” because the “/” is not easily distinguishable.

B. Carton Labeling-Commercial

- i. See recommendations under section 4.2 A, items i, ii, and iii.
- ii. Remove the (b) (4) from the vial image (b) (4)
- iii. On the principal display panel (PDP), consider revising the statement (b) (4) and moving the statement “discard unused portion” so that it reads “single-dose vial- discard unused portion” to minimize the risk of the entire contents of the vial being given as a single dose.
- iv. Remove the trailing zero (i.e., 1.0 mL) so that the statement reads “10 x 1 mL (b) (4)
- v. Move the storage information on the PDP to the side display panel.
- vi. For improved clarity of the storage instructions, remove the (b) (4) from the carton labeling and only leave the statement “store at 2° to 8°C (36°to 46°F) in the original container to protect from light.”
- vii. Consider revising the statement (b) (4) to “For Intravenous Use after Dialysis”. We recommend this to minimize the risk of administering the drug as an intravenous bolus outside of the dialysis tubing.



Please acknowledge the receipt of this email.

Please respond by EOB, May 31, 2016.

Thanks,

Meghna

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/s/  
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MEGHNA M JAIRATH  
05/25/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer](#)  
**Subject:** IR NDA 208325  
**Date:** Thursday, May 12, 2016 10:48:36 AM

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## Information Request

**NDA 208325**

**Drug Name: etelcalcetide injection**

**Proposed Indication: treat Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis**

**Applicant: KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc**

Hello,

Please submit a response to our comments below in *italics*.

*We are completing our review for Parsabiv (etelcalcetide), NDA 208325, based on the labels and labeling submitted on August 24, 2015. We also noticed that you submitted* (b) (4)

(b) (4)

Please acknowledge the receipt of this email and respond by EOB, May 16, 2016.

Thanks,  
Meghna

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MEGHNA M JAIRATH  
05/13/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** First round PI NDA 208325  
**Date:** Wednesday, May 04, 2016 1:43:14 PM  
**Attachments:** [NDA 203825 PI first round to spnsr npi.doc](#)

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Hello,

I am sending the attached PI with track changes/comment bubbles. Please place comments within the bubble with the changes you do not agree when sending the label back. The changes you agree with, please accept them and state in the bubble “ To FDA: changes accepted.” Please follow the regulatory format and changes to your package insert.

Please do not submit anything to the NDA until we have agreed on a final label.

Please respond by **May 11, 2016**.

Please acknowledge the receipt of this email.

Thanks,  
Meghna M. Jairath, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II (ODEII)

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MEGHNA M JAIRATH  
05/05/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** IR NDA 208325  
**Date:** Wednesday, May 04, 2016 11:50:38 AM

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## Information Request

**NDA 208325**

**Drug Name: etelcalcetide injection**

**Proposed Indication: treat Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis**

**Applicant: KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc**

Hello,

Please submit a response to our comments below immediately.

- 1. With regards to the case of liver injury in subject 22921002001 in study 20130213 the case narrative in the study report states that he was given a rechallenge with a lower dose which was discontinued because of worsening liver tests, but the narrative in the ISS for this subject mentions the drug was discontinued without a rechallenge test. Can you confirm that this patient had a positive rechallenge test with respect to liver testing?*
- 2. Also subject 36066073001 from study 20120360 also had a positive rechallenge test so the drug was discontinued. Correct?*
- 3. Neither of these cases was mentioned in your analysis of Liver Tests. Where there any other subjects in your safety database that had positive rechallenge liver tests after etelcalcetide was initially discontinued for elevations in either transaminases or total bilirubin?*
- 4. Is there a reason why we should not consider positive rechallenge tests as evidence of potential liver toxicity?*
- 5. Given the large distribution of etelcalcetide to the liver in the nonclinical studies is there any reason for concern with the use of this drug in subjects with active liver disease?*

Please acknowledge the receipt of this email.

Please respond by EOB, May 6, 2016.

Thanks,

Meghna

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MEGHNA M JAIRATH  
05/05/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** IR NDA 208325  
**Date:** Monday, April 25, 2016 12:35:22 PM

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## Information Request

**NDA 208325**

**Drug Name: etelcalcetide injection**

**Proposed Indication: treat Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis**

**Applicant: KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.**

Hello,

Please submit a response to our comments below immediately.

*With regards to subject 23066026008, what was the reason for the “sponsor’s decision” for early termination at week 17 in the ADSL dataset? The narrative mentions that the subject had coffee ground vomit at an unknown date and nausea and abdominal distension that lasted one week. Was that while the patient was still receiving etelcalcetide? Specifically did this subject have evidence of GI hemorrhage while on etelcalcetide?*

Please acknowledge the receipt of this email.

Please respond by EOB, April 26, 2016.

Thanks,  
Meghna

Meghna M. Jairath, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II (ODEII)/ Office of New Drugs (OND)/ Center of Drug Evaluation and Research (CDER)  
[Meghna.jairath@fda.hhs.gov](mailto:Meghna.jairath@fda.hhs.gov)  
301-796-4267

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/s/  
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MEGHNA M JAIRATH  
04/26/2016

## Executive CAC

**Date of Meeting: March 1, 2016**

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair  
Paul Brown, Ph.D., OND IO, Member  
Tim McGovern, Ph.D., ONDIO, Member  
Bayo Lanionu, Ph.D., DMIP, Alternate Member  
Lee Elmore, Ph.D., DMEP, Acting Supervisory Pharmacologist  
Miyun Tsai-Turton, Ph.D., M.S., DMEP, Presenting Reviewer

**The following information reflects a brief summary of the Committee discussion and its recommendations.**

**NDA #:** 208325

**Drug Name:** Etelcalcetide

**Sponsor:** Amgen

**Background:** AMG 416 (etelcalcetide) is a synthetic peptide that functions as an allosteric activator of the calcium-sensing receptor (CaSR) in the parathyroid gland. AMG 416 is designed to treat secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis. AMG 416 is intended for chronic administration in patients by the intravenous route three times per week as a bolus dose at the end of hemodialysis.

The carcinogenicity of AMG416 was evaluated in 2-year rat and 6-month transgenic rasH2 mouse studies with subcutaneous injection. A saline control was included in both carcinogenicity studies to account for effects of the vehicle. The vehicle consisted of 0.27% sodium succinate dibasic hexahydrate (2.7 g/L), 2% D-mannitol (20 g/L), 1% glycine (10 g/L), 1% trehalose (10 g/L), and 0.9% benzyl alcohol (9 g/L) in sterile water for injection. AMG416 is intended for IV administration in humans, but was administered subcutaneously in the carcinogenicity studies; the vehicle utilized in the carcinogenicity studies differs substantially from the product intended for marketing.

**Rat Carcinogenicity Study:** Sprague-Dawley rats (65/sex/group) were dosed by once daily subcutaneous injection with test article (AMG416 - 0.2, 0.4, 0.8, and 1.6 mg/kg/day) or control (saline or vehicle). Dose selections were based on mortality and reduction in body weight gain observed in a 3 month dose range-finding study. The Executive CAC concurred with doses of 0.2, 0.4, and 0.8 mg/kg/day, but did not concur with the highest dose of 1.6 mg/kg/day. **Findings:** There were no AMG 416-related tumors identified in males and females. Females in the 0.8 and 1.6 mg/kg/day dose groups were terminated during Week 89 when the number of survivors reached 15 animals. All male and remaining female groups were terminated during Week 92 when the number in the vehicle control group reached 20 animals.

**Tg.rasH2 Mouse Carcinogenicity Study:** Transgenic rasH2 mice (25/sex/group) were dosed by once daily subcutaneous injection for 26 weeks with test article (AMG416 - 0.375, 0.75 and 1.5 mg/kg/day, males; 0.30, 1.0 and 3 mg/kg/day, females) or control (saline, vehicle) or positive control (3 doses of urethane by the IP route). Dose selections were based on to mortality and adverse clinical signs in a 1 month dose range-finding study in wild-type mice. The Executive CAC concurred with doses on May 8, 2013. **Findings:** There were no AMG 416-related tumors identified in males and females. The positive control (urethane) group showed the expected profile and incidence of tumors for this strain of mice administered three times by the IP route.

## **Executive CAC Recommendations and Conclusions:**

### **Rat:**

- The Committee agreed that the study was acceptable despite the earlier termination of the study in males and females due to decreased survival in the vehicle control.
- The Committee concurred that there were no drug-related neoplasms in the study.

### **Tg.rasH2 mouse:**

- The Committee agreed that the study was acceptable, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the study.

Abigail Jacobs, Ph.D.  
Acting Chair, Executive CAC

cc:\n  
/Division File, DMEP  
/Lee Elmore, Ph.D., Acting Pharm/Tox Supervisor, DMEP  
/Miyun Tsai-Turton, Ph.D., M.P.H., Reviewer, DMEP  
/Meghna Jairath, Project Manager, DMEP  
/Adele Seifried, OND IO

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/s/  
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ADELE S SEIFRIED  
03/03/2016

ABIGAIL C JACOBS  
03/03/2016



NDA 208325

**MID-CYCLE COMMUNICATION**

KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen, Inc.  
Attention: Jennifer Steinbock  
Manager, Regulatory Affairs  
One Amgen Center Drive; Mail Stop: 17-2-A  
Thousand Oaks, CA 91320-1799

Dear Ms. Steinbock:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for etelcalcetide injection.

We also refer to the teleconference between representatives of your firm and the FDA on February 8, 2016. 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) 796-4267.

Sincerely,

*{See appended electronic signature page}*

Meghna M. Jairath, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
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:** February 8, 2016, from 12:00 pm to 1:00 pm

**Application Number:** NDA 208325

**Product Name:** Etelcalcetide injection

**Indication:** Treatment of secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis

**Applicant Name:** KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen, Inc.

**Meeting Chair:** Marina Zemskova, M.D, Clinical Team Leader

**Meeting Recorder:** Meghna Jairath, Pharm.D, Regulatory Project Manager

**FDA ATTENDEES**

*Division of Metabolism and Endocrinology Products*

Marina Zemskova, M.D.	Clinical Team Leader
William (Bill) Lubas, M.D.	Clinical Reviewer
Julie Van der Waag, M.P.H.	Chief, Project Management Staff
Meghna M. Jairath, Pharm.D.	Regulatory Project Manager

**APPLICANT ATTENDEES**

Monica Batra, M.S.	Director, Regulatory Affairs
Laura Bloss, Ph.D.	Executive Director, Regulatory Affairs
Sunfa Cheng, M.D.	Medical Director, Global Development
Mark Fielden, Ph.D.	Scientific Director, Comparative Biology and Safety
Cesar Medina	Senior Manager, Regulatory Affairs CMC
Michael Serenko, M.D.	Medical Director, Global Safety
Jennifer Steinbock, M.A.	RAC, Manager, Regulatory Affairs
Yan Sun, M.Sc.	Senior Manager, Global Biostatistical Science
Raju Subramanian, Ph.D.	Scientific Director, Pharmacokinetics and Drug Metabolism
John Sullivan, M.D.	Executive Medical Director, Global Safety
Amy Xia, Ph.D.	Executive Director, Global Biostatistical Science

Cindy McDonald-Everett, B.A. Global Product General Manager

**EASTERN RESEARCH GROUP ATTENDEE**

(b) (4)

Independent Assessor

**1.0 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.

**2.0 SIGNIFICANT ISSUES**

We have no significant issues that have been identified to date.

**3.0 INFORMATION REQUESTS**

*Sponsor stated that they will provide the responses to all information requests by the end of February. FDA had no further comment.*

**Clinical**

1. With the greater efficacy, as evidenced by the larger number of subjects with mean iPTH at the EAP of < 130pg/mL (2xULN) and bone-specific Alkaline Phosphatase (BSAP) levels < 15mcg/L, comparing Etelcalcetide to Sensipar in CSR 20120360, please justify that a greater risk of adynamic bone disease that adversely impacts the benefit-risk assessment is not expected in Etelcalcetide group. We refer you the publication of Behets et al. 2015 where two subjects with similar laboratory profiles of low serum iPTH and BSAP levels were diagnosed with adynamic bone disease.
2. Provide how many patients had vitamin D analogs doses increased during the phase 3 studies. Submit a dataset with the subject IDs (USUBJID) and the study day (ADY) when the doses were increased. Perform a subgroup analysis on the primary endpoint for patients with and without increases in vitamin D analog doses during the study.
3. Provide how many patients had increase in doses of calcium supplements during the phase 3 studies. Submit a dataset with the subject IDs (USUBJID), the study day (ADY) the calcium supplements were increased and the dose of investigational drug at the time of the increase. Justify if increase in calcium supplements doses minimized the observed risk of hypocalcemia.

- Explain efficacy differences in subgroups:
  - a. North American vs. rest of the world
  - b. Blacks vs. whites
  - c. Calcium phosphate binders
  - d. Calcium concentration in dialysate
  - e. Baseline Vitamin D sterol use

## **Clinical Pharmacology**

4. Submit complete bioanalytical report(s) for the study 20130139 titled “A Double-Blind, Randomized, Placebo-Controlled Study to Assess the Safety and Tolerability of Single Ascending Doses of KAI-4169 in Hemodialysis Subjects with Secondary Hyperparathyroidism”.
5. Incurred sample reanalysis for study 20130107 titled “A Double-Blind, Randomized, Placebo-Controlled, Rising Single Intravenous Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of KAI-4169 in Healthy Male Volunteers”, showed that approximately 50% of the samples reanalyzed have differences in value of greater than 20% of the original value. In your bioanalytical report you have provided investigational summary and attributed this to matrix related instability of the plasma samples. Please provide complete report of this investigation with data on QC samples in different scenarios that you tested in your investigation.
6. In your analysis of study samples from Phase 2 and Phase 3 studies, you identified that most of the runs have carryover effect from one sample to another. You have identified a carryover on each day by injecting a double blank sample after ULOQ sample. However, you should also provide information for the following:
  - a. In your analysis, each day the carryover factor (COF) was calculated by dividing the peak area ratio of the blank IS sample by the peak area ratio of the ULOQ point for all the runs that had carryover effect. Then the COF was used to calculate the carryover effect from one sample to another. Provide if the COF was similar or different for entire concentration range of your standard curve.
  - b. In your report the carryover factor seems highly variable from one batch to another. Provide further information if the COF was similar or different with in the same batch. Also, justify if this COF was similar or different between several batches that were analyzed on the same day.

## **4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

No major safety concerns have been identified at this time and there is currently no need for a REMS.

## **5.0 ADVISORY COMMITTEE MEETING**

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

## **6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES**

At this time, the Late Cycle Meeting will occur on June 1, 2016. The format of this meeting will be face-to-face unless the applicant decides to change the format to a teleconference. FDA will inform the applicant should this date change.

The projected date that the proposed labeling for this application will be sent to the Applicant is May 4, 2016.

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/s/  
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MEGHNA M JAIRATH  
02/17/2016



NDA 208325

**MID-CYCLE COMMUNICATION**

KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen, Inc.  
Attention: Jennifer Steinbock  
Manager, Regulatory Affairs  
One Amgen Center Drive; Mail Stop: 17-2-A  
Thousand Oaks, CA 91320-1799

Dear Ms. Steinbock:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for etelcalcetide injection.

We also refer to the teleconference between representatives of your firm and the FDA on February 8, 2016. 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) 796-4267.

Sincerely,

*{See appended electronic signature page}*

Meghna M. Jairath, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure: Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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MID-CYCLE COMMUNICATION

**Meeting Date and Time:** February 8, 2016 from 12:00 pm to 1:00 pm

**Application Number:** 208325

**Product Name:** Etelcalcetide injection

**Indication:** Treat Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis

**Applicant Name:** KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen, Inc.

**Meeting Chair:** Marina Zemskova, M.D, Clinical Team Leader

**Meeting Recorder:** Meghna Jairath, Pharm.D, Regulatory Project Manager

**FDA ATTENDEES**

*Division of Metabolism and Endocrinology Products*

Jean-Marc Guettier, M.D.	Director
Marina Zemskova, M.D.	Clinical Team Leader
William (Bill) Lubas, M.D.	Clinical Reviewer
Pamela Lucarelli, B.S.	Chief, Project Management Staff
Meghna M. Jairath, Pharm.D.	Regulatory Project Manager

**APPLICANT ATTENDEES**

Monica Batra, M.S.	Director, Regulatory Affairs
Laura Bloss, Ph.D.	Executive Director, Regulatory Affairs
Sunfa Cheng, M.D.	Medical Director, Global Development
Mark Fielden, Ph.D.	Scientific Director, Comparative Biology and Safety
Cesar Medina	Senior Manager, Regulatory Affairs CMC
Michael Serenko, M.D.	Medical Director, Global Safety
Jennifer Steinbock, M.A.	RAC, Manager, Regulatory Affairs
Yan Sun, M.Sc.	Senior Manager, Global Biostatistical Science
Raju Subramanian, Ph.D.	Scientific Director, Pharmacokinetics and Drug Metabolism
John Sullivan, M.D.	Executive Medical Director, Global Safety

Benjamin Wu, Ph.D.

Senior Scientist, Clinical Pharmacology, Modeling and  
Simulation

Amy Xia, Ph.D.

Executive Director, Global Biostatistical Science

## 1.0 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.

## 2.0 SIGNIFICANT ISSUES

We have no significant issues that have been identified to date.

## 3.0 INFORMATION REQUESTS

### Clinical

1. With the greater efficacy, as evidenced by the larger number of subjects with mean iPTH at the EAP of < 130pg/mL (2xULN) and bone-specific AlkPhos (BSAP) levels < 15mcg/L, comparing Etelcalcetide to Sensipar in CSR 20120360, please justify that a greater risk of adynamic bone disease that adversely impacts the Benefit-Risk assessment is not expected in Etelcalcetide group. We refer you the publication of Behets et al. 2015 where two subjects with similar laboratory profiles of low serum iPTH and BSAP levels were diagnosed with adynamic bone disease.
2. How many pts had vitamin D analogs doses increased during the phase 3 studies? Submit a dataset with the subject IDs (USUBJID) and the study day (ADY) when the doses were increased. Perform a subgroup analysis on the primary endpoint for patients with and without increases in vitamin D analog doses during the study.
3. How many pts had increase in doses of calcium supplements during the phase 3 studies? Submit a dataset with the subject IDs (USUBJID), the study day (ADY) the calcium supplements were increased and the dose of investigational drug at the time of the increase. Justify if increase in calcium supplements doses minimized the observed risk of hypocalcemia.
  - Explain efficacy differences in subgroups:
    - a. North American vs. rest of the world
    - b. Blacks vs. whites

- c. Calcium phosphate binders
- d. Calcium concentration in dialysate
- e. Baseline Vitamin D sterol use

### **Clinical Pharmacology**

4. Submit complete bioanalytical report(s) for the study 20130139 titled "A Double-Blind, Randomized, Placebo-Controlled Study to Assess the Safety and Tolerability of Single Ascending Doses of KAI-4169 in Hemodialysis Subjects with Secondary Hyperparathyroidism".
5. Incurred sample reanalysis for study 20130107 titled "A Double-Blind, Randomized, Placebo-Controlled, Rising Single Intravenous Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of KAI-4169 in Healthy Male Volunteers", showed that approximately 50% of the samples reanalyzed have differences in value of greater than 20% of the original value. In your bioanalytical report you have provided investigational summary and attributed this to matrix related instability of the plasma samples. Please provide complete report of this investigation with data on QC samples in different scenarios that you tested in your investigation.
6. In your analysis of study samples from Phase 2 and Phase 3 studies, you identified that most of the runs have carryover effect from one sample to another. You have identified a carryover on each day by injecting a double blank sample after ULOQ sample. However, you should also provide information for the following:
  - a. In your analysis, each day the carryover factor (COF) was calculated by dividing the peak area ratio of the blank IS sample by the peak area ratio of the ULOQ point for all the runs that had carryover effect. Then the COF was used to calculate the carryover effect from one sample to another. Provide if the COF was similar or different for entire concentration range of your standard curve.
  - b. In your report the carryover factor seems highly variable from one batch to another. Provide further information if the COF was similar or different with in the same batch. Also, justify if this COF was similar or different between several batches that were analyzed on the same day.

#### **4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

No major safety concerns have been identified at this time and there is currently no need for a REMS.

#### **5.0 ADVISORY COMMITTEE MEETING**

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

## **6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES**

At this time, the Late Cycle Meeting will occur on June 1, 2016. The format of this meeting will be face-to-face unless the applicant decides to change the format to a teleconference. FDA will inform the applicant should this date change.

The projected date that the proposed labeling for this application will be sent to the Applicant is May 4, 2016.

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/s/  
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MEGHNA M JAIRATH  
02/03/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** IR NDA 208325  
**Date:** Thursday, January 21, 2016 9:34:14 AM  
**Attachments:** [Subject\\_36066013011.pdf](#)

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## Information Request

### NDA 208325

**Drug Name:** etelcalcetide injection

**Proposed Indication:** treat Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis

**Applicant:** KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.

Hello,

Please submit a response to our comments below immediately.

*We have an FDA field investigator currently at one of the sites for Protocol 20120360 who is having a hard time comparing the source e-diary file to the data line listings submitted in the application.*

*Looking at Listing 16.88.9 with the “Days of Nausea/Vomiting” data, can you explain how the values were calculated?*

*We believe the Episodes of Vomiting/Week are adjusted for missed entries but we are unable to reach the reported value. We are attaching an example e-diary file for Subject 11. If you keyword search for “In the past 24 hours” and look at the entries for 11/30-12/6, you get a total of 35 events over 6 days. If you average that over the seven days, the total is 40.83. The table says 46.667, which would be that number averaged over 8 days. Similarly, there are 39 events for 12/7-12 (a six day time period) but the table states 40.600.*

*For Subject 017, can you explain how you arrived at 2.8 days of nausea/vomiting at week 6? There is nausea (severity = 4) and vomiting (3 times) only on 12/19. No entry was made on 12/18. All other days for 12/11-19 were = 0/0.*

Please acknowledge the receipt of this email.

Please respond **immediately**.

Thanks,  
Meghna

Meghna M. Jairath, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II (ODEII)/ Office of New Drugs (OND)/ Center of Drug Evaluation and Research (CDER)  
[Meghna.jairath@fda.hhs.gov](mailto:Meghna.jairath@fda.hhs.gov)  
301-796-4267

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/s/  
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MEGHNA M JAIRATH  
01/21/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** IR NDA 208325  
**Date:** Friday, January 08, 2016 3:02:45 PM  
**Importance:** High

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## Information Request

### NDA 208325

**Drug Name:** etelcalcetide injection

**Proposed Indication:** treat Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis

**Applicant:** KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.

Hello,

Please submit a response to our comments below.

1. Please provide or direct us to the location of the following:

- The programs used for multiple imputation (including seed number), for the non-inferiority analysis (using Koch method) for the primary analysis (<30% reduction in iPTH) for study 21020360.
  - We do note that you have sent “Sample Code for Primary Endpoint” in Appendix B in files such as adrg.pdf (“Analysis Data Reviewer’s Guide”) for study 20120360. These files also give useful information for analysis data sets and how flags are used. However some programming is not given but only described. Also some variables are not included in the dataset referred to in the code.
- The dataset which contains every variable needed to do the analysis in #1 above.
- The programs that generate the randomized treatment assignments, including seed number.
- If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.
- The SAS programs for pooled data for safety.

2. Submit data files and scripts described below.

- Script and control stream files used for simulations included in Study Report 119344. Submit source data for each simulation accordingly.
- All code files and control stream files used for the external validation and the final covariate analysis for PKPD. Submit the test dataset for the external validation and the combined dataset used for the final covariate analysis.

Please acknowledge the receipt of this email.

Please respond by **January 14, 2016**.

Thanks,  
Meghna

[Meghna M. Jairath, Pharm.D.](#)

Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II (ODEII)/ Office of New Drugs (OND)/ Center of Drug Evaluation  
and Research (CDER)  
[Meghna.jairath@fda.hhs.gov](mailto:Meghna.jairath@fda.hhs.gov)  
301-796-4267

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/s/  
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MEGHNA M JAIRATH  
01/08/2016

**From:** [Jairath, Meghna](#)  
**To:** [Steinbock, Jennifer \(jsteinbo@amgen.com\)](mailto:jsteinbo@amgen.com)  
**Subject:** IR NDA 208325  
**Date:** Monday, December 21, 2015 1:39:12 PM  
**Importance:** High

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## Information Request

**NDA 208325**

**Drug Name: etelcalcetide injection**

**Proposed Indication: treat Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis**

**Applicant: KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.**

Hello,  
Please submit a response to our comment below.

*Please submit all data to the sites, immediately.*

Please acknowledge the receipt of this email.  
Please respond by December 22, 2015.

Thanks,  
Meghna

Meghna M. Jairath, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II (ODEII)/ Office of New Drugs (OND)/ Center of Drug Evaluation and Research (CDER)  
[Meghna.jairath@fda.hhs.gov](mailto:Meghna.jairath@fda.hhs.gov)  
301-796-4267

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MEGHNA M JAIRATH  
01/04/2016



NDA 208325

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.  
One Amgen Center Drive; Mail Stop: 17-1-B  
Thousand Oaks, CA 91320-1799

ATTENTION: Cecile Savarin, PhD, MS, RAC  
Senior Manager, Regulatory Affairs

Dear Dr. Savarin:

Please refer to your New Drug Application (NDA) dated and received August 24, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Etelcalcetide Injection, 2.5 mg, 5 mg, and 10 mg.

We also refer to your correspondence, dated and received August 25, 2015, requesting review of your proposed proprietary name, Parsabiv.

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

If any of the proposed product characteristics as stated in your August 25, 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 Deveonne Hamilton-Stokes, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2253. For any other information regarding this application, contact Meghna Jairath, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4267.

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/

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DEVEONNE G HAMILTON-STOKES  
11/18/2015

TODD D BRIDGES  
11/18/2015



NDA 208325

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen, Inc.  
Attention: Cecile Savarin, Ph.D., M.S., RAC  
Senior Manager, Regulatory Affairs  
One Amgen Center Drive; Mail Stop: 17-1-B  
Thousand Oaks, CA 91320-1799

Dear Dr. Savarin:

Please refer to your New Drug Application (NDA) dated and received on August 24, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for etelcalcetide injection.

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 **Standard**. Therefore, the user fee goal date is **August 24, 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>).

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 commitment requests by **May 4, 2016**.

In addition, the planned date for our internal mid-cycle review meeting is **February 8, 2016**. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Chemistry, Manufacturing, and Controls (CMC)

1. Clarify if there is a type III DMF for the information on the 13-mm stopper by (b) (4) and if yes, provide a letter of authorization for us to access this DMF.
2. Regarding the (b) (4) powder formulation used in Phase 3 studies and the commercial solution formulation, submit the comparison of (b) (4) (b) (4) will not affect the In Vivo PK performance and clinical outcome (efficacy/safety).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

**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.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by November 27, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **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). 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 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.

### **REQUIRED PEDIATRIC ASSESSMENTS**

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.

We acknowledge receipt of your requests for a partial waiver and partial deferral of pediatric studies for this application. Once we have reviewed your requests, we will notify you if the partial waiver and partial deferral requests are denied.

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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JENNIFER R PIPPINS

11/06/2015

Signed on behalf of Dr. Guettier.

**From:** [Jairath, Meghna](#)  
**To:** [Savarin, Cecile \(csavarin@amgen.com\)](mailto:csavarin@amgen.com)  
**Subject:** NDA 208325 IR  
**Date:** Friday, October 09, 2015 2:24:45 PM

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## Information Request

**NDA 208325**

**Drug Name: etelcalcetide injection**

**Proposed Indication: treat Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis**

**Applicant: KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.**

Hello,

Please submit a response to our comment below.

*Please provide a derived dataset containing the efficacy endpoints and every important baseline factor (including age, sex, race, and geographical region) for each subject that is one line per subject. Please also provide the SAS program used to create the derived dataset.*

Please acknowledge the receipt of this email.

Please respond by October 16, 2015.

Thanks,  
Meghna

Meghna M. Jairath, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II (ODEII)/ Office of New Drugs (OND)/ Center of Drug Evaluation and Research (CDER)  
[Meghna.jairath@fda.hhs.gov](mailto:Meghna.jairath@fda.hhs.gov)  
301-796-4267

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/s/  
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MEGHNA M JAIRATH  
10/14/2015



NDA 208325

**NDA ACKNOWLEDGMENT**

KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen, Inc.  
Attention: Cecile Savarin, Ph.D., M.S., RAC  
Senior Manager, Regulatory Affairs  
One Amgen Center Drive; Mail Stop: 17-1-B  
Thousand Oaks, CA 91320-1799

Dear Dr. Savarin:

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

Name of Drug Product: **Etelcalcetide Injection**

Date of Application: **August 24, 2015**

Date of Receipt: **August 24, 2015**

Our Reference Number: **NDA 208325**

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 **October 23, 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 21 CFR 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).

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 Metabolism and Endocrinology 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](mailto: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, at (301) 796-4267.

Sincerely,

*{See appended electronic signature page}*

Meghna M. Jairath, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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MEGHNA M JAIRATH  
09/03/2015



IND 109773

**MEETING PRELIMINARY COMMENTS**

KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen, Inc.  
Attention: Cecile Savarin, Ph.D., M.S., RAC  
Senior Manager, Regulatory Affairs  
One Amgen Center Drive; Mail Stop: 17-1-B  
Thousand Oaks, CA 91320-1799

Dear Dr. Savarin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for etelcalcetide intravenous.

We also refer to your correspondence, dated and received, March 9, 2015, requesting a meeting to discuss the development program for etelcalcetide.

Our preliminary responses to your meeting questions are enclosed. You should provide me a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

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

If you have any questions, call me, at (301) 796-4267.

Sincerely,

*{See appended electronic signature page}*

Meghna M. Jairath, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** B

**Meeting Category:** Pre-NDA

**Meeting Date and Time:** May 13, 2015 from 1:00 pm to 2:00 pm

**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1315  
Silver Spring, Maryland 20903

**Application Number:** IND 109773

**Product Name:** etelcalcetide intravenous

**Indication:** treatment of secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD) on hemodialysis therapy

**Sponsor/Applicant Name:** KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen, Inc.

**Introduction:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 13, 2015, from 1:00 pm to 2:00 pm between Amgen and the Division of Metabolism and Endocrinology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact Meghna M. Jairath, Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

## BACKGROUND

Etelcalcetide is being formulated for intravenous (IV) administration for the treatment of secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis therapy.

Secondary HPT is a disorder characterized by parathyroid gland hyperplasia and increased concentrations of circulating parathyroid hormone (PTH). Calcium-sensing receptor (CaSR) is the principal regulator of PTH secretion in parathyroid tissue. Etelcalcetide is an allosteric activator of the CaSR, thereby lowering serum PTH levels upon binding to this receptor.

On July 9, 2012, FDA met with Amgen for an End-Of-Phase 2 (EOP2) meeting.

FDA issued a correspondence dated December 11, 2014, containing an agreed initial Pediatric Study Plan (PSP).

On March 9, 2015, the sponsor submitted a Pre-NDA meeting request.

Amgen plans on submitting a New Drug Application (NDA) in August 2015.

## DISCUSSION

Repeated below in regular text are Amgen's question followed by FDA's response written in **bold text**.

**Sponsor Question 1:** An overview of the clinical studies to be included in the marketing authorization application, including the status and type of report to be provided for each study, is presented in Appendix 6. Amgen's position is that the proposed data package, primarily the 2 pivotal phase 3 placebo-controlled studies and the active-controlled study, and the current plan for integration of the clinical study data (Section 8.5 for efficacy and Section 8.6 for safety) support the proposed indication. Does the Agency agree that the proposed data package constitutes a complete NDA?

**FDA Preliminary Comment:** Yes, we agree there is sufficient data in the proposed data package to support the NDA submission. However, whether the results of the two pivotal phase 3 placebo-controlled studies and the one active-controlled study will support the proposed indication will be a review issue.

Does the Agency require any clarifications regarding Amgen's approach for inclusion of information from completed and ongoing studies in the NDA submission?

**FDA Preliminary Comment:** No.

**Sponsor Question 2:** The plan for the 120-day safety update is presented in Section 8.8. Does the Agency agree to the proposed structure, content, and analysis for the 120-day safety update?

**FDA Preliminary Comment:** While we accept that datasets and case report forms will not be provided as part of this safety update, we ask that narratives be included for all deaths, serious adverse reactions or adverse reactions leading to discontinuation, with as much available information as possible, to permit a clinical assessment of causality.

Does the Agency agree that hyperlinked case report form PDFs will not be included as part of the 120-day safety update for Study 20120231 or Study 20130213?

**FDA Preliminary Comment:** This plan is acceptable.

**Sponsor Question 3:** Based upon the available safety database from the clinical development program, Amgen considers routine risk minimization and pharmacovigilance as described in Section 8.9 to be appropriate to communicate and mitigate the risks of AMG 416. Does the Agency agree that a REMS will not be required for AMG 416?

**FDA Preliminary Comment:** At this time, we have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of AMG416 outweigh the risks, and if it is necessary, what the required REMS elements will be. The NDA submission does not need to include a REMS proposal. However, we remind you that the need for a REMS will be determined during the review of the application.

**Sponsor Question 4:** As a follow-up to the Type C Structure and Format meeting written responses received April 11, 2014 (Reference ID: 3488622), Amgen plans to provide case report forms from phase 2 and phase 3 studies supporting the NDA submission where Amgen is the sponsor (and excluding phase 1) for subjects who died on study or within 30 days from last dose of investigational product, or who discontinued from the investigational product because of adverse events. The case report forms will be referenced under the appropriate study's tagging file to which they belong, organized by study and site as per the specifications and tagged as "case report form." Does the Agency agree with the proposal?

**FDA Preliminary Comment:** This plan is acceptable.

**Sponsor Question 5:** Amgen plans to include safety narratives (Council for International Organizations of Medical Sciences [CIOMS]) for all on-treatment deaths and serious adverse events. In addition, for AMG 416-treated subjects, case summaries for all on-treatment deaths and treatment-related serious adverse events as well as adverse events resulting in treatment discontinuation will be provided in Module 5. Does the Agency agree with the proposal for inclusion of these safety narratives and case summaries?

**FDA Preliminary Comment:** We request narratives for all deaths, serious adverse events and discontinuations in your clinical program. We also ask for narratives on subjects with

symptomatic hypocalcemia even if they were not coded as serious adverse events, focusing on presenting symptoms, ECG data if available, concomitant medications or risk factors (e.g. recent illness) that could be contributing to the symptoms, and dose adjustments (e.g. medications withheld, restarted at lower dose or discontinued).

**Sponsor Question 6:** Does the Agency agree that the biopharmaceutics package as summarized in Section 8.2 and clinical pharmacology studies summarized in Section 8.3 **Error! Reference source not found.** constitute a complete package that supports the registration of AMG 416 and the proposed commercial drug product?

**FDA Preliminary Comment:** We agree that the proposed Clinical Pharmacology studies support filing of your NDA. The acceptability of these studies will be a review issue. In your NDA submission please submit the pharmacokinetic (PK) and pharmacodynamic (PD) datasets including individual concentration vs. time and corresponding PK and PD parameters by patient as SAS transport files. The following are the general expectations for submitting pharmacometric data and models:

- All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).
- A model development decision tree and/or table which gives an overview of modeling steps.
- For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

**Sponsor Question 7:** In support of AMG 416 phase 3 studies, Amgen had proposed both

(b) (4)

(b) (4)

**FDA Preliminary Comment: No.**

(b) (4)

(b) (4)

**Sponsor Question 8: Proposed Text to be Included in the Label**

(b) (4)

(b) (4)

**Sponsor Question 9:** As a follow-up to the Type C Structure and Format meeting written responses received April 11, 2014 (Reference ID: 3488622), an updated Data Standardization Plan (DSP) is included in Appendix 1. The following points are a list of updates to the DSP:

a. Addition of the following datasets:

- DA, OI to the list of SDTM datasets
- ADCMSP, ADFI, ADQS, ADTTE to the list of ADaM datasets

b. Addition of 2 tables of programming deliverables to display:

- the studies that will be provided in Clinical Data Interchange Standards Consortium (CDISC) format
- the studies that will be provided in legacy format

Does the Agency agree that the changes in the DSP are acceptable and sufficient for the reviewers' needs?

**FDA Preliminary Comment: The changes in the DSP appear to be acceptable, but the SAS program should also be provided for the active-controlled study 20120360.**

**Sponsor Question 10:** For the bioresearch monitoring site selection process, Amgen plans to



(b) (4)

**FDA Preliminary Comment: No.**

(b) (4)



(b) (4)

**Question 11:** A table of contents for module 1 is provided in Appendix 3? Does the Agency agree with the proposed content of Module 1?

**FDA Preliminary Comment: Yes. This plan is acceptable.**

### **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our March 26, 2015 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at  
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>3.0

### **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 (iPSP) 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. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the 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](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* 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 related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MEGHNA M JAIRATH  
05/08/2015



**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**DATE:** 17 December 2012

**TO:** Rebecca McKnight  
Regulatory Health Project Manager  
CDER/OPS/ONDQA

**FROM:** Jessica G. Cole, PhD  
Review Microbiologist  
CDER/OPS/New Drug Microbiology Staff  
(301) 796-5148

**THROUGH:** Bryan Riley, PhD  
Microbiology Team Leader  
CDER/OPS/New Drug Microbiology Staff

**SUBJECT:** IND: 109,773  
Submission Date: 15 October 2012  
Drug Product: AMG 416 (KAI-4169)  
Applicant: KAI Pharmaceuticals, Inc

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A product quality microbiology review of the End of Phase 2 (EOP2) meeting package for IND 109,773 is complete. AMG-416 is an 8 amino acid synthetic peptide agonist of the human calcium-sensing receptor. AMG-416 is being developed as an intravenous drug product to treat secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis. The drug product is administered in the dialysis tubing into whole blood at the end of the hemodialysis procedure. This meeting package requests feedback on the CMC development and an EOP2 clinical meeting was held on 09 July 2012. (b) (4)

(b) (4) the applicant plans to commercialize a ready to use, single use, 10 mg/vial liquid formulation. The applicant states that the manufacturing information for the liquid product was submitted to the IND on 20 April 2012. The drug substance will be manufactured by (b) (4)

(b) (4)  
The drug product is (b) (4)

(b) (4) ompendial methods were referenced for drug substance and drug product testing. There were two questions regarding the adequacy of the proposed liquid product and specifications. No product quality microbiology response was required but the following comments should be included in the meeting package response. After

**MEMORANDUM**

receipt of the agency's preliminary comments Amgen canceled the sponsor meeting scheduled for 17 December 2012 and committed to investigate the use of (b) (4)

**Microbiology Comments:**

While we recognize that the proposed drug product is a peptide we encourage you to evaluate the potential for (b) (4)

We note that (b) (4) in AMG 416 appeared to be (b) (4) If at the time of NDA submission you propose to manufacture using (b) (4)

We encourage you to evaluate (b) (4) For additional information we refer you to the (b) (4)

(b) (4)

(b) (4)

**END**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JESSICA COLE  
12/17/2012

BRYAN S RILEY  
12/17/2012  
I concur.



IND 109773

**MEETING MINUTES**

KAI Pharmaceuticals, Inc.  
Attention: Gregory Bell, M.D.  
Senior Vice President of Development and Chief Medical Officer  
270 Littlefield Avenue  
South San Francisco, CA 94080

Dear Dr. Bell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for KAI-4169 intravenous bolus injection.

We also refer to the End-of-Phase 2 (EOP2) meeting between representatives of your firm and the FDA on July 9, 2012. The purpose of the meeting was to discuss your global Phase 3 clinical development program for KAI-4169 intravenous bolus.

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

If you have any questions, call me at (301) 796-4267.

Sincerely,

*{See appended electronic signature page}*

Meghna M. Jairath, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
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:** End of Phase 2

**Meeting Date and Time:** July 9, 2012  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1315  
Silver Spring, Maryland 20903

**Application Number:** IND 109773  
**Product Name:** KAI-4169 intravenous bolus  
**Indication:** (1) for the treatment of secondary hyperparathyroidism (SHPT) in CKD patients on hemodialysis (b) (4)  
(b) (4)

**Sponsor/Applicant Name:** KAI Pharmaceuticals, Inc.

**Meeting Chair:** Mary Parks, M.D.  
**Meeting Recorder:** Meghna M. Jairath, Pharm.D.

**FDA ATTENDEES**

**Division of Metabolism and Endocrinology Products (DMEP)**

Mary Parks, M.D., Division Director  
Meghna M. Jairath, Pharm.D., Regulatory Project Manager  
Dragos Roman, M.D., Clinical Team Leader  
William (Bill) Lubas, M.D., Clinical Reviewer  
Karen Davis-Bruno, Ph.D., Pharmacology/Toxicology Team Leader

**Division of Clinical Pharmacology II (DCP II), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)**

Sang Chung, Ph.D., Clinical Pharmacology Reviewer  
Immo Zadezensky, Ph.D., Clinical Pharmacology Team Leader

**Division of Biometrics II (DB II), Office of Biostatistics**

Todd Sahlroot, Ph.D., Statistical Team Leader  
Lee Ping Pian, Ph.D., Biometric reviewer

Meeting Minutes for End of Phase 2  
July 9, 2012

**Division of New Drug Assessment III, Office of New Drug Quality Assessment  
(ONDQA), Office of Pharmaceutical Sciences (OPS)**

Martin Haber, Ph.D., Chemistry Reviewer

Denise Miller, Ph.D., Microbiology Reviewer

**Division of Cardiovascular and Renal Products, QT Interdisciplinary Review Team**

Monica L. Fiszman M.D., Ph.D., Clinical Reviewer

Kevin Krudys, M.D.

**Office of Surveillance and Epidemiology**

Ermias Zerislassie, Pharm.D., LCDR USPHS, Regulatory Project Manager

**SPONSOR ATTENDEES**

Gregory Bell, M.D.

Susan Wilson, Ph.D.

Saling Huang, Ph.D.

Karen Pickthorn, D.V.M.

Kim Trobaugh, B.S.

Reshma Kewalramani, M.D., FASN

Arline Nakanishi, M.S.

Steven Galson, M.D., M.P.H.

David Essayan, M.D.

Andrew Vick, Ph.D.

Geoff Block, M.D.

Peter Kowey, M.D., FACC, FHRS

## 1.0 BACKGROUND

KAI Pharmaceuticals submitted this End of Phase 2 (EOP2) meeting request to discuss their KAI-4169 intravenous bolus injection. KAI-4169 is a novel, long-acting, eight amino acid peptide agonist of calcium-sensing receptor (CaSR). KAI is seeking an indication of treatment for secondary hyperparathyroidism (SHPT) in Chronic Kidney Disease (CKD) patients on hemodialysis (HD) (b) (4)

KAI-4169 can be administered both as a bolus injection into the venous tubing of the dialysis and intravenously.

Regulatory History: On August 201, KAI-4169 was originally submitted under IND 109773 and the sponsor was placed on partial clinical hold (PCH) for nonclinical deficiencies on September 2010 after the 30-day safety review. On January 2011, the PCH was removed. On August 2011, the sponsor requested a Type C nonclinical guidance meeting. FDA provided written responses on November 2011 in lieu of the August meeting request. On October 2011, the sponsor was placed on full clinical hold (FCH) due to Chemistry, Manufacturing, and Controls deficiencies and the FCH was removed on November 2011. In December 2011, the sponsor requested a Type C clinical guidance meeting to discuss their Phase 3 program, which FDA granted and issued preliminary comments on February 2012. The sponsor cancelled their December meeting request after receiving the preliminary comments. The sponsor requested this EOP2 meeting on April 24, 2012. FDA granted this face-to-face meeting for July 9, 2012.

Repeated below in regular text are KAI Pharmaceutical's questions followed by FDA's preliminary responses written in **bold** text. KAI Pharmaceutical's pre-meeting comments sent by email dated July 7, 2012 are also repeated below followed by the meeting discussion in *italic*.

## DISCUSSION

Sponsor sent comments to our preliminary comments in an email dated July 7, 2012. Sponsor's comments are attached below.

### 2.0 Questions

#### 2.1 SHPT Investigational Plan

**Sponsor Question 1:** The KAI-4169 SHPT development program will consist of two identical randomized, double-blind, placebo-controlled clinical studies to be conducted in hemodialysis subjects with SHPT. Each study will be 26 weeks in duration, will enroll approximately 500 subjects randomized 1:1 to KAI-4169 or placebo, and will utilize the proportion of subjects with at least a 30% reduction in intact iPTH as the primary endpoint. In addition, an extension protocol will allow for open label treatment of subjects from the two SHPT studies for at least an additional 52 weeks to evaluate long-term safety and durability of effect. An analysis of data from the open-label extension study will be performed when a sufficient number of subjects complete the required duration of treatment in the open-label extension study to meet the safety

database requirement. In total, data from these three studies, which will include at least 500 subjects treated with KAI- 4169 for 6 months and at least 100 subjects treated with KAI-4169 for 1 year at the time of New Drug Application (NDA) filing, will be used to support an indication for the treatment of SHPT.

Does the FDA agree that our proposed investigational plan is adequate to support an NDA for KAI-4169 for the treatment of SHPT in patients with CKD on hemodialysis?

**FDA Preliminary Comment: The plan is adequate to support the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis.**

Sponsor Pre-Meeting Comment (July 7, 2012): The Agency's preliminary comment to Question 1 is clear, and no further discussion is required.

*Meeting Discussion: No further discussion.*

## **2.2 Phase 3 SHPT Primary Endpoint**

**Sponsor Question 2:** In consideration of the feedback received from the FDA on February 14, 2012, KAI proposes using a responder analysis for the primary endpoint in the SHPT Phase 3 program based on serum iPTH. As suggested by the FDA, KAI proposes to define a responder as a subject whose iPTH is reduced > 30% from baseline during the efficacy assessment period.

KAI would like to confirm with the FDA that this proposed primary endpoint, as detailed in the proposed Phase 3 SHPT clinical trials, is appropriate to demonstrate efficacy to support an NDA for KAI-4169 for the treatment of SHPT?

**FDA Preliminary Comment: The proposed primary endpoint is adequate to demonstrate the efficacy of KAI-4169 for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis.**

Sponsor Pre-Meeting Comment (July 7, 2012): The Agency's preliminary comment to Question 2 is clear, and no further discussion is required.

*Meeting Discussion: No further discussion.*

## **2.3 Starting Dose and Titration**

**Sponsor Question 3:** KAI proposes a KAI-4169 starting dose of 5 mg. The dose of KAI-4169 may be increased at 4-week intervals by 2.5 mg or 5 mg to achieve an iPTH level  $\leq 300$  pg/mL or a maximum dose of KAI-4169, whichever comes first, while maintaining serum corrected calcium within an acceptable range as described in Section 11.2. Dose adjustment for low serum

calcium or low serum iPTH will be incorporated into the dosing algorithm in the Phase 3 protocols, which are included in this briefing document.

Does the FDA agree with the proposed dosing algorithm for the Phase 3 program?

**FDA Preliminary Comment:** The starting dose and titration scheme are acceptable. We recommend that you also specifically mention symptomatic hypocalcemia in the study protocol as a reason to suspend study drug dosing. The protocol should also include a list of hypocalcemia and hypercalcemia symptoms for investigators to consider; this list should be added to the sections of the protocol that deal with management of these conditions and drug administration, and not just under the Adverse Events of Interest section where they maybe overlooked.

**Sponsor Pre-Meeting Comment (July 7, 2012):** The Agency's preliminary comment to Question 3 is clear. KAI will specifically mention symptomatic hypocalcemia as a reason to suspend drug dosing in the Phase 3 protocols.

Additionally, KAI proposes to include Table 1 and Table 2 listing common symptoms of hypocalcemia and hypercalcemia, respectively, for investigators to consider (Coe, F & Favus, M [ed]. Disorders of Bone and Mineral Metabolism. Second Edition. Philadelphia: Lippincott Williams & Wilkins, 2002.). These tables will be added to the appropriate sections of protocol including Section 9 (Treatment of Subjects), Section 10 (Signs and Treatment of Hypocalcemia), and Section 12 (Assessment of Safety).

The list is not exhaustive, and includes symptoms thought to be relatively common in clinical presentations. Note that each must be interpreted within the clinical context of the study population. For example, Hypertension from Hypercalcemia may be difficult to distinguish from underlying Hypertension secondary to ESRD, and Fatigue can be a presenting symptom of either condition. In addition, KAI proposes to include a comprehensive list of the signs and symptoms of hypocalcemia and hypercalcemia in an appendix to the protocol (draft included at end of this document).

**Table 1: Proposed Common Symptoms of Hypocalcemia**

Paresthesias (fingertips, toes or perioral)
Fatigue
Muscle cramps
Irritability or anxiety
Tetany (e.g., carpopedal spasm, laryngospasm)
Seizures

**Table 2: Proposed Common Symptoms of Hypercalcemia**

Anorexia
Nausea, vomiting or constipation
Fatigue or weakness
Musculoskeletal pain
Hypertension
Impaired concentration
Confusion or lethargy

**Does the FDA agree with the proposed list of hypocalcemia and hypercalcemia symptoms?**

*Meeting Discussion: FDA agreed to sponsor's comments sent by email dated July 7, 2012. FDA asked that Chvostek's sign and Prolonged QT interval be included in Table 1 listing signs and symptoms of hypocalcemia and the sponsor agreed to do this.*

## **2.4 Phase 3 Safety Management Plan**

**Sponsor Question 4:** KAI proposes to monitor safety during the Phase 3 program by capturing and characterizing adverse events, medical history, laboratory abnormalities, and by adjudicating prespecified adverse events using an independent event adjudication committee (Duke Clinical Research Institute). In addition, KAI proposes to have an independent data monitoring committee to review unblinded safety data on a periodic basis across all pivotal studies in the Phase 3 program. The event adjudication charter and data monitoring committee (DMC) charter are provided in this briefing document.

Does FDA agree with KAI's proposed Phase 3 safety management plan?

**FDA Preliminary Comment: The proposed Phase 3 safety management plan is acceptable.**

**Sponsor Pre-Meeting Comment (July 7, 2012):** The Agency's preliminary comment to Question 4 is clear, and no further discussion is required.

*Meeting Discussion: No further discussion.*

## 2.5 Cardiac Safety Proposals

**Sponsor Question 5:** Agonists of the CaSR lower serum parathyroid hormone and calcium levels; the latter may delay cardiac repolarization and prolong the QT/QTc interval. Anticipating this effect in the nonclinical program, KAI carefully evaluated the QTc interval with continuous electrocardiogram (ECG) monitoring following single bolus doses of KAI-4169 in a dog safety pharmacology study. In that study, QTc prolongation was temporally associated with reductions in serum calcium but not plasma concentrations of KAI-4169. Consistent with that observation, KAI-4169 neither binds to nor inhibits the hERG channel in vitro.

KAI has carefully evaluated the feasibility of conducting a thorough QTc study in accordance with guidance provided in the ICH E14 document. However, based upon our experience in the KAI-4169-001 Phase 1 study in healthy volunteers, a thorough QTc study cannot be safely conducted with KAI-4169 in healthy subjects because hypocalcemia was observed following a single 10 mg dose, limiting the exposure that can be safely achieved in healthy volunteers. In addition, a thorough QTc study in either healthy volunteers or hemodialysis subjects will produce results that are confounded by the direct effect of reductions in serum calcium on QTc, making any meaningful interpretation difficult. Therefore, KAI requests a waiver of a thorough QTc study. The rationale for this position and the limitations of potential trial alternatives considered by KAI and its advisors are outlined Section 11.4.2.

As described in Section 11.4.2.3, KAI has evaluated the effects of KAI-4169 on clinical ECGs at multiple time points under controlled settings during the single and multiple dose studies performed to date in healthy volunteers and hemodialysis subjects (b) (4) conducted a blinded, independent evaluation of the ECGs obtained in these studies to assess the potential relationship between changes in QTcF and KAI-4169 plasma concentrations, as well as the relationship between serum calcium and changes in QTcF. These analyses are included in this briefing document. The main findings were that changes in QTcF observed during these studies were related to reductions in serum calcium (an expected secondary pharmacodynamic effect of KAI-4169) but not to exposure to KAI-4169 itself. The observed hypocalcemia-related changes in QTcF support the assay sensitivity of these evaluations. Based upon these findings, KAI believes the ECG data and analyses to date adequately evaluate the potential effect of KAI-4169 on cardiac repolarization in support of an NDA. In addition, KAI proposes to conduct intensive ECG monitoring in one of the two identical placebo-controlled Phase 3 studies in support of the indication for the treatment of SHPT. This proposal and its rationale are outlined in Section 11.4.4.

Does the FDA agree with the proposed waiver for a thorough QTc study? Does the FDA agree with KAI's proposal for ECG monitoring in Phase 3?

**FDA Preliminary Comment:** We are still in the process of reviewing your request for a waiver of a thorough QTc study and your proposal for ECG monitoring. We will send additional comments once the review is complete.

**Sponsor Pre-Meeting Comment (July 7, 2012):** KAI looks forward to discussing this with the Agency.

*Meeting Discussion:* FDA agreed with sponsor's request for a waiver of the thorough QTc study but stated that we are still reviewing their ECG monitoring proposal. FDA agreed to provide comments on ECG monitoring one week from July 9, 2012. Sponsor acknowledged this.

*There was agreement that there were two separate issues here. One dealing with the need for measuring QT with respect to drug Cmax as per the ICH 14 guidance and one dealing with measuring QT at a time at which it would be maximal because of pharmacodynamic and physiological concerns in dialysis patients which would address clinical safety concerns. FDA stated that sponsor should consider doing ECG monitoring pre-dialysis since calcium levels are likely to be the lowest at this time and as such might have the greatest affect on prolonging the QT interval. The sponsor mentioned that for technical reasons it would be hard for them to perform ECGs for QTc measurements at both pre and post dialysis, and they had originally proposed to measure them only post dialysis to address the ICH 14 guidance as potential direct drug effects on QTc would be expected near the maximal drug concentration immediately after dosing. FDA mentioned that while it is known that hypocalcemia can prolong the QT interval, their drug's affect on PTH is likely to affect other electrolytes besides calcium, which could affect the timing and degree of QT prolongation.*

*Sponsor proposed to conduct a smaller sub-study protocol to evaluate Cmax and collect 24 hour ECG monitoring to better address the safety concerns but stated it would not be powered like a thorough QTc study. Sponsor mentioned that this could be an option in addition to doing the ECG monitoring pre-dialysis in one of their larger two Phase 3 studies as they had originally proposed. FDA inquired if the sponsor had conducted this type of study before. Sponsor stated that they hadn't but that they had collected some data from their Phase 1, 12- week study which they could use to estimate the level of variability they might expect to observe in dialysis patients.*

*Sponsor stated that they will wait for FDA's pending comments on ECG monitoring on their Phase 3 studies before they sending a draft sub-study protocol for us to review. FDA agreed to this.*

## 2.6 Drug-Drug Interaction Proposal

**Sponsor Question 6:** In vitro drug metabolism studies indicate that KAI-4169 is not subject to hepatic metabolism and is neither a substrate for nor inducer of CYP450 enzymes. Further, KAI-4169 does not possess immunomodulatory properties (i.e., is not a cytokine or cytokine modulator), so modification of the metabolism of drugs that are metabolized by the CYP450 enzymes through interaction with the regulation pathways of CYP450 enzymes is unlikely. Therefore, KAI believes the risk of pharmacokinetic (PK) drug-drug interactions is quite low and KAI does not intend to perform specific clinical drug-drug interaction trials. In accordance with the recently published draft Guidance for Industry on Drug Interaction Studies (February 2012), KAI does intend to conduct in vitro transporter studies as outlined in this briefing document (Section 11.5).

Does the FDA agree with KAI's proposed plan concerning drug-drug interaction studies?

**FDA Preliminary Comment:** We agree with your proposal to assess the potential for drug-drug interactions of KAI-2169 by conducting *in vitro* studies as described in the Draft Guidance on Drug Interactions Studies

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>).

**Sponsor Pre-Meeting Comment (July 7, 2012):** The Agency's preliminary comment to Question 6 is clear, and no further discussion is required.

*Meeting Discussion: No further discussion.*

## 2.7 Pediatric Waiver Request

**Sponsor Question 7:** KAI believes that the pediatric hemodialysis population with SHPT is so limited in size, both within the US and internationally, that it is impracticable to conduct adequate clinical studies in support of a pediatric indication (Section 11.6). Therefore, KAI requests a waiver for pediatric studies.

Does the FDA agree with KAI's request for a waiver for pediatric studies?

**FDA Preliminary Comment:** You must provide scientific rationale supported by sufficient data to justify each applicable waiver criterion (found in 21 U.S.C. 355c) cited in your request. If you are requesting a waiver based on safety concerns or lack of efficacy in pediatric patients, you must submit proposed labeling which reflects the safety concern and/or lack of efficacy.

Any request will require review by the Pediatric Review Committee (PeRC) and a final decision will not be made until the time of approval.

**Sponsor Pre-Meeting Comment (July 7, 2012):** The Agency's preliminary comments to Question 7 are clear. KAI feels that our data and analyses in Section 11.6 of the EOP2 Briefing Document dated 04 June 2012 support a Request for Full Pediatric Waiver in accordance with 355c(a)(4)(A)(i). We request the Agency's recommendations on the appropriate timing and format for filing such an official Request for Full Pediatric Waiver.

*Meeting Discussion: FDA acknowledged sponsor's comments sent by email dated July 7, 2012. Please see attachment below. FDA further stated at this time sponsor should submit the Pediatric Study Plan at the time of NDA submission. FDA is waiting to receive internal feedback on this and will inform the sponsor if the time to submit the Pediatric Study Plan prior to NDA submission changes.*

*Post meeting note: Upon internal feedback we have the following recommendation about submitting the Pediatric Study Plan prior to submitting the NDA: The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a Pediatric Study Plan, and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes.*

(b) (4)



*Meeting Discussion: No further discussion.*



(b) (4)

**FDA Preliminary Comment:** It is premature to comment on [redacted] (b) (4)  
This is decided at the Filing Meeting.

**Sponsor Pre-Meeting Comment (July 7, 2012):** The Agency's preliminary comments to Question 10 are clear, and no further discussion is required.

*Meeting Discussion: No further discussion.*

## **DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for 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 studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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 the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

Sponsor stated that they will wait on FDA's comment on ECG monitoring and then decide if they would need to submit a draft protocol as discussed during the meeting.

### **4.0 ACTION ITEMS**

<b>Action Item/Description</b>	<b>Owner</b>	<b>Due Date</b>
ECG monitoring comments	FDA	FDA sent email correspondence to the sponsor on July 17, 2012.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MEGHNA M JAIRATH  
08/01/2012

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 208325

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen, Inc.  
Attention: Jennifer Steinbock  
Manager, Regulatory Affairs  
One Amgen Center Drive; Mail Stop: 17-2-A  
Thousand Oaks, CA 91320-1799

Dear Ms. Steinbock:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for etelcalcetide injection.

We also refer to the Late-Cycle Meeting (LCM) scheduled for June 1, 2016. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE: Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** June 1, 2016

**Meeting Location:** Teleconference

**Application Number:** 208325

**Product Name:** Etelcalcetide injection

**Indication:** Treat Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis

**Applicant Name:** KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.

### 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**

No Discipline Review letters have been issued to date.

**2. Substantive Review Issues**

No substantive review issues have been identified to date.

### **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 (RPM)  
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – none
3. Discussion of Minor Review Issues – none
4. Additional Applicant Data –none
5. Information Requests – none
6. Discussion of Upcoming Advisory Committee Meeting – no Advisory Committee meeting
7. REMS or Other Risk Management Actions – No REMS or other Risk Management Actions
8. Postmarketing Requirements/Postmarketing Commitments – none
9. Major labeling issues – Labeling negotiations are ongoing.
10. Review Plans – FDA will continue review of the NDA and, at this time, there appear to be no significant review issues that would prevent FDA from taking an action on or before the PDUFA goal.
11. Wrap-up and Action Items – None

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/s/  
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JEAN-MARC P GUETTIER  
05/27/2016