

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208325Orig1s000**

**OTHER REVIEW(S)**



3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
  
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
  
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

---

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

---

Other

---

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

---

(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

---

NDA/BLA #                      NDA 208325  
Product Name:                 PARSABIV (etelcalcetide) injection

---

PMR #2 Description:         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 17 years (inclusive) (Part 1), and subjects aged 1 month to 2 years (Part 2), both with secondary hyperparathyroidism receiving hemodialysis.

---

|                             |                            |                   |
|-----------------------------|----------------------------|-------------------|
| PMR #2 Schedule Milestones: | Final Protocol Submission: | <u>05/31/2018</u> |
|                             | Study Completion:          | <u>01/31/2023</u> |
|                             | Final Report Submission:   | <u>06/30/2023</u> |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Parsabiv is ready for approval for use in adults; however, pediatric studies had been deferred until adequate safety data were available from the adult program.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this PMR is to establish pharmacokinetics and safety of Parsabiv in pediatric patients aged 1 month to (b) (4) years.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
  
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
  
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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)</sup><sub>(4)</sub> years (Part 1), and subjects aged 1 month to 2 years (Part 2), both with secondary hyperparathyroidism receiving hemodialysis.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

---

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

---

Other

---

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

---

(signature line for BLAs)



3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

---

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

---

Other

---

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

---

(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

---

NDA/BLA # NDA 208325  
Product Name: PARSABIV (etelcalcetide) injection

---

PMR #4 Description: 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.

---

|                             |                            |                   |
|-----------------------------|----------------------------|-------------------|
| PMR #4 Schedule Milestones: | Feasibility Analysis:      | <u>07/31/2017</u> |
|                             | Final Protocol Submission: | <u>12/31/2017</u> |
|                             | Interim Reports:           | <u>05/31/2018</u> |
|                             |                            | <u>05/31/2019</u> |
|                             |                            | <u>05/31/2020</u> |
|                             | Study Completion:          | <u>06/30/2020</u> |
| Final Report Submission:    | <u>12/31/2020</u>          |                   |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Given the low number of events in the clinical development program, it was determined that an observational study would be the most appropriate next step in evaluating this safety signal. Such a study is only feasible to conduct post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In the Parsabiv clinical program, two patients treated with Parsabiv in 1253 patient-years of exposure had upper GI bleeding noted at time of death, while no patient in the control groups in 384 patients-years of exposure had upper GI bleeding noted at time of death. This numeric imbalance observed in clinical program is concerning based on the severity of the event, Parsabiv animal findings (GI ulcerations at near-human exposure), possible class effect (ulcerations and bleeding were also observed in cinacalcet clinical program) and the fact that these events might be explained on mechanistic grounds (gastrin-induced effect of the drug on calcium sensing receptors in stomach, nausea and vomiting induced by the drug).

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A hypothesis-testing observational study evaluating 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. A feasibility analysis supporting the study design should be submitted to and reviewed by FDA prior to protocol finalization.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

---

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

---

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

---

- Other

---

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

\_\_\_\_\_  
(signature line for BLAs)

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

/s/  
-----

JENNIFER R PIPPINS  
02/08/2017

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

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

## Memorandum

**Date:** January 13, 2017

**To:** Meghna M. Jairath, Regulatory Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)

**From:** Meena Ramachandra, PharmD, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** NDA 208325  
OPDP labeling comments for PARSABIV™ (etelcalcetide) injection,  
for intravenous use  
**Focused Review**

---

On December 12, 2016, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI) for PARSABIV™ (etelcalcetide) injection, for intravenous use (Parsabiv). DMEP requested a focused review of the adverse reactions under the highlights section and Table 3 of the PI.

OPDP's review of the proposed substantially complete version of the draft labeling is based on the version titled "annotated version Amgen PI 12\_9\_16 NDA 208325.doc."

OPDP's comment is provided on the version of the proposed PI attached to this consult.

Thank you for the opportunity to comment on this material.

If you have any questions, please contact Meena Ramachandra at 240-402-1348 or [Meena.Ramachandra@fda.hhs.gov](mailto:Meena.Ramachandra@fda.hhs.gov).

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

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

/s/  
-----

MEENA RAMACHANDRA  
01/13/2017

---

## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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

---

**Date of This Memorandum:** January 5, 2017

**Requesting Office or Division:** Division of Metabolism and Endocrinology Products (DMEP)

**Application Type and Number:** NDA 208325

**Product Name and Strength:** Parsabiv (etelcalcetide), injection, 2.5 mg/0.5 mL, 5 mg/mL, 10 mg/2 mL

**Submission Date:** December 9 and 13, 2016

**Applicant/Sponsor Name:** Amgen Inc.

**OSE RCM #:** 2015-2018-3

**DMEPA Primary Reviewer:** Ariane O. Conrad, PharmD, BCACP, CDE

**DMEPA Team Leader:** Hina Mehta, PharmD

---

#### 1 PURPOSE OF MEMO

Parsabiv (etelcalcetide), NDA 208325, received a Complete Response letter dated August 24, 2016 after Amgen and the Agency were unable to reach an agreement on the proposed product labeling. Amgen resubmitted the NDA after addressing the deficiencies identified in the letter on December 9, 2016.

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the resubmitted prescribing information (PI), container labels and carton labeling for Parsabiv (Appendix A) to determine if this labeling is acceptable from a medication error perspective. Revisions were made in response to recommendations that we made during the previous label and labeling reviews conducted during the previous review cycle.<sup>a</sup>

---

<sup>a</sup> Conrad A. Label and Labeling Review for Parsabiv (NDA 208325). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 May 20. 12 p. OSE RCM No.: 2015-2018.

Conrad A. Review of Revised Label and Labeling Memorandum for Parsabiv (NDA 208325). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 July 18. 7 p. OSE RCM No.: 2015-2018-1.  
Conrad A. Review of Revised Label and Labeling Memorandum for Parsabiv (NDA 208325). Silver Spring (MD): Food

## **2 CONCLUSION**

The resubmitted labels and labeling for Parsabiv are acceptable from a medication error perspective. We have no further recommendations at this time.

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

---

and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Aug 23. 18. 3 p. OSE RCM No.: 2015-2018-2.

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

/s/  
-----

ARIANE O CONRAD  
01/05/2017

HINA S MEHTA  
01/05/2017

## MEMORANDUM TO FILE

U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF DRUG EVALUATION II  
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS

---

**NDA/BLA #:** NDA 208325  
**PRODUCT:** etelcalcetide injection  
**APPLICANT:** KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen, Inc.  
**FROM:** Jennifer Rodriguez Pippins, M.D., M.P.H.  
Deputy Director for Safety, Division of Metabolism and Endocrinology  
**DATE:** September 8, 2016  
**TOPIC:** **Addendum:** PMR Development Templates

---

### PURPOSE

This memorandum to file is an addendum to the postmarketing requirement (PMR) Development Templates filed on August 22, 2016, and pertains to the Division of Metabolism and Endocrinology Products' (DMEP's) requirement for postmarketing studies as a condition of approval for NDA 208325 (etelcalcetide injection). Please see the PMR Development Templates for a full description of these studies.

### BACKGROUND

As documented in the reviews filed by Drs. Marina Zemskova and Curtis Rosebraugh on August 24, 2016, DMEP was not able to reach agreement on the final content of the full prescribing information for etelcalcetide injection (proposed proprietary name, Parsabiv). FDA issued a Complete Response letter for this application on August 24, 2016. Please refer to these reviews and letter for additional details of the deficiencies.

The Complete Response letter issued on August 24, 2016, included placeholder language for a postmarketing study that would be required under Section 505(o)(3) of the FDCA in the event that the product is approved. This hypothesis-testing observational study to provide data regarding the potential association between etelcalcetide and fatal and non-fatal gastrointestinal bleeding was described in the templates as PMR #4. The additional planned PMRs #1-3 were intended to address requirements under the Pediatric Research Equity Act (PREA); therefore no placeholder language was required to be included in the letter.

### CONCLUSION

DMEP did not issue the PMRs for NDA 208325 as described in the PMR Development Templates filed on August 22, 2016, because the application was not approved. These PMRs will be re-evaluated, along with any potential additional safety issues, when and if the application is resubmitted.

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

/s/  
-----

JENNIFER R PIPPINS  
09/08/2016

---

## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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

---

**Date of This Memorandum:** August 23, 2016

**Requesting Office or Division:** Division of Metabolism and Endocrinology Products (DMEP)

**Application Type and Number:** NDA 208325

**Product Name and Strength:** Parsabiv (etecalcetide) injection, 2.5 mg/0.5 mL, 5 mg/mL, 10 mg/2 mL

**Submission Date:** August 15, 2016

**Applicant/Sponsor Name:** Amgen Inc.

**OSE RCM #:** 2015-2018-2

**DMEPA Primary Reviewer:** Ariane O. Conrad, PharmD, BCACP, CDE

**DMEPA Team Leader (Acting):** Hina Mehta, PharmD

---

#### 1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised professional sample container labels for Parsabiv (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.<sup>a</sup>

#### 2 CONCLUSION

The revised professional sample container labels for Parsabiv are acceptable from a medication error perspective. We have no further recommendations at this time.

---

<sup>a</sup> Conrad A. Label and Labeling Review for Parsabiv (etecalcetide), NDA 208325. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 May 20. 12 p. OSE RCM No.: 2015-2018.

Conrad A. Memorandum Review of Revised Label and Labeling Review for Parsabiv (etecalcetide), NDA 208325. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 July 18. 6p. OSE RCM No.: 2015-2018-1.

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

/s/  
-----

ARIANE O CONRAD  
08/23/2016

HINA S MEHTA  
08/23/2016



3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

---

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

---

Other

---

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

---

(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

---

NDA/BLA #                      NDA 208325  
Product Name:                 PARSABIV (etelcalcetide) injection

---

PMR #2 Description:         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.

---

|                             |                            |                   |
|-----------------------------|----------------------------|-------------------|
| PMR #2 Schedule Milestones: | Final Protocol Submission: | <u>05/31/2018</u> |
|                             | Study Completion:          | <u>01/31/2023</u> |
|                             | Final Report Submission:   | <u>06/30/2023</u> |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Parsabiv is ready for approval for use in adults; however, pediatric studies had been deferred until adequate safety data were available from the adult program.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this PMR is to establish pharmacokinetics and safety of Parsabiv in pediatric patients aged 1 month to (b) (4) years.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

---

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

---

Other

---

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

---

(signature line for BLAs)



3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

---

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

---

Other

---

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

---

(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

---

NDA/BLA #                      NDA 208325  
Product Name:                 PARSABIV (etelcalcetide) injection

---

PMR #4 Description:         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.

---

|                             |                            |                   |
|-----------------------------|----------------------------|-------------------|
| PMR #4 Schedule Milestones: | Feasibility Analysis:      | <u>01/31/2017</u> |
|                             | Final Protocol Submission: | <u>06/30/2017</u> |
|                             | Interim Reports:           | <u>11/30/2017</u> |
|                             |                            | <u>11/30/2018</u> |
|                             |                            | <u>11/30/2019</u> |
|                             | Study Completion:          | <u>12/31/2019</u> |
| Final Report Submission:    | <u>06/30/2020</u>          |                   |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Given the low number of events in the clinical development program, it was determined that an observational study would be the most appropriate next step in evaluating this safety signal. Such a study is only feasible to conduct post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In Parsabiv clinical program there were three deaths fatal upper GI bleeding events in 1253 patient-years of exposure compared to no fatal GI bleeding events in patients treated with placebo or active comparator (cinacalcet) in 384 patient-years of exposure. This numeric imbalance observed in clinical program is concerning based on the severity of the event, Parsabiv animal findings (GI ulcerations at near-human exposure), possible class effect (ulcerations and bleeding were also observed in cinacalcet clinical program) and the fact that these events might be explained on mechanistic grounds (gastrin-induced effect of the drug on calcium sensing receptors in stomach, nausea and vomiting induced by the drug).

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A hypothesis-testing observational study evaluating 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. A feasibility analysis supporting the study design should be submitted to and reviewed by FDA prior to protocol finalization.

Required

- Observational pharmacoepidemiologic study  
 Registry studies  
 Primary safety study or clinical trial  
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
 Thorough Q-T clinical trial  
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)  
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)  
 Pharmacokinetic studies or clinical trials  
 Drug interaction or bioavailability studies or clinical trials  
 Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials  
 Immunogenicity as a marker of safety  
 Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)  
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
 Dose-response study or clinical trial performed for effectiveness  
 Nonclinical study, not safety-related (specify)
- 
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

\_\_\_\_\_  
(signature line for BLAs)

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

/s/  
-----

JENNIFER R PIPPINS  
08/22/2016

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)**

**Epidemiology: ARIA Sufficiency Memo**

Date: August 19, 2016

Reviewer: Christian Hampp, PhD  
Division of Epidemiology I

Team Leader: Patricia L. Bright, MSPH, PhD,  
Division of Epidemiology I

Deputy Division Director:  
(Acting) Simone P. Pinheiro, ScD, MSc  
Division of Epidemiology I

Subject: ARIA Sufficiency Memo: Etelcalcetide and Fatal Gastrointestinal  
Bleeding

Drug Name: Etelcalcetide

Application Type/Number: NDA 208325

Applicant/sponsor: KAI Pharmaceuticals, Inc./Amgen, Inc.

OSE RCM #: 2016-1485

**EXECUTIVE SUMMARY** (place "X" in appropriate boxes)

|  |   |
|--|---|
| <b>Memo type</b>   |   |
| -Initial   |   |
| -Interim   |   |
| -Final   | X |
| <b>Source of safety concern</b>                                    |   |
| -Peri-approval   | X |
| -Post-approval   |   |
| <b>Is ARIA sufficient to help characterize the safety concern?</b> |   |
| -Yes   |   |
| -No  | X |
| <b>If "No", please identify the area(s) of concern.</b>            |   |
| -Surveillance or Study Population                                  | X |
| -Exposure  |   |
| -Outcome(s) of Interest  |   |
| -Covariate(s) of Interest  |   |
| -Surveillance Design/Analytic Tools                                | X |

## 1. BACKGROUND INFORMATION

### 1.1. Medical Product

Etelcalcetide is a calcium sensing receptor agonist intended for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease (ESRD) on hemodialysis. It is used as a bolus injection 3 times per week into the venous line of the dialysis circuit at the end of the hemodialysis treatment during rinse back or intravenously after rinse back.

Etelcalcetide is currently undergoing FDA review with a PDUFA goal date of August 24, 2016.

### 1.2. Describe the Safety Concern

Staff from the Office of New Drugs/Division of Metabolism and Endocrinology Products (OND/DMEP) is concerned about the potential for increased *fatal* gastrointestinal bleeding (GIB) with etelcalcetide. The sponsor conducted two phase 3 placebo-controlled studies with a total of 503 patients randomized to etelcalcetide vs. 513 on placebo. There were 2 fatal GIB cases on etelcalcetide vs. 0 on placebo across this pool. A third fatal GIB occurred in an open-label extension phase 2 trial:

- Case 1 (from exposed arm of a placebo controlled trial) – 73 year-old female developed vomiting of “dark contents” and diarrhea **during the second week** of treatment (after 5<sup>th</sup> dose); a day later she was observed to have hematemesis and coded. Autopsy showed mucosal stress ulcers.
- Case 2 (from exposed arm of a placebo controlled trial) – 75 year-old male with history of GERD on Prilosec, also on steroids and heparin. Was treated for 17 weeks and then discontinued for “sponsor’s decision” (details not provided). Was noted to have **coffee ground emesis on an unknown date**, and nausea/abdominal distension x 1 week. (b) (6)  
**weeks after study discontinuation, subject had upper GIB.** Endoscopy revealed severe esophagitis, hiatal hernia, Mallory-Weiss tear, gastritis. One week later he became hypotensive, had ECG with evidence of ischemia, and arrested. He was noted to have a Hct drop (33 to 29%) and had hematemesis during the code.
- Case 3 (from open label extension) – 54 year-old male with history of GERD, history of intermittent nausea, vomiting, on aspirin, on heparin (DMEP staff believes this was just bolus heparin for HD, but are not sure), on ranitidine, had subendocardial MI on study day 33, **on study day 43 had GIB** resulting in cardiogenic shock/death.

According to DMEP staff, etelcalcetide is associated with the GI events of nausea/vomiting, but no imbalance was seen in relevant preferred terms, including erosions, ulcers. Apart from GIB, no other bleeding signal was observed. Although any GIB is of interest, the specific outcome sought for this analysis is *fatal* GIB.

Staff from DMEP suggested biological plausibility for adverse GI effects with etelcalcetide, due to purported effects of the drug on gastrin secretion and the observation of stomach erosions in nonclinical studies conducted in rats.

Instead of a formal Signal Assessment Meeting, staff from the Office of Surveillance and Epidemiology (OSE), including the Division of Epidemiology-I (DEPI-I) discussed ARIA sufficiency through email and in-person conversations internally and with staff from DMEP. In addition, a phone conference between OSE staff, the Sentinel Operations Center (SOC), and representatives from select Data Partners (DPs) was held on July 25, 2016, to discuss the availability and completeness of data for ESRD patients in Sentinel. Finally, the SOC provided data on cinacalcet use as a possible comparator and counts of patients with secondary hyperparathyroidism of renal origin.

This memorandum documents OSE's determination that ARIA is not sufficient to characterize the risk of fatal GIB after exposure to etelcalcetide.

**1.3. FDAAA Purpose (per Section 505(o)(3)(B))**

*Purpose (place an "X" in the appropriate boxes; more than one may be chosen)*

|  |   |
|--|---|
| Assess a known serious risk  |   |
| Assess signals of serious risk   | X |
| Identify unexpected serious risk when available data indicate potential for serious risk |   |

**1.4. Statement of Purpose**

The purpose is to conduct an inferential analysis of fatal GIB with etelcalcetide to provide sufficient data to support labeling decisions.

**1.5. Effect Size of Interest or Estimated Sample Size Desired**

Skipped, given responses in Sections 2 and 6.

**2. SURVEILLANCE OR DESIRED STUDY POPULATION**

**2.1 Population**

The population of interest consists of patients with the proposed indication: secondary hyperparathyroidism in patients with ESRD who are on hemodialysis.

**2.2 Is ARIA sufficient to assess the intended population?**

ARIA was deemed insufficient to establish an ESRD cohort with complete data. This is mainly due to a multiple payer situation that affects much of the ESRD population, which may result in incomplete data available from any given DP. However, such a cohort may

be established in the Sentinel Distributed Database (SDD) with additional programming in form of a protocol-based assessment (PBA). This section describes unique challenges to studying the ESRD population based on administrative claims data. These challenges arise from dual insurance status due to Medicare eligibility once patients with employer-sponsored health plans are started on dialysis.

Data capture for ESRD patients

In the United States, Medicare is the health insurance for:<sup>1</sup>

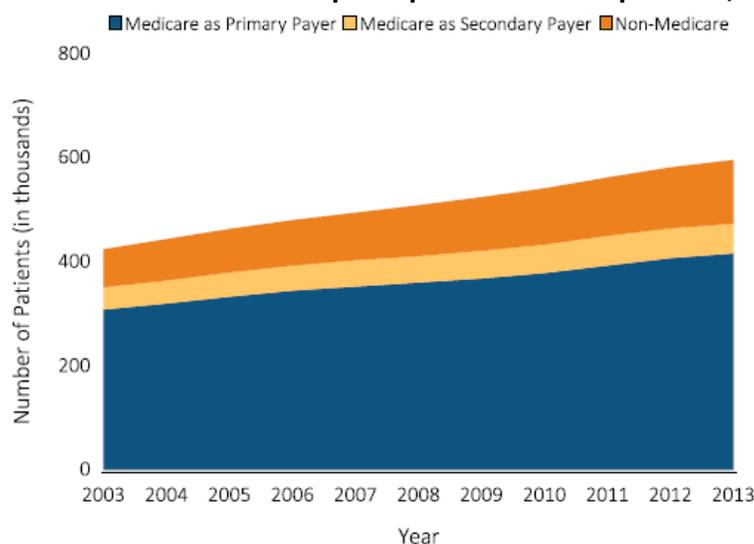
- People 65 and older
- People under 65 with certain disabilities
- People of any age with ESRD

Patients who have employer-sponsored health insurance (mostly under the age of 65) become Medicare eligible due to ESRD according to the following schedule:

- **Waiting period:** Medicare coverage usually does not start until the fourth month of dialysis. The employer-sponsored health plan is the only payer for the first 3 months of dialysis.
- **Coordination of benefits period:** For next 30 months, the employer-sponsored health plan is the primary and Medicare is the secondary payer.
- At the end of the 30-month coordination period, Medicare will pay first for all Medicare-covered services.

As Figure 1 illustrates, the large majority of prevalent ESRD patients are covered by Medicare. In 2013, 407,432 ESRD patients were covered by Medicare as primary payer, 57,677 had Medicare as secondary payer, and 122,551 ESRD patients did not have Medicare coverage.

**Figure 1. Trends in numbers of point prevalent ESRD patients, 2003-2013<sup>2</sup>**



*Data Source: USRDS ESRD Database. December 31 point prevalent ESRD patients. Abbreviations: ESRD, end-stage renal disease.*

Similarly, Table 1 shows that Medicare is the most common payer for hospitalization with a discharge diagnosis of secondary hyperparathyroidism of renal origin, the sought indication for etelcalcetide. Only 11.5% of discharges were covered by private insurance.

**Table 1. Healthcare Cost and Utilization Project: 2013 National statistics – all listed ICD-9\_CM diagnosis code 588/81 Secondary Hyperparathyroidism of Renal Origin<sup>3</sup>**

|                |                   | Total number of discharges | Standard errors            |
|----------------|-------------------|----------------------------|----------------------------|
|                |                   |                            | Total number of discharges |
| All discharges |                   | 243,155<br>(100.00%)       | 6,625                      |
| Age group      | <1                | 195 (0.08%)                | 45                         |
|                | 1-17              | 1,435 (0.59%)              | 193                        |
|                | 18-44             | 32,860 (13.51%)            | 1,229                      |
|                | 45-64             | 88,860 (36.54%)            | 2,618                      |
|                | 65-84             | 100,935<br>(41.51%)        | 2,909                      |
|                | 85+               | 18,835 (7.75%)             | 650                        |
|                | Missing           | *                          | *                          |
| Payer          | Medicare          | 182,765<br>(75.16%)        | 5,090                      |
|                | Medicaid          | 22,640 (9.31%)             | 1,167                      |
|                | Private insurance | 27,895 (11.47%)            | 966                        |
|                | Uninsured         | 5,750 (2.36%)              | 639                        |
|                | Other             | 3,880 (1.60%)              | 332                        |
|                | Missing           | *                          | *                          |

A 2014 report<sup>4</sup> of algorithms to identify cohorts of interest in Mini-Sentinel included several observations regarding the establishment of an ESRD cohort. First, the workgroup found only a few studies that had evaluated algorithms for identifying persons with ESRD, but found that much more attention has been paid to the validity of algorithms for identifying persons with chronic kidney disease (CKD). Second, the workgroup found that data partners contributing to the distributed database likely begin to lose follow-up of ESRD patients from their datasets as Medicare becomes the primary payment source for these individuals. Thus, while a selected population of persons with ESRD could be identified within the distributed database, they would likely be non-representative of a typical ESRD population, that is, a younger population with greater access to personal

resources that may preclude their reliance on Medicare and/or ESRD patients in the early months of their diagnosis while awaiting transition to Medicare. The workgroup determined that the identification of a cohort of ESRD patients should be abandoned in favor of a cohort of CKD patients. As an alternative to Sentinel data, the workgroup recommended the use of the United States Renal Data System (USRDS) dataset.

However, the July 25, 2016, phone conference with the SOC and representatives of the DPs provided additional insight into data availability in ESRD patients. Data Partners contributing to the SDD primarily consist of employer-based health plans, but include also Medicare Advantage plans. For patients with an employer-sponsored health plan, the SDD captures full patient data during the 3-months waiting period. However, particular attention needs to be given to data capture during (1) the subsequent 30 months of coordination of benefits period when Medicare becomes the secondary payer and (2) the period after the coordination of benefits, when Medicare becomes the primary payer and the employer-based health plan, if still available, becomes the secondary payer. In theory, a healthcare provider should bill the primary payer first, even though the claim may ultimately be denied and referred to the secondary payer. Accordingly, data from the employer-based health plan should be complete during the coordination of benefits period for patients younger than 65. However, data may be less complete during the period that follows these 30 months, when the employer-sponsored health plan becomes the secondary payer. Yet, during the July 25, 2016, phone conference, one call participant reported that dialysis centers would typically bill both the primary and secondary payer simultaneously, thus creating claims in both databases. However, this practice was reported anecdotally and we are unable to verify that simultaneous billing occurs universally and also for claims that are not dialysis-related. In addition, representatives of DPs reported that some DPs contribute denied claims to the SDD, while others do not. Representatives of the latter DPs reported that these denied claims could be provided for a study, if requested.

Even though Medicare is the predominant payer for ESRD patients and those with secondary hyperparathyroidism of renal origin, preliminary data show sizeable patient counts in the SDD (Table 2), including those younger than 65 and those older than 65 years of age (Table 3).

**Table 2. Count of patients with secondary hyperparathyroidism of renal origin (ICD-9-CM code 588.81) by calendar year, Sentinel Distributed Database.**

| Year  | Sum of Patients |
|-------|-----------------|
| 2011  | 69,813          |
| 2012  | 78,161          |
| 2013  | 83,902          |
| 2014  | 94,014          |
| 2015* | 75,309          |

\*Data for 2015 are incomplete

**Table 3. Count of patients with secondary hyperparathyroidism of renal origin (ICD-9-CM code 588.81) in 2014, by age, Sentinel Distributed Database.**

| Year | Age   | Sum of Patients |
|------|-------|-----------------|
| 2014 | 0-1   | 46              |
|      | 2-4   | 31              |
|      | 5-9   | 55              |
|      | 10-14 | 82              |
|      | 15-18 | 111             |
|      | 19-21 | 194             |
|      | 22-44 | 6,365           |
|      | 45-64 | 29,113          |
|      | 65-74 | 26,858          |
|      | 75+   | 31,159          |

An advantage of using employer-based health plan data to study ESRD patients is the capture of the early dialysis experience during the waiting period and the coordination of benefits period. Especially for patients under the age of 65, these periods may not be fully captured in Medicare data. However, because of the complexity associated with dual insurance, OSE staff concluded that a PBA would likely be necessary to establish an ESRD cohort with nearly complete data, including data diagnostics that can provide confidence for data completeness. Because of the need for ad-hoc programming, ARIA was deemed insufficient.

### 3 EXPOSURES

#### 3.1 Treatment Exposure

The exposure of interest is etelcalcetide, used as a bolus injection 3 times per week into the venous line of the dialysis circuit at the end of the hemodialysis treatment.

#### 3.2 Comparator Exposure

The only other drug with the same indication is cinacalcet, which is available as an oral tablet. Cinacalcet carries additional indications (hypercalcemia in adult patients with parathyroid carcinoma, hypercalcemia in adult patients with primary hyperparathyroidism for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but who are unable to undergo parathyroidectomy). Therefore, a study comparing etelcalcetide with cinacalcet would need to be restricted to patients with secondary hyperparathyroidism who are on hemodialysis.

The SOC provided summary tables of the frequency of cinacalcet use in the SDD. During 2014, (b) (4) patients initiated cinacalcet, considering a 180-day washout period, and (b) (4) patients were prevalent users (Table 4). Of note, these counts include all cinacalcet users and were not limited to patients with secondary hyperparathyroidism of renal origin.

**Table 4. Count of users of cinacalcet by calendar year, Sentinel Distributed Database.**

| Year  | Sum of Incident Users (180-Day Washout Period) | Sum of Prevalent Users |
|-------|--|------------------------|
| 2011  | (b) (4)  |                        |
| 2012  |  |                        |
| 2013  |  |                        |
| 2014  |  |                        |
| 2015* |  |                        |

\*Data for 2015 are incomplete

**3.3 Is ARIA sufficient to identify the exposure of interest?**

Skipped, given responses in Sections 2 and 6.

**4 OUTCOME(S)**

**4.1 Outcomes of Interest**

The primary outcome of interest is fatal GIB, with non-fatal GIB as secondary outcome.

**4.2 Is ARIA sufficient to assess the outcome of interest?**

ARIA was deemed sufficient to ascertain fatal GIB. However, challenges to ascertaining cause of death are worth noting. The following lists three different approaches and their main advantages and disadvantages:

1. Using vital statistics data (death certificates) linked to claims data:
  - a. Advantage: contain information on underlying and contributing cause of death as assigned by coroner.
  - b. Disadvantage: typically subject to 2-year data delay in United States.
  
2. Using medical records linked to claims data:
  - a. Advantage: earlier availability
  - b. Disadvantages:
    - i. Cause of death may have to be inferred from provider notes. May be less accurate than death certificates.
    - ii. May not include fatal events that occurred at home.
    - iii. Need for access to medical records may reduce available sample size.
  
3. Using only claims data, that is, based on a hospital discharge status of death and based on diagnostic claims during the final hospitalization:
  - a. Advantage: timely availability for large numbers of patients
  - b. Disadvantages:
    - i. Less accurate: a patient may have had some form of GIB during the final hospitalization, but it may not have contributed to death.

- ii. Would not include fatal events that occurred at home.

The third approach, provided by participants of the July 25, 2016, phone conference, was considered acceptable by staff from DMEP and OSE.

## **5 COVARIATES**

Skipped, given responses in Sections 2 and 6.

## **6 SURVEILLANCE DESIGN / ANALYTIC TOOLS**

The challenges to establish an ESRD cohort with complete data (described in Section 2) are related to both data availability and analytic tools. As described in Section 2, ARIA tools were deemed insufficient to ensure complete data. Instead, a PBA could be conducted in the SDD with ad-hoc programming to maximize data completeness. Ad-hoc programming as part of a PBA should specifically address two areas:

1. Establishment of a cohort of patients with ESRD. This likely requires development of an algorithm that consists of diagnoses and a sequence procedure codes for dialysis. The challenge is to distinguish ESRD from conditions that require temporary dialysis treatment.
2. Ensuring complete data among a cohort patients with ESRD. Because of the multiple payer situation described above, ad-hoc programming is likely needed to ensure that DPs contribute rejected claims to the SDD and to use eligibility criteria that help ensure complete data coverage. In addition, diagnostics, such as the presence of expected claims given the patient population, can be used to verify likely data completeness.

## **7 NEXT STEPS**

Because ARIA was deemed insufficient, DEPI-I recommends that DMEP issue a PMR for an observational study of etelcalcetide and fatal GIB. However, even though ARIA was deemed insufficient, Sentinel may offer study options with additional programming. A PBA may be conducted in Sentinel alongside the sponsor's PMR study.

## **8 REFERENCES**

- 1 Centers for Medicare and Medicaid Services: Medicare Coverage of Kidney Dialysis and Kidney Transplant Services, May 1, 2016.  
<https://www.medicare.gov/Publications/Search/results.asp?PubID=10128&PubLanguage=1&Type=PubID>, accessed 7/12/2016

- 2 United States Renal Data System, 2015 Annual Report. <https://www.usrds.org/adr.aspx>, accessed 7/12/2016
- 3 Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). <http://www.ahrq.gov/research/data/hcup/index.html>, accessed 7/12/2016
- 4 Mini-Sentinel Methods – 15 Cohorts of Interest for Surveillance Preparedness SS. February 27, 2014.  
[http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0ahUKEwjGntaCqe7NAhUEGz4KHeoXC\\_YQFggeMAA&url=http%3A%2F%2Fwww.mini-sentinel.org%2Fwork\\_products%2FStatistical\\_Methods%2FMini-Sentinel\\_Methods\\_15-Cohorts-of-Interest-for-Surveillance-Preparedness.pdf&usg=AFQjCNFhxZwXubboxWktJjNsKp07GoQNPw](http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0ahUKEwjGntaCqe7NAhUEGz4KHeoXC_YQFggeMAA&url=http%3A%2F%2Fwww.mini-sentinel.org%2Fwork_products%2FStatistical_Methods%2FMini-Sentinel_Methods_15-Cohorts-of-Interest-for-Surveillance-Preparedness.pdf&usg=AFQjCNFhxZwXubboxWktJjNsKp07GoQNPw), accessed 7/12/2016

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

/s/  
-----

PATRICIA L BRIGHT on behalf of CHRISTIAN HAMPP  
08/19/2016

SIMONE P PINHEIRO  
08/20/2016

GERALD J DALPAN on behalf of ROBERT BALL  
08/22/2016

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

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

## Memorandum

**Date:** August 18, 2016

**To:** Meghna M. Jairath, Regulatory Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)

**From:** Ankur Kalola, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** OPDP Labeling Consult Request

NDA 208325 PARSABIV™ (etelcalcetide) injection, for intravenous use

---

On January 21, 2016, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI) and Carton and Container labeling for Parsabiv. OPDP's comments on the proposed draft PI are based on the version obtained from the DMEP Sharepoint on August 18, 2016. OPDP's comments on the proposed Carton and Container labeling are based on the version dated August 16, 2016, and obtained from DARRTS on August 18, 2016.

OPDP's comments on the PI are provided directly on the marked version below. We have no comments on the Carton and Container labeling at this time.

Thank you for the opportunity to comment on these materials. If you have any questions, please contact Ankur Kalola at 301-796-4530 or [Ankur.Kalola@fda.hhs.gov](mailto:Ankur.Kalola@fda.hhs.gov).

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

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

/s/  
-----

ANKUR S KALOLA  
08/18/2016



Food and Drug Administration  
Office of New Drugs  
Division of Pediatric and Maternal Health  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9744

### PLLR Labeling Memorandum

**Date:** July 27, 2016

**From:** Melissa S Tassinari, PhD DABT, Sr. Clinical Advisor  
Division of Pediatric and Maternal Health

**Through:** Tamara Johnson, MD, MS, Team Leader, Maternal Health  
Division of Pediatric and Maternal Health  
  
Lynne P. Yao, MD, OND, Division Director  
Division of Pediatric and Maternal Health

**To:** Division of Metabolic and Endocrine Products (DMEP)

**Drug:** Parsabiv (etelcalcetide injection)

**NDA:** 208325

**Applicant:** KAI Pharmaceuticals (subsidiary of Amgen)

**Drug Class:** calcium-sensing receptor antagonist

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

**Subject:** Pregnancy and Lactation Labeling Rule (PLLR) – Labeling review only

**Submission Date:**

**Consult Date:** April 15, 2016

**Materials Reviewed:** Proposed and revised labeling for etelcalcetide injection

## **BACKGROUND**

DPMH was consulted by DMEP on April 15, 2016 to assist in the labeling for a new NDA, Parsabiv (etelcalcetide injection). Due to the short timeframe, DPMH agreed to assist in the labeling format and deferred to the review team for the verification of labeling content. DPMH provide its labeling recommendations at a meeting held on April 25, 2016. The Applicant submitted responses to the proposed labeling on May 13, 2016. DPMH prepared responses to the Applicant's concerns in that label and provided to DMEP on May 26, 2016.

## **PLLR**

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*," also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirement include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

## **Recommendations**

DPMH revised highlights, subsections 8.1, 8.2, and section 17 in Parsabiv labeling for compliance with the PLLR (see attached). Sub-section 8.3 was not included in this labeling. DPMH refers to the final NDA action for final labeling.

In addition, DPMH recommends that DMEP consider issuance of a

(b) (5)

[REDACTED]

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

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

/s/  
-----

MELISSA S TASSINARI  
07/27/2016

LYNNE P YAO  
07/27/2016

---

## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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

---

**Date of This Memorandum:** July 18, 2016  
**Requesting Office or Division:** Division of Metabolism and Endocrinology Products (DMEP)  
**Application Type and Number:** NDA 208325  
**Product Name and Strength:** Parsabiv (etelcalcetide), injection, 2.5 mg/0.5 mL, 5 mg/mL, 10 mg/2 mL  
**Submission Date:** June 14, 2016  
**Applicant/Sponsor Name:** Amgen Inc.  
**OSE RCM #:** 2015-2018-1  
**DMEPA Primary Reviewer:** Ariane O. Conrad, PharmD, BCACP, CDE  
**DMEPA Team Leader (Acting):** Hina Mehta, PharmD

---

#### 1 PURPOSE OF MEMO

DMEP requested that we review the revised commercial container label and carton labeling and the sample carton labeling for Parsabiv (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1</sup> Of note, Amgen has proposed to (b) (4) (b) (4) instead of developing a (b) (4) (b) (4). We consulted with Associate Director for Regulatory Affairs (ADRA) staff and they do not agree with Amgen's proposal to (b) (4) (b) (4).

#### 2 CONCLUSION

---

<sup>1</sup> Conrad A. Label and Labeling Review for Parsabiv (etelcalcetide), NDA 208325.. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 May 20. 12 p. OSE RCM No.: 2015-2018.

The revised commercial container label and carton labeling and the sample carton labeling for Parsabiv are acceptable from a medication error perspective. We accept Amgen's assertion that space limitations on the container label would not allow for some of the additional text recommended in the review. We have no further recommendations for these items at this time. However, we do not agree with Amgen's proposal regarding the use of [REDACTED] (b) (4)

### 3 RECOMMENDATIONS FOR AMGEN

We continue to recommend that [REDACTED] (b) (4)

We do not agree with the assertion that the [REDACTED] (b) (4)

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

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

/s/  
-----

ARIANE O CONRAD  
07/18/2016

HINA S MEHTA  
07/19/2016

---

## LABEL AND LABELING REVIEW

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

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

---

**Date of This Review:** May 20, 2016

**Requesting Office or Division:** Division of Metabolic and Endocrinology Products (DMEP)

**Application Type and Number:** NDA 208325

**Product Name and Strength:** Parsabiv (etelcalcetide), injection, 2.5 mg/0.5 mL, 5 mg/mL, 10 mg/2 mL

**Product Type:** Single ingredient

**Rx or OTC:** RX

**Applicant/Sponsor Name:** Amgen Inc.

**Submission Date:** August 24, 2015

**OSE RCM #:** 2015-2018

**DMEPA Primary Reviewer:** Ariane O. Conrad, PharmD, BCACP, CDE

**DMEPA Team Leader:** Yelena Maslov, PharmD

---

## 1 REASON FOR REVIEW

As part of the review process for Parsabiv (etelcalcetide), NDA 208325, submitted to the FDA on August 24, 2015, DMEP requested that DMEPA review the proposed label and labeling for areas that may lead to medication errors.

## 2 MATERIALS REVIEWED

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

| <b>Material Reviewed</b>                    | <b>Appendix Section (for Methods and Results)</b> |
|---|---|
| Product Information/Prescribing Information | A   |
| Previous DMEPA Reviews                      | N/A   |
| Human Factors Study                         | N/A   |
| ISMP Newsletters                            | N/A   |
| FDA Adverse Event Reporting System (FAERS)* | N/A   |
| Other                                       | N/A   |
| Labels and Labeling                         | B   |

N/A=not applicable for this review

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

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA reviewed the proposed labels and labeling provided by Amgen and this review identified several deficiencies in the container label, carton labeling, and prescribing information. We provide recommendations in sections 4.1 and 4.2 and recommend their implementation prior to approval of this application.

## 4 CONCLUSION & RECOMMENDATIONS

We recommend that Amgen increase the readability and prominence of important information in the proposed labels and labeling to clarify information and mitigate confusion that may interfere with the safe use of Parsabiv (etelcalcetide).

### 4.1 RECOMMENDATIONS FOR THE DIVISION

#### A. Prescribing Information (PI) Labeling

- i. We recommend OPQ reviews the statement (b) (4) vial to determine if it should be revised to “single dose” vial.<sup>1</sup>

- ii. Highlights of Prescribing Information-Dosage Forms and Strengths
  - a. Consider revising the statements (b) (4)
    - (b) (4)
    - (b) (4) to state “2.5 mg/0.5 mL”, “5 mg/mL”, and “10 mg/2 mL”.
- iii. Section 2.1 Recommended Dosing
  - a. In order to improve clarity, recommend revising the statement “The recommended (b) (4) dose of [TRADENAME] is 5 mg administered by bolus injection 3 times per week.” to include the phrase “with hemodialysis” to read “The recommended initial dose of [TRADENAME] is 5 mg administered by bolus injection 3 times per week with hemodialysis.”
- iv. Section 3 Dosage Forms and Strengths
  - a. Consider revising the statements “(b) (4)
    - (b) (4)
    - (b) (4) to state “2.5 mg/0.5 mL”, “5 mg/mL”, and “10 mg/2 mL”.
- v. Section 16 How Supplied/Storage and Handling
  - a. Include identifying characteristics to facilitate identification of this product (i.e., clear and colorless solution).
  - b. Remove the word (b) (4) from the phrase “[TRADENAME] for injection” (b) (4)
    - (b) (4)
    - (b) (4) Rephrase to state “[TRADENAME] injection.
  - c. Recommend rephrasing the statement “Store in refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton in order to protect from light.” to “Store in the original carton at 2°C to 8°C (36°F to 46°F) to protect from light.” in order to increase prominence of the directives to retain in the original carton.

#### 4.2 RECOMMENDATIONS FOR AMGEN INC:

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

##### 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

---

<sup>1</sup> Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>.

- 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.<sup>2</sup>
- 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-

---

<sup>2</sup> United States Pharmacopoeia (USP) General Chapter <1> Injections

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.

(b) (4)

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Parsabiv that Amgen submitted on August 24, 2015.

| <b>Table 2. Relevant Product Information for Parsabiv</b> |   |
|---|---|
| <b>Initial Approval Date</b>                              | N/A   |
| <b>Active Ingredient</b>                                  | etelcalcetide   |
| <b>Indication</b>   | Treatment of secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD) on maintenance hemodialysis therapy   |
| <b>Route of Administration</b>                            | intravenous   |
| <b>Dosage Form</b>  | solution  |
| <b>Strength</b>   | 2.5 mg/0.5 mL, 5 mg/mL, 10 mg/2 mL  |
| <b>Dose and Frequency</b>                                 | Starting dose is 5 mg administered by bolus administration 3 times weekly into the venous line of the dialysis circuit at the end of hemodialysis treatment during rinse back or intravenously after rinse back. Dose is titrated in 2.5 or 5 mg increments every 4 weeks to a maximum dose of 15 mg 3 times weekly until parathyroid hormone (PTH) is within desired range.  |
| <b>How Supplied</b>                                       | (b) (4) glass vials are packaged in a carton. Each carton will contain 10 vials per dose strength. The carton is constructed of paperboard that serves to shield the drug product from light.   |
| <b>Storage</b>  | Store in a refrigerator at 2-8°C (36-46°F) in the original carton in order to protect from light. Once removed from the refrigerator, the product must not be exposed to temperatures above 25°C (77°F), must be used within 7 days if stored in the original carton, and must be used within 4 hours and not exposed to direct sunlight if removed from the original carton. |
| <b>Container Closure</b>                                  | Type 1 glass vial with stopper (fluoropolymer laminated elastomeric) and an aluminum seal with flip-off dust cover.   |

## APPENDIX B. LABELS AND LABELING

### B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>3</sup> along with postmarket medication error data, we reviewed the following labels and labeling submitted by Amgen on August 24, 2015. These labels were submitted prior to the approval of the proprietary name, Parsabiv, on November 18, 2015. In addition, Amgen submitted Sample SKU carton labeling for our review on April 29, 2016.

- Container (vial) labels
- Carton labeling

(b) (4)

### B.2 Label and Labeling Images

#### Vial labels

(b) (4)

---

<sup>3</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

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

/s/  
-----

ARIANE O CONRAD  
05/20/2016

YELENA L MASLOV  
05/20/2016

## Clinical Inspection Summary

|                         |   |
|-------------------------|---|
| Date:                   | 4/21/2016   |
| From:                   | Cynthia F. Kleppinger, M.D., OSI/DCCE/GCPAB, Clinical Reviewer<br>Janice Pohlman, M.D., M.P.H., OSI/DCCE/GCPAB, Team Leader<br>Kassa Ayalew, M.D., M.P.H., OSI/DCCE/GCPAB, Branch Chief   |
| To:                     | William Lubas, M.D., Ph.D., Clinical Reviewer<br>Marina Zemskova, M.D., Medical Team Leader<br>Meghna M. Jairath, Pharm.D., Regulatory Health Project Manager<br>Division of Metabolism and Endocrinology Products (DMEP)   |
| Application(s):         | NDA 208325  |
| Applicant:              | KAI Pharmaceuticals, Inc., subsidiary of Amgen, Inc.  |
| Drug:                   | etelcalcetide (AMG 416, KAI-4169)   |
| NME:                    | Yes   |
| Therapeutic Class:      | Calcimimetic  |
| Proposed Indication(s): | Treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis  |
| Consult Request Date:   | 10/20/2015  |
| Summary Goal Date:      | 5/5/2016  |
| Action Goal Date:       | 8/24/2016   |
| PDUFA Date:             | 8/24/2016   |
| Cc:                     | Central Doc. Rm./ NDA 208325<br>DMEP/Division Director/ Jean-Marc Guettier<br>DMEP /Deputy Director/Jim P. Smith<br>DMEP/Team Lead/ Marina Zemskova<br>DMEP/Medical Officer/William Lubas<br>DMEP /Regulatory Project Manager/Meghna M. Jairath<br>OSI/DCCE/Division Director/Ni Aye Khin<br>OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew<br>OSI/DCCE/GCPAB/Team Leader/Janice Pohlman<br>OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger<br>OSI/DCCE/GCPAB/Program Analyst/Joseph Peacock/Yolanda Patague<br>OSI/DCCE/Database Project Manager/Dana Walters |

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of six domestic clinical sites as well as the Sponsor. The inspection of one clinical investigator listed below revealed regulatory violations. The inspection of the Sponsor and the remaining five clinical investigators revealed no regulatory violations. In general, based on the inspections of the six clinical sites and the Sponsor, the inspectional findings support validity of data as reported by the Sponsor under this NDA.

The classification for Dr. Sakhrani is Voluntary Action Indicated (VAI). Although regulatory violations were noted (as described below), they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from this site is acceptable for use in support of the indication for this application. The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results are based on review of the Form FDA 483 and information communicated by the FDA ORA field investigator.

The classification for Drs. Block, Minasian, Ntoso, Sidhu, and Lanier is No Action Indicated (NAI). Data from these sites are considered reliable based on the available information. The full EIR was submitted for review for all sites.

The classification for the Sponsor is NAI. Data from this Sponsor are considered reliable based on the available information. The full EIR was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending EIRs.

There were additional findings at the Sponsor site regarding temperature excursions of the investigational product (IP) at Dr. Sakhrani's site in the on-going open-label extension studies. This is discussed below.

NOTE: (b) (4) participated in joint inspections at the Sakhrani clinical site (San Gabriel, CA) and the Sponsor Amgen (Thousand Oaks, CA). (b) (4)

There were no critical findings.

## II. BACKGROUND

Amgen, Inc. is seeking approval of etelcalcetide (AMG 416) on behalf of KAI Pharmaceuticals, Inc. for treatment of secondary hyperparathyroidism (sHPT) in patients with chronic kidney disease (CKD) on hemodialysis.

Inspections were requested for the following three clinical studies.

- **20120229** A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of AMG 416 in the Treatment of Secondary Hyperparathyroidism in Subjects With Chronic Kidney Disease on Hemodialysis

The study began March 12, 2013 and completed June 12, 2014; conducted at 111 international centers and the United States. There were 508 subjects randomized and 413 subjects who completed the study. Subjects received AMG 416 or placebo at a starting dose of 5 mg three times a week, titrated to a maximum of 15 mg. The primary endpoint was the proportion of subjects with > 30% reduction from baseline in predialysis parathyroid hormone (PTH) during the efficacy assessment phase (defined as weeks 20 to 27, inclusive).

- **20120230** A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of AMG 416 in the Treatment of Secondary Hyperparathyroidism in Subjects With Chronic Kidney Disease on Hemodialysis

The study began March 12, 2013 and completed May 12, 2014; conducted at 97 international centers and the United States. There were 515 subjects randomized and 422 subjects who completed the study. Subjects received AMG 416 or placebo at a starting dose of 5 mg three times a week, titrated to a maximum of 15 mg. The primary endpoint was the proportion of subjects with > 30% reduction from baseline in predialysis parathyroid hormone (PTH) during the efficacy assessment phase (defined as weeks 20 to 27, inclusive).

- **20120360** A Multicenter, Multiple-dose, Two-arm, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet HCl With Intravenous Doses of AMG 416 in Hemodialysis Subjects With Secondary Hyperparathyroidism

The study began August 13, 2013 and completed January 8, 2015; conducted at 164 international centers and the US. There were 683 subjects randomized and 581 subjects that completed the study. The starting dose of AMG 416 was 5 mg, titrated to a maximum of 15 mg. The starting dose of oral investigational product (cinacalcet) was 30 mg and was titrated up to 180 mg. The primary endpoint was the achievement of a > 30% reduction from baseline in mean predialysis serum PTH level during the efficacy assessment phase (weeks 20 to 27, inclusive).

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 208325 in accordance with Compliance Programs 7348.810 and 7348.811. General instructions were also provided with this assignment.

Sites were chosen based on the OSI site selection tool. Only domestic sites were chosen to be inspected.

- (b) (6) was ranked #3 for Study (b) (6) and had reported financial interest.
- Minasian was ranked #1 for Study 230 and had a previous inspection in February 2015 with OAI, downgraded to VAI.
- Sakhrani was ranked #4 for Study 360 and was a high US enroller.
- Ntoso was ranked #3 for Study 229 and was the highest enroller. The site was also involved with Study 360; ranked #131 with two subjects enrolled.
- Sidhu was ranked #6 for Study 229 with many adverse events reported
- Lanier was ranked #22 for Study 360. (b) (4)

### III. RESULTS (by Site):

| Name of CI/ Address Site#   | Protocol # and # of Subjects Randomized                       | Inspection Date                                    | Classification                    |
|---|---|--|-----------------------------------|
| Geoffrey A. Block, M.D.<br>130 Rampart Way, Suite 175<br>Denver, CO 80230<br>Site 66004   | 20120230<br><br>23 subjects                                   | 01/11 –<br>01/15/2016                              | No Action Indicated (NAI)*        |
| Raffi R. Minasian, M.D.<br>1427 South Glendale Avenue<br>Glendale, CA 91205<br>Site 66006   | 20120230<br><br>23 subjects                                   | 01/11–<br>01/14/2016                               | No Action Indicated (NAI)         |
| Lakhi H. Sakhrani, M.D.<br>801 South San Gabriel Boulevard<br>San Gabriel, CA 91776<br>Site 66059   | 20120360<br><br>18 subjects                                   | 02/01–<br>02/05/2016                               | Voluntary Action Indicated (VAI)* |
| Kwabena Ntoso, M.D.<br>150 South Independence Mall<br>Suite 100, Public Ledger Building<br>Philadelphia, PA 19106<br>Site 66009<br>Site 66086 | 20120229<br><br>18 subjects<br><br>20120360<br><br>2 subjects | 12/15 –<br>12/18/2015<br><br>01/07 –<br>01/08/2016 | No Action Indicated (NAI)         |
| Prince J. Sidhu, M.D.<br>521 East Michigan Avenue<br>Kalamazoo, MI 49007<br>Site 66089  | 20120229<br><br>7 subjects                                    | 01/13 –<br>01/19/2016                              | No Action Indicated (NAI)         |
| Douglas C. Lanier, Jr., M.D.<br>South Mississippi Medical Research<br>4300 B West Railroad Street<br>Gulfport, MS 39501<br>Site 66013         | 20120360<br><br>9 subjects                                    | 01/19 –<br>01/22/2016                              | No Action Indicated (NAI)*        |

| Name of CI/ Address Site#   | Protocol # and # of Subjects Randomized | Inspection Date       | Classification             |
|---|---|-----------------------|----------------------------|
| Amgen Inc.<br>1 Amgen Center Drive<br>Thousand Oaks, California 91320 | 20120229<br>20120230<br>20120360        | 02/08 –<br>02/12/2016 | No Action Indicated (NAI)* |

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

\*Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending letter to site.

**NOTE:** Site inspections focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor’s data line listings.

**1. Geoffrey Block/ Site 66004**

There were 32 subjects screened; 23 subjects enrolled into the study and 20 subjects completed. Two subjects were withdrawn by the Sponsor and one subject withdrew consent (due to personal reasons). There were 32 subject records reviewed. The records at this site were well organized. The study director developed worksheets and check lists for the study for each dialysis unit to maintain continuity. The forms were filled out legibly, the information was reviewed and Dr. Block signed off after his review.

The IRB of record was (b) (4). The informed consent was obtained appropriately for each subject. During the course of the study, there were two subjects who were blind and had to have the consent form read to them. According to the site's Standard Operating Procedures, a person who is independent of the trial and attends the informed consent process training may read the informed consent form to the potential subject. This was noted in each of the subjects’ files.

In addition to the consulting fees reported, (b) (6) served as a scientific advisor for (b) (6) and served as a (b) (6) was a member of the (b) (6) (b) (6)

Source documents in the clinical investigator records were compared to the electronic case report forms and the submitted data line listings. There were no discrepancies noted. Additionally the clinical laboratory testing, as noted in the case report forms, was

documented by the presence of completed laboratory records among the source documents. There was no under-reporting of adverse events and the primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

## **2. Raffi Minasian/ Site # 66006\***

(b) (6)

There were 31 subjects screened and 23 subjects enrolled into the study; there were 21 subjects who completed the study. One subject withdrew due to having a kidney transplant and one moved away. There were 31 subject records reviewed. Records were organized and legible.

The IRB of record was (b) (4). The informed consent was obtained appropriately for each subject.

Source records were compared to data line listings. There were no discrepancies. There was no under-reporting of adverse events. The source documents for the primary and secondary endpoints were generated by the study's centralized clinical lab, (b) (4). The calculations for mean iPTH were verified as correct. (The (b) (4) data only had the lab values whereas the Amgen listing included the calculation results). The primary endpoint was verifiable. Ten records were reviewed for secondary endpoints and these were also verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

## **3. Lakhi Sakhrani/ Site # 66059**

There were 24 subjects screened and 18 subjects enrolled into the study. There were 10

subject records reviewed. The site withdrew from the study prematurely and considered six subjects as withdrawn from the study since they did not want to transfer to another site. These subjects had completed the study drug dosing, but not the 30 day follow-up visit (*See discussion below*).

Most of the adverse events were captured except one as noted below. The primary efficacy endpoint was verifiable.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

(b) (4)



(b) (4)



(b) (4)



(b) (4)

(b) (4)

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data for the study requested to be inspected (Study 20120360). Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses for 20120360. Data from this site appear acceptable for Study 20120360.

The Sponsor was asked to submit to the OSI enforcement team all information gathered regarding the activities surrounding Study AMG 20130213. (*See discussion for Sponsor inspection*).

#### **4. Kwabena Ntoso/ Site #s 66009 and 66086**

For Study 20120229, there were 24 subjects screened and 18 subjects enrolled into the study; 16 subjects completed. One subject was terminated for rising parathyroid hormone levels and one subject was terminated due to relocation. Source documents were

compared with eCRFs and data listings for 10 subjects (001, 003, 004, 007, 009, 012, 014, 017, 020, and 021).

For Study 20120360, there were four subjects screened and two enrolled into the study. One subject completed and one was terminated due to non-compliance. Source documents were compared with eCRFs and data listings for both enrolled subjects (002 and 003).

The site records were organized and legible. There were site-generated study worksheets and sponsor-provided study worksheets,

The IRB for both studies was (b) (4). Informed consent documents were verified for all enrolled subjects. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

For Study 20120229, there was a monitor-documented protocol deviation dated 5/30/13. The site (b) (4) the drug incorrectly and administered only half the intended dose. Doses for 13 subjects were affected for the first two months of the study. The site reported the error to the Sponsor and IRB promptly after discovery, and made corrections thereafter, readjusting the 13 subjects' doses going forward in line with the protocol. However, the Sponsor did not report the (b) (4) error to FDA as a protocol deviation.

Dr. Ntoso contacted the Sponsor during the inspection for the rationale about not identifying the error as a protocol deviation. Amgen staff stated that it did not report the deviation because it involved under-dosing as opposed to overdosing.

There were three discussion points for Study 20120229. Dr. Ntoso promised corrections to all discussion points.

(b) (4)

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

## 5. Prince Sidhu/ Site # 66089

There were 14 subjects screened and seven subjects enrolled into the study; six subjects completed the study. One subject withdrew from the study due to use of the prohibited medication, cinacalcet, during one of multiple hospitalizations. There were 14 subject records reviewed. Records were organized and legible.

The IRB of record was (b) (4). All subjects were consented properly. There was no under-reporting of adverse events except as noted below. A comparison of source records and data listings for primary (iPTH) and secondary endpoints (iPTH, calcium, and phosphorus) was performed for all six subjects that remained in the study. No data discrepancies were identified.

There were several observations that were discussion points. These included:

1. Subject randomization was stratified based on whether they had recent exposure to cinacalcet (Sensipar) defined as within 8 weeks prior to randomization. The last dose of cinacalcet for Subject 010 was taken on 08/27/2013 approximately 6 weeks prior to randomization on 10/07/2013. The subject was randomized as not having recent cinacalcet exposure. Handwritten correction was made on the randomization worksheet and it was noted as faxed; however, there was no confirmation the corrected document was transmitted. Data listings continue to indicate the subject did not have recent cinacalcet exposure.
2. Subjects were to remain on a stable dose of Vitamin D through randomization to be eligible for participation. On 07/01/2013, Subject 001 began to receive 4 mcg of Zemplar® at each treatment versus 3 mcg. The subject was randomized 07/12/2013. *The deviation was identified by the site and reported to the Sponsor and IRB during the study.*
3. The protocol states that local iPTH labs “should” be suspended. However, local labs were not fully suspended and were collected unpredictably during the study. Additional explanation and documentation was obtained indicating the iPTH testing continued due to the inability of the local laboratory to comply with the request to suspend testing. Documentation was available that the site requested that the lab suspend testing; physicians were trained not to discontinue subjects if they became aware of their iPTH values and not to make clinical decisions based on this data. In addition, lab values were lined through in the subject binders by an independent party to try and blind the results; however, the data was readily visible to the FDA field investigator in spite of being covered with marker or a stamp. *(See further discussion of this issue in the Sponsor inspection section).*

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability

of the submitted data. Data from this site appear acceptable.

## 6. Douglas C. Lanier/ Site # 66013

There were 18 subjects screened and nine subjects enrolled into the study. Eight of the nine randomized subjects completed the study. One had to withdraw due to relocation. There were 18 subject records reviewed. Records were organized and legible. (b) (6)

The IRB of record was (b) (4). All subjects were consented properly.

The inspection revealed a few errors in dosing, which were identified and reported to the Sponsor and IRB. There was a single event wherein the subject was administered drug from a vial assigned to an earlier visit and he was not titrated up to 10 mg from 5 mg at that visit (Subject 3008 at Week 9 on 12/30/13). This under-dosing event did not appear as a deviation in the study data tables.

One eligibility deviation (cardiac history criteria) was discovered after randomization and the decision was made by the Sponsor to keep the subject (3007) in the trial. This deviation was reported in the data listings and to the IRB.

Subjects on this trial were stratified by the Sponsor based on the screening predialysis serum iPTH value but it was not clear which screening result was to be used. Subject 3005 had screening iPTH values both above and below 900 pg/mL (screening iPTH value was 717.7 pg/mL on 9/12/13 and 1009.2 pg/mL on 9/17/13). The most recent at the time of randomization was 1009.2 pg/mL yet the subject was placed in the <900 pg/mL group. This subject's pre-dialysis serum PTH values throughout the trial were consistently above 900 pg/mL.

It was documented that the PI asked that local testing be suspended but the dialysis center and/or laboratory failed to comply with this request. The local iPTH values were present in the electronic medical records. It appears the investigator made every attempt to blind himself and the study team from this data. (*See further discussion of this issue above and in the Sponsor inspection section*).

There was no under-reporting of adverse events. A comparison of the source documents to the data tables revealed only one omission in the AE listings (a second instance of hypocalcemia on 4/6-10/14 for Subject 3006). Primary and secondary endpoints were verifiable. The secondary efficacy endpoint of the mean number of days of vomiting or nausea per week (Listing 16-88.9) could not be verified during the inspection so the electronic diary data was collected. The sponsor's explanation of the calculation methods was provided after closeout and a post-inspection review using these calculations found the diary data and study tables to be in agreement.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

## 7. Amgen, Inc./Sponsor

The inspection focused on the three clinical protocols and the selected sites with regards to delegation of responsibilities, contractual agreements, selection of sites, training, financial disclosure, translation of documents, data management, the interactive voice/web response system, the evaluation of the adequacy of monitoring and corrective actions taken by the sponsor/monitor/CRO, deviations related to key safety and efficacy endpoints, test article labelling and accountability, quality assurance and audits, adverse events evaluation and reporting, selection of the adjudication committee members and oversight, the data and safety monitoring board oversight, and general monitoring practices.

All three studies were registered with ClinicalTrials.gov. A central IRB [REDACTED] (b) (4) [REDACTED] was used by most of the US sites. There was adequate oversight of the studies. Site selection processes were in place and there was documented training of all staff. The Monitoring Plans for all three studies were followed. Monitoring reports were prepared in a timely manner. There were only a few late reports and most were attributed to a change in monitor or illness of the monitor.

Dates of approval, dates of translation and dates of submission to the sites for informed consent forms/ amendments and protocol/protocol amendments were sampled by reviewing information for sites in Russia and Poland. Translations of documents were done in a timely manner.

Per protocol section 6.1.5 “Investigators will be blinded to central laboratory serum PTH values. Routine local PTH monitoring during the study **should** be suspended. Investigational product dose titration will be managed by an IXRS and will be based on predialysis serum PTH and cCa results obtained during the prior week”.

The Sponsor staff stated that the protocol asked (but did not require) that local iPTH be suspended during the study. For sites that could not suspend the local iPTH, they were to draft a site memo formalizing their plan to maintain the blind. In the US, the majority of the sites were part of the Large Dialysis Organizations (LDOs) – DaVita and Fresenius. The LDOs prepared template memos to aid any of their sites that could not suspend local iPTH. EU and the remaining US sites were handled site by site. There were several sites found during the inspection that had iPTH levels drawn on subjects due to local requirements (the two inspected sites Sidhu and Lanier as noted above, all sites in Turkey, a site in Poland, a site in Canada, a site in Australia). These sites each had a Note to File but some did not have a formal plan. The memo was collected and reviewed by the

monitor; however, no formal approval was given for any plan. The Sponsor was unable to confirm the total number of sites that had local iPTH levels drawn.

Suspending local iPTH was covered in the site initiation visit (SIV) presentation and discussed in the monitoring plan (“In the event local PTH monitoring cannot be suspended, please request sites draft memo outlining plan to maintain blind among research staff”).

A clarification note was sent to all investigators regarding the protocol language of “should” versus “must”. No deviation was captured if the protocol said “should”.

During the inspection of the sponsor, a memo to investigators was noted that stated, “Please keep in mind that (b) (4) PTH values have traditionally been 10-20% lower than many facility’s routine central laboratory and therefore you should continue to screen all subjects close to this inclusion range.” Amgen staff was questioned regarding this statement. Communication between Amgen and (b) (4) regarding the assay for the PTH was requested. The (b) (4) was provided.

The Duke Clinical Research Institute (DCRI) Clinical Events Classification (CEC) Event Adjudication Committee (EAC) was responsible for event adjudication activities related to studies 20120229 and 20120230. All EAC files were paper-based and stored outside of the trial master file (TMF). All files were reviewed during the inspection. The clinical trial coordinator (CTC) was to review the data on all the adjudication forms for accuracy and completeness. If the adjudication form was not complete, the CTC was to follow the CEC Charter regarding completion. Not all the files had the required information. However, there were no inconsistencies with the adjudicated events and the data line listings.

There were no clinical investigators whose studies were terminated by the IRB/EC and/or sponsor for studies 20120229 and 20120230. For Study 20120360, two clinical sites were put on hold and subsequently closed by the Sponsor: USA Site 66059, Dr. Lakhi Sakhrani, and German Site 26012, Dr. Bosselman. Both sites were closed due to GCP non-compliance.

The closure of the Sakhrani site was extensively reviewed. The monitor was doing a site visit for Amgen Study 20130213 on October 30-31, 2014. This study is an ongoing long-term, open-label, phase 3 extension study. It began March 25, 2014 (first subject enrolled) and the data cutoff for the interim analysis report was January 15, 2015. Dr. Sakhrani was Site 66081. The monitor noted an IP refrigerator was in the process of defrosting. The refrigerator and its temperature were unmonitored during the period of October 18-31, 2014 by the site while the person tasked with this responsibility was on vacation. The monitor took photos of IP boxes that appeared wet. The monitor then checked a second IP refrigerator, which was found to be in a farther state of defrost than the first, showing 16°C vs. the required 2-8°C. IP boxes in this refrigerator were also noted to be wet, and the monitor took photos of the affected boxes of IP and shared them with Amgen. The monitor, in consultation with Amgen, immediately directed the site to stop further dosing of all subjects participating in Amgen AMG 416 studies at the site. *Of note, the IP for study 20120360 was stored in a separate refrigerator/freezer.*

Amgen's Clinical Supply/Product Quality group was not able to confirm stability of the drug due to the lack of temperature monitoring during the period of October 18 to October 31, 2014. Amgen determined that, per the clinical temperature excursion disposition reports of the IPs, the IPs were compromised on Nov 07, 2014 for Study 20120231 and on Nov 10, 2014 for Study 20130213. Approximately 60 subjects may have been dosed with potentially compromised IP. In discussions with the Medical Monitor, there were no increased adverse events noted during this timeframe.

A letter was sent by the Sponsor to Dr. Sakhrani November 12, 2014 placing the site on hold due to unresolved GCP issues and protocol compliance. On November 20, 2014 Dr. Sakhrani responded to Amgen's hold letter rejecting the monitor's "unfounded allegations". Dr. Sakhrani then sent a letter to the Sponsor November 25, 2014 withdrawing from Amgen protocols AMG41620130213, AMG41620120213, AMG 41620120360, NESP 20110226, Evolocumab 20110118 and 20130385.

During the inspection, it was stressed that Amgen should report their findings to the FDA (as there were activities of a potential cover-up of the temperature excursions for the open-label extension studies). It was also discussed that there was very little information in the clinical study report about issues found at the Sakhrani site and the fact that the site was terminated. The footnote at the end of Table 9-1 does not reflect all the actions that had taken place ("Eight subjects from Site 66059 withdrew consent from the study. Of the 8 subjects, 6 subjects withdrew consent on 21 November 2014. Subjects withdrew consent subsequent to the investigator's decision to withdraw from the study").

The inspection revealed adequate adherence to the regulations and the investigational plan regarding the three studies requested to be inspected. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

In preparation for inspections, the primary endpoint data had not been sent to the sites and had to be sent. It was stressed to Amgen staff that all data need to be sent to the sites once the trials have closed.

It is recommended that there be further follow-up regarding the temperature excursions found by the Sponsor for studies 20120231 and 20130213. In reviewing the 20130213 interim report, it states that the most frequent important protocol deviations (reported for  $\geq 3$  subjects) were compromised doses of AMG 416 (because of temperature excursions) (13 subjects; 2.4%). None of the subjects listed were from Dr. Sakhrani's site 66081.

Attention is also directed towards the routine local PTH monitoring during the study that was not suspended. Potential unblinding could have easily occurred and was not considered a deviation by the Sponsor.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data for the three studies inspected. Data from this Sponsor appear acceptable for these studies. Concerns found regarding the on-going open-label extension studies performed at

Dr. Sakhrani's site have been communicated above.

*{See appended electronic signature page}*

Cynthia F. Kleppinger, M.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

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

/s/  
-----

CYNTHIA F KLEPPINGER  
04/21/2016

JANICE K POHLMAN  
04/21/2016

KASSA AYALEW  
04/21/2016



**Division of Biotechnology Research and Review II  
Office of Biotechnology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Department of Health and Human Services  
Silver Spring, MD 20993**



**Memorandum of Review (Immunogenicity Consult – AMG 416 (etelcalcetide))**

**Date:** March 29, 2016

**Revised:** April 7, 2016

**Subject:** NDA 208325 [AMG 416 (etelcalcetide)]

**From:** Bruce Huang, Ph. D.  
Division of Biotechnology Research and Review II  
Center for Drug Evaluation and Research, FDA

**Through:** Juhong Liu, Ph. D.  
Acting Review Chief  
Division of Biotechnology Research and Review II  
Center for Drug Evaluation and Research, FDA

**Sponsor:** Amgen Inc., Thousand Oaks, CA

**Product:** AMG 416 (etelcalcetide injection for treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis)

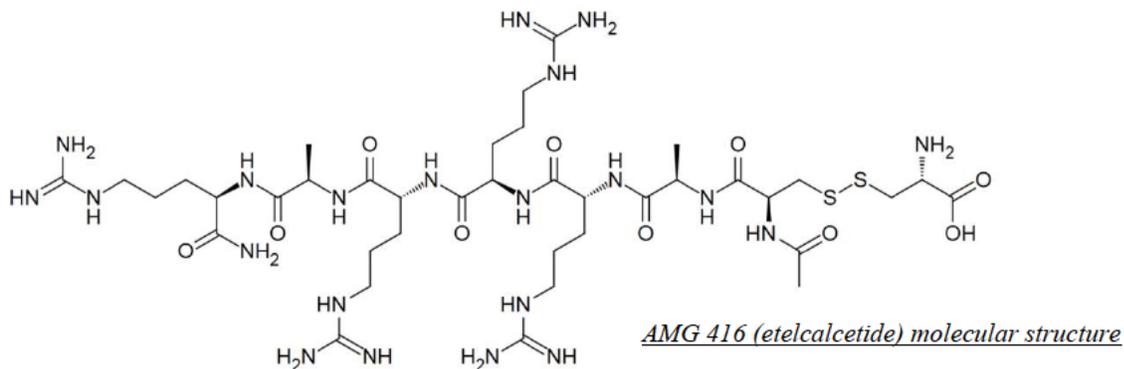
**Consult Aim:** To review the Integrated Immunogenicity Report submitted with this NDA (Section 5.3.5.3 of the original submission Seq 0000 (1) 8/24/2015); and make recommendations on draft labelling under Section 1.14.1.2 of the original submission Seq 0000 (1) 8/24/2015 (Section 6.2 Immunogenicity)

**Review Recommendation:** The data presented by the sponsor demonstrate that the SPR-based immunogenicity assay is properly validated with reasonable binding and confirmatory cut points, sensitivity, specificity and resistance to onboard drug concentration. The assay is suitable for evaluation of the potential presence of anti-AMG 416 antibodies in patient sera. The sponsor provided sufficient data to justify that a neutralizing antibody assay was impractical. The proposed claim on AMG 416 immunogenicity in Section 6.2 of the labelling is supported by the results from this assay. No edits for Section 6.2, paragraph 1 are needed from an immunogenicity perspective.

**REVIEW MEMO**

**Summary of drug and use in proposed indication:**

AMG 416 (etelcalcetide) is a novel synthetic peptide calcimimetic agonist of the calcium-sensing receptor (CaSR), developed for the treatment of secondary hyperparathyroidism (sHPT) in patients with Chronic Kidney Disease (CKD) who are receiving hemodialysis. The structure of AMG 416 is comprised of seven *D*-amino acids linked to an *L*-cysteine via a disulfide bond, which acts as an allosteric activator of the CaSR. The molecular formula is  $C_{38}H_{73}N_{21}O_{10}S_2 \cdot (HCl)_n$  with the hydrochloride salt described chemically as N-acetyl-*D*-cysteinyl-*D*-alanyl-*D*-arginyl-*D*-arginyl-*D*-arginyl-*D*-alanyl-*D*-argininimide, disulfide with *L*-cysteine, hydrochloride; the molecular weight of the monoisotopic free base form is 1047.5. The interaction of AMG 416 with the CaSR in the parathyroid gland results in reversible suppression of parathyroid hormone (PTH) secretion.



### **5.3.5.3 AMG 416 Integrated Immunogenicity Report**

#### ***5.3.5.3 Section 1 – Executive Summary***

Presence of anti-drug antibodies (ADA) in sera from clinical study patients was analyzed by a validated SPR immunoassay. Binding antibodies to AMG 416 was detected in 71 individuals out of 995 total patients administered with AMG 416 (7.1%). However, 80.3% of the 71 ADA positive patients showed pre-existing ADA in their sera.

#### ***5.3.5.3 Section 2 – Risk Assessment***

Prediction of AMG 416 immunogenicity using computer modeling was not performed, because such *in silico* algorithms are largely based on *L*-amino acids, and all the amino acids comprising the main peptide chain of AMG 416 are *D*-amino acids. Additionally, the small size of AMG 416 (seven amino acids total) make processing and presentation to T cells in the context of MHC class II molecules improbable. Furthermore, immunogenicity is unpredictable for compounds in the MW range of 1000 to 5000, (per FDA Guidance for Industry: Immunotoxicology Evaluation). However it is possible that AMG 416 may conjugate to human serum albumin, thus it is conceivable that AMG 416 could be processed and presented to TCR within the context of the serum albumin carrier protein. It is therefore plausible that patients may develop anti-AMG-

416 antibodies and the antibodies may potentially result in unpredictable pharmacokinetics, allergic hypersensitivity, and diminished therapeutic effectiveness. Consequently, Amgen has developed antibody assays to evaluate potential development of anti-AMG 416 antibodies in patient serum samples.

*Reviewers comment: This is an acceptable rationale. The development of antibodies against AMG 416 in the context of conjugation with HSA is a plausible scenario that is worthwhile to screen for, especially as AMG 416 is of relatively small size.*

### **5.3.5.3 Section 3 – Bioanalytical methods**

Two bioanalytical methods have been employed to detect anti-AMG 416 antibodies (ADA) in human serum: 1) a validated ELISA immunoassay (Method protocol GCL-233, see 5.3.1.4: 4169-NC-137; Validation Reports MVR 10-184 [May 2011] and MVR 12-203 [March 2013]) was utilized in the midst of earlier clinical studies; and 2) a validated surface plasmon resonance assay (SPR) (Analytical Method MET-003428; Method Validation MVP-000310 and MVR-000472).

The rationale for exploration of the SPR approach included the ability of the methodology to detect ADA of any isotype, with both low- and high- affinities (thus permitting recognition of both early and mature immune responses), and allowing the usage of both AMG 416 and SAPC (AMG 416 in the context of HSA; also known as HSA-416) as the capture antigen. Therefore, the Sponsor believes that the SPR immunoassay methodology is a more sensitive system than ELISA, and would be a preferable technique for the detection of ADA in the blood of patients receiving AMG 416. Furthermore, in a limited set of patient serum samples tested by both ELISA and SPR immunoassays, a single specimen was found positive for ADA by ELISA, whereas SPR detected the same specimen, and additional samples from the same subject, suggesting a greater sensitivity by the SPR assay. Thus, immunogenicity reported in the Executive Summary (5.3.5.3 Section 1) exclusively refers to data collected by the SPR platform.

*Reviewers comment: This is an acceptable rationale for utilization of an established commercial immunoassay-capable device. The SPR immunoassay methodology is label-free, as detection and measurement of antibody binding is a direct process, and is not dependent on a secondary marker for quantitation of signal. Additionally, the ability to detect all isotypes of ADA is consistent with the recommendations of the “Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins”.*

### **5.3.5.3 Section 3.1 – Generation of Polyclonal Control Reagents**

Three independent immunization campaigns were applied to generate AMG 416-specific antibodies in rabbits (for use as positive controls in AMG 416 immune assays), utilizing the carrier proteins bovine serum albumin (BSA), keyhole limpet hemocyanin (KLH), and/or a boost with AMG 416 complexed with nanoparticles of the biocompatible polymer PLGA. Antibodies

specific for AMG 416 were produced by all three campaigns, however none of the individual or pooled anti-AMG 416 antibodies were shown to have *in vitro* neutralizing ability.

*Reviewer comment: The non-covalent complexing of AMG 416 with PLGA occurs in a conformation-independent manner, so there is no immunological “favoritism” in the choice of epitopes that are available for stimulating naïve B cells having AMG 416 specificity.*

#### **5.3.5.3 Section 3.2 – ELISA-format Immunoassay (method protocol GCL-233)**

*Reviewer comment: The ELISA method for detection of ADA against AMG 416 was not used for the analysis of clinical samples and therefore is not reviewed here.*

#### **5.3.5.3 Section 3.3 – Surface Plasmon Resonance (Biacore) Immunoassay (Method protocol MET-003428)**

The Surface Plasmon Resonance (SPR) immunoassay was developed as a more sensitive, and versatile assay for the detection of ADA against AMG 416 in the serum of patients. Briefly, AMG 416 and AMG 416-HSA conjugates (HSA-416 or AMG 416-HSA) are covalently immobilized to the sensor chip surface on separate flow cells to be used as capture antigens for simultaneous quantitation of ADA in the serum of patients receiving AMG 416. The mass accumulation due to the initial binding of ADA to the AMG 416 or AMG 416-HSA results in alteration of refractive index, and is recorded on the sensorgram as a plot of SPR signal, referred to as binding response units (BRU). The BRU signal is directly proportional to the mass accumulation on the chip surface due to binding of ADA. To confirm if the BRU is due to patient-origin ADA binding to the AMG 416 and/or AMG 416-HSA immobilized to the Biacore chips, goat anti-human IgA+IgG+IgM antibodies are injected to the chips after each sample injection; the mass accumulation due to the anti-human antibodies binding to ADA is referred to as confirmatory response units (CRU). Confirmatory mass increase would only occur in the presence of initial binding by patient ADA to the covalently immobilized AMG 416 and/or AMG 416-HSA. See Table below (3.0 Method Parameters, Doc. No. MET-003428, “Analytical Method for the Detection of Antibodies Against AMG 416 and AMG 416-HSA in Human Serum Using the Biacore 3000”).

#### Method Parameters:

The following chart (Section 3.0 Method Parameters, Doc. No. MET-003428; also: Section 1.0 Analytical Method Validation Report, Doc. MVR-000472) indicates the validated assay parameters that were defined for the SPR assay that was developed for the detection of AMG 416-specific antibodies in the blood of patients.

| Validation Parameter                                     | Results                        |
|--|--------------------------------|
| Sensitivity  | AMG 416 surface: 1289 ng/mL    |
|  | AMG 416-HSA surface: 244 ng/mL |
| LLRD   | AMG 416 surface: 2.0 µg/mL     |
|  | AMG 416-HSA surface: 500 ng/mL |
| Drug Tolerance : AMG 416 surface at LLRD (2 µg/mL)       | 100 ng/mL of AMG 416 drug      |
|  | 1 µg/mL of AMG 416-HSA drug    |
| Drug Tolerance : AMG 416-HSA surface at LLRD (500 ng/mL) | 150 ng/mL of AMG 416 drug      |
|  | 200 ng/mL of AMG 416-HSA drug  |
| Drug Tolerance : AMG 416-HSA surface at 1 µg/mL          | 200 ng/mL of AMG 416 drug      |
|  | 1 µg/mL of AMG 416-HSA drug    |
| Drug Tolerance : AMG 416-HSA surface at 2 µg/mL          | 200 ng/mL of AMG 416 drug      |
|  | 5 µg/mL of AMG 416-HSA drug    |

## **Document MVR-000472 Analytical Method Validation Report**

### **Assay Cut Points:**

Assay cut points (ACP) for both the AMG 416 and AMG 416-HSA-bound SPR assay plate surfaces were established using samples collected from 48 healthy donors, and 48 patients with end-stage renal disease (ESRD). ACPs were assigned for both the Screening and Confirmatory phases of the assay by calculating the upper limit of a one-sided 95% prediction interval for the distribution of the Screening and Confirmatory response units, allowing for a 5% false positive rate for both cut points. The sponsor chose to use the data obtained from the ESRD patient population for ACP determination, claiming that there is no statistical difference in ACP between diseased and normal populations.

*Reviewer comment: It is acceptable to use data obtained from diseased patients for calculation of the ACPs, but the Sponsors assertion that no significant difference exists in ACP between the diseased and normal populations does not seem entirely accurate. While the table depicting the data obtained for the AMG 416 Surface Screen Cut Point Calculation (MVR-000472, Table 2) shows that the Diseased ACP is 100.86 and the Healthy ACP is 101.21, Table 3 (data for AMG 416-HSA Surface Screen Cut Point Calculation) lists the Diseased ACP as 32.47, and the Healthy ACP as 41.29. Furthermore, the Surface Confirmatory Assay Cut Point Calculation for AMG-416 (Table 4) shows 169.59 for the Diseased ACP, and 122.95 for the Healthy ACP; the AMG 416-HSA Surface Confirmatory Assay Cut Point Calculations (Table 5) shows 37.75 for the Diseased ACP, and 28.08 for the Healthy ACP. In some of these cases, the difference in*

calculated ACP values for the Diseased and corresponding Normal patients seems quite large, rather than “not significantly different”. In any case, it makes more sense to use the figures obtained from ESRD patients, rather than healthy donors; in a clinical setting, it does not seem likely that AMG 416 would be administered to healthy patients

### Calculated Assay Cut Points

| Assay Cut Point Name                  | Calculation   | Value                        |
|---------------------------------------|---|------------------------------|
| Screen Assay Cut Point (Screen ACP)   | Upper bound of a one-sided 95% reference interval for the distribution of BRU values to set the Screen ACP. Statistically determined outlier responses were excluded from the final Screen ACP calculation.   | AMG 416 surface: 100.9 RU    |
|                                       |   | AMG 416-HSA surface: 32.5 RU |
| Confirm Assay Cut Point (Confirm ACP) | Upper bound of a one-sided 95% reference interval for the distribution of CRU values to set the Confirm ACP. Statistically determined outlier responses were excluded from the final Confirm ACP calculation. | AMG 416 surface: 169.6 RU    |
|                                       |   | AMG 416-HSA surface: 37.8 RU |

### Assay Sensitivity:

The assay sensitivity was defined as the lowest concentration of antibody detected by the assay that produced a BRU reading above the Screen ACP value. For this determination, rabbit-raised polyclonal antibody against AMG 416 was serially diluted in pooled serum from end-stage renal disease patients at concentrations ranging from 200-25,600 ng/ml, and analyzed over immobilized AMG 416 and AMG 416-HSA SPR assay plate surfaces. The assay was performed on each of 4 days, using 2 separate instruments each day on newly immobilized surfaces, for a total of 8 runs per day. Interpolation of the resulting sensitivity curves produced sensitivity values of 1289 ng/ml for the AMG 416 plate surface, and 244 ng/ml for the AMG 416-HSA plate surface. Though the target sensitivity of <500 ng/ml was achieved for the AMG 416-HSA plate surfaces, the AMG 416 plate surfaces failed to achieve this same level of target sensitivity, and therefore both AMG 416 and AMG 416-HSA SPR assay surfaces will be utilized for testing until clinical data demonstrates that the AMG 416-HSA plate surfaces alone are sufficient for detection of the anti-AMG 416 antibodies in patient serum.

*Reviewer comment: This failure of AMG 416 plate readings to conform to the 500 ng/ml target is not an ideal outcome for the purpose of assay validation, but it appears as though AMG 416-HSA plate readings may be an acceptable alternative. Overall, the Sponsor’s proposed strategy*

of utilizing purified antibody against the DP for this testing is consistent with the FDA “Guidance for Industry” document, as is also their stated target sensitivity of 500 ng/ml.

### Assay Precision:

Utilizing the ADA standard curves that were generated for the Assay Sensitivity assessment (above), inter- and intra-assay precision for AMG 416 and AMG 416-HSA SPR assay surfaces were evaluated by calculation of the %CV for tested standards (analyzed in duplicate) above the measured assay sensitivity. The targeted inter- and intra-assay precision was %CV  $\leq$  20.0 (see table below).

| sample_ID     | AMG 416 Surface              |      |      |                              |      |      | AMG 416-HSA Surface          |       |      |                              |       |      |
|---------------|------------------------------|------|------|------------------------------|------|------|------------------------------|-------|------|------------------------------|-------|------|
|               | Binding Response Units (BRU) |      |      | Confirm Response Units (CRU) |      |      | Binding Response Units (BRU) |       |      | Confirm Response Units (CRU) |       |      |
|               | Avg.RU                       | SD   | %CV  | Avg.RU                       | SD   | %CV  | Avg.RU                       | SD    | %CV  | Avg.RU                       | SD    | %CV  |
| NC1           | 31.9                         | 7.6  | 23.9 | 89.3                         | 19.6 | 21.9 | 10.0                         | 7.9   | 79.0 | 14.8                         | 4.2   | 28.7 |
| PC-200 ng/mL  | 45.3                         | 8.6  | 18.9 | 99.2                         | 20.0 | 20.2 | 29.5                         | 8.2   | 27.6 | 27.7                         | 4.8   | 17.2 |
| PC-400 ng/mL  | 55.9                         | 9.7  | 17.5 | 106.5                        | 19.0 | 17.8 | 46.3                         | 9.5   | 20.4 | 40.3                         | 5.6   | 13.8 |
| PC-600 ng/mL  | 61.3                         | 8.5  | 14.0 | 110.2                        | 18.8 | 17.0 | 54.5                         | 8.6   | 15.8 | 47.8                         | 5.4   | 11.3 |
| PC-800 ng/mL  | 77.4                         | 9.8  | 12.7 | 122.2                        | 16.6 | 13.6 | 81.6                         | 12.3  | 15.1 | 67.2                         | 9.6   | 14.2 |
| PC-1.6 µg/mL  | 119.8                        | 14.5 | 12.1 | 157.0                        | 16.2 | 10.3 | 148.6                        | 18.6  | 12.5 | 120.0                        | 17.3  | 14.4 |
| PC-3.2 µg/mL  | 190.9                        | 11.1 | 5.8  | 214.3                        | 15.4 | 7.2  | 274.6                        | 28.3  | 10.3 | 213.9                        | 28.6  | 13.4 |
| PC-6.4 µg/mL  | 333.6                        | 18.7 | 5.6  | 326.3                        | 14.9 | 4.6  | 505.6                        | 36.2  | 7.2  | 372.2                        | 45.5  | 12.2 |
| PC-12.8 µg/mL | 553.1                        | 32.2 | 5.8  | 474.5                        | 27.1 | 5.7  | 943.8                        | 72.9  | 7.7  | 615.1                        | 76.2  | 12.4 |
| PC-25.6 µg/mL | 837.1                        | 62.9 | 7.5  | 635.5                        | 43.8 | 6.9  | 1634.8                       | 150.6 | 9.2  | 871.6                        | 111.1 | 12.7 |

Of note, the %CV  $\leq$  20.0 target for precision is not met at certain low quantities of ADA (200 and 400 ng/ml, red circle in table), however, the sponsor argues that this should still be regarded as an acceptable result, as 200 ng/ml standard is below the amount corresponding to the ACPs for both the AMG 416 and AMG 416-HSA SPR assay surfaces. Furthermore, the BRU result obtained for PC-400 ng/ml on the AMG 416-HSA surface (20.4) is regarded as acceptable, as 400 ng/ml is below the 600 ng/ml LLOQ of the AMG 416-HSA surface.

*Reviewer comment: The data for this analysis were collected with the Assay Sensitivity experiment (see previous section), therefore an ADA standard curve was prepared on each of 4 assay days, and analysis was conducted using 2 different instruments on newly immobilized AMG 416 or AMG 416-HSA plate surfaces, resulting in 8 separate assay runs. This is not exactly consistent with the recommendations of the FDA Guidance for Industry, which calls for analysis of three replicates on three different days (for Inter-assay Precision), and at least six replicates per plate (for Intra-assay Precision). Overall, the %CV values that were recorded for the BRUs and CRUs are within the targeted range of  $\leq$  20.0%, and these results are acceptable. The values that were noted above for not meeting the targeted %CV  $\leq$  20.0 were either at standard quantities below the amount corresponding to the ACPs, or below the LLOQ.*

### Immobilization Range:

Analyses of multiple immobilization densities (16 each for both AMG 416 and AMG 416-HSA) that were used during assessment of sensitivity and precision were conducted for establishment of the immobilization range for each SPR assay surface. The standard curves were analyzed on immobilizations ranging from 2.2 to 20 RU’s for AMG 416 surfaces, and 2500 to 7206 RU’s for AMG 416-HSA surfaces. The %CV for the standards (average) was 12.7 for AMG 416 and 20.0 for the AMG 416-HSA surfaces. Therefore, the validated immobilization range for the AMG 416 surface is 2.2 to 20 RU’s and 2500 to 7206 RU’s for the AMG 416-HSA surfaces.

Reviewers comment: These data do not seem to have any meaningful significance, as the Sponsor does not indicate any standardized target values or expectations for the Immobilization Range.

### Immuno-reactivity of Immobilized AMG 416 and AMG 416-HSA Surface Over Time:

To analyze the potential for immobilized AMG 416 and AMG 416-HSA on the surface of SPR assay chips to lose immunological reactivity, 101 assay cycles were performed on each surface, with assay controls utilized every 10 cycles. It was found that immobilized AMG 416 and AMG 416-HSA Biacore plate surfaces could tolerate >101 regenerative cycles while maintaining readings within the %CV < 20% acceptance criteria, thus validating immobilized drug surfaces for 101 cycles (see table below).

Reviewer comment: These results demonstrate an acceptable level of durability for the immunological reactivity of immobilized surfaces of plates used in the Biacore assay. The stability of crucial equipment components over multiple usage cycles is essential for demonstrating the consistency of data collection in regards to analytical values that can be compared over the lifetime of the product manufacture.

Table 7. Surface Durability – Summary of assay controls over 101 cycles on each surface

| NC-AMG 416 Surface  |    |            |       |       | NC-AMG 416-HSA Surface  |    |              |       |       |
|---------------------|----|------------|-------|-------|-------------------------|----|--------------|-------|-------|
| Cycle               | Fc | sample_ID  | BRU   | CRU   | Cycle                   | Fc | sample_ID    | BRU   | CRU   |
| 8                   | 1  | NC1        | 25.5  | 40.4  | 109                     | 2  | NC9          | 6     | 12.7  |
| 21                  | 1  | NC2        | 24.1  | 39.7  | 122                     | 2  | NC10         | 5.1   | 12.5  |
| 34                  | 1  | NC3        | 22.6  | 38.9  | 135                     | 2  | NC11         | 4     | 13.1  |
| 47                  | 1  | NC4        | 22.7  | 38.5  | 148                     | 2  | NC12         | 4.4   | 12.7  |
| 60                  | 1  | NC5        | 22.8  | 37.6  | 161                     | 2  | NC13         | 4.3   | 11.8  |
| 73                  | 1  | NC6        | 22.1  | 38.1  | 174                     | 2  | NC14         | 4     | 12.3  |
| 86                  | 1  | NC7        | 21.9  | 36.9  | 187                     | 2  | NC15         | 4.4   | 12.3  |
| 99                  | 1  | NC8        | 21.8  | 35.6  | 200                     | 2  | NC16         | 4.3   | 9.8   |
|                     |    | Avg.       | 22.9  | 38.2  |                         |    | Avg.         | 4.6   | 12.2  |
|                     |    | SD         | 1.3   | 1.5   |                         |    | SD           | 0.7   | 1.0   |
|                     |    | %CV        | 5.5   | 4.0   |                         |    | %CV          | 14.8  | 8.4   |
| LPC-AMG 416 Surface |    |            |       |       | LPC-AMG 416-HSA Surface |    |              |       |       |
| Cycle               | Fc | sample_ID  | BRU   | CRU   | Cycle                   | Fc | sample_ID    | BRU   | CRU   |
| 9                   | 1  | LPC-416 #1 | 146.7 | 141.6 | 110                     | 2  | LPC-416H #1  | 49.4  | 40.8  |
| 22                  | 1  | LPC-416 #2 | 144.8 | 131.5 | 123                     | 2  | LPC-416H #2  | 43    | 35.5  |
| 35                  | 1  | LPC-416 #3 | 145.4 | 133   | 136                     | 2  | LPC-416H #3  | 44.8  | 42.3  |
| 48                  | 1  | LPC-416 #4 | 144   | 130.5 | 149                     | 2  | LPC-416 H #4 | 48.4  | 43.1  |
| 61                  | 1  | LPC-416 #5 | 144.2 | 123.7 | 162                     | 2  | LPC-416H #5  | 48.1  | 41.1  |
| 74                  | 1  | LPC-416 #6 | 136.4 | 125.4 | 175                     | 2  | LPC-416H #6  | 44.9  | 38.2  |
| 87                  | 1  | LPC-416 #7 | 149.6 | 131.5 | 188                     | 2  | LPC-416H #7  | 43    | 35.4  |
| 100                 | 1  | LPC-416 #8 | 145   | 123.5 | 201                     | 2  | LPC-416H #8  | 43.9  | 33.9  |
|                     |    | Avg.       | 144.5 | 130.1 |                         |    | Avg.         | 45.7  | 38.8  |
|                     |    | SD         | 3.7   | 6.0   |                         |    | SD           | 2.6   | 3.5   |
|                     |    | %CV        | 2.6   | 4.6   |                         |    | %CV          | 5.6   | 9.1   |
| HPC-AMG 416 Surface |    |            |       |       | HPC-AMG 416-HSA Surface |    |              |       |       |
| Cycle               | Fc | sample_ID  | BRU   | CRU   | Cycle                   | Fc | sample_ID    | BRU   | CRU   |
| 10                  | 1  | HPC1       | 321   | 270.8 | 111                     | 2  | HPC9         | 430.5 | 299.1 |
| 23                  | 1  | HPC2       | 270.4 | 226.3 | 124                     | 2  | HPC10        | 415.9 | 275.4 |
| 36                  | 1  | HPC3       | 314.6 | 264.5 | 137                     | 2  | HPC11        | 399.3 | 313.8 |
| 49                  | 1  | HPC4       | 333.9 | 270.9 | 150                     | 2  | HPC12        | 399.7 | 295.1 |
| 62                  | 1  | HPC5       | 336.3 | 258.8 | 163                     | 2  | HPC13        | 372.1 | 264.7 |
| 75                  | 1  | HPC6       | 333.8 | 280.3 | 176                     | 2  | HPC14        | 415.1 | 288.8 |
| 88                  | 1  | HPC7       | 340.5 | 273.9 | 189                     | 2  | HPC15        | 402.4 | 259   |
| 101                 | 1  | HPC8       | 315.7 | 245.6 | 202                     | 2  | HPC16        | 422   | 249.4 |
|                     |    | Avg.       | 320.8 | 261.4 |                         |    | Avg.         | 407.1 | 280.7 |
|                     |    | SD         | 22.6  | 17.7  |                         |    | SD           | 18.0  | 22.2  |
|                     |    | %CV        | 7.0   | 6.8   |                         |    | %CV          | 4.4   | 7.9   |

### Lower Limit of Reliable Detection:

Data calculated from a pilot experiment of 8 ESRD patients indicated the LLRD values of 1885.7 ng/ml for the AMG 416 SPR assay surface, and 383.6 ng/ml for the AMG 416-HSA SPR

assay surface. To confirm the LLRD values determined by the pilot experiment, a positive control antibody spike of 2 µg/ml was used to assay the AMG 416 surface, and 500 ng/ml was used to assay the AMG 416-HSA surface. The confirmatory experiment utilized 24 additional ESRD donor sera; SPR assay experiments resulted in all spiked donors (except one) recovering BRU above the ACP for the tested binding surfaces (see table below). The one spiked donor that was below the ACP was re-tested, and the new repeat reading was found to be within acceptable range.

*Reviewers comment: These findings are generally acceptable for validating the lower limit of reliable detection. It is notable that some ESRD donor sera already read above the ACP before the addition of the control antibody spike, indicating that these donors may already have pre-existing AMG 416-specific antibodies in their blood before having been administered the drug. Interestingly, in most instances, an unspiked sample that shows an SPR reading above the cut point for AMG 416 also shows an SPR reading above the AMG 416-HSA cutpoint (but this is not always the case, see sample\_ID's BRH793200, and BRH793214).*

| sample ID | AMG 416 Surface: ACP=100.9 BRU                   |       |        |       | AMG 416-HSA Surface: ACP=32.5 BRU |      |        |      |
|-----------|--|-------|--------|-------|-----------------------------------|------|--------|------|
|           | Unspiked   |       | Spiked |       | Unspiked                          |      | Spiked |      |
|           | BRU  | CRU   | BRU    | CRU   | BRU                               | CRU  | BRU    | CRU  |
| BRH793186 | 52.1   | 29.5  | 162.1  | 103.9 | 18.2                              | 8.3  | 78.7   | 42.6 |
| BRH793187 | 58.4   | 43.3  | 166.9  | 101.1 | 14.2                              | 12.9 | 66.4   | 40.5 |
| BRH793188 | 31.6   | 129.2 | 130.6  | 156   | -10.5                             | 21.6 | 39.5   | 50.1 |
| BRH793211 | 246  | 95    | 255.7  | 124.6 | 42.8                              | 19.2 | 79.1   | 45.6 |
| BRH793212 | 68.1   | 19.9  | 136.9  | 81.2  | -6.4                              | 10.4 | 43.2   | 39.7 |
| BRH793213 | 41.1   | 68.4  | 113.7  | 105.7 | 5.1                               | 16.6 | 57.2   | 43.7 |
| BRH793189 | 170.1  | 216.3 | 261.7  | 275   | 65.4                              | 44.8 | 105.4  | 76.4 |
| BRH793190 | 11.8   | 81.5  | 116    | 155.6 | 15.8                              | 12.7 | 64.2   | 50.9 |
| BRH793191 | 55.6   | 137.6 | 157.6  | 213.7 | 21.3                              | 24.9 | 72.1   | 69.1 |
| BRH793192 | -6.1   | 61.5  | 110.3  | 138.6 | 6.5                               | 10.1 | 54.1   | 48.1 |
| BRH793193 | -2.5   | 45.4  | 103.4  | 127.5 | -1.5                              | 9    | 50.2   | 48.2 |
| BRH793194 | 39   | 117.7 | 148.7  | 195.8 | 23.4                              | 26.7 | 70.4   | 63.3 |
| BRH793195 | 34.9   | 116.1 | 140.4  | 181.8 | 10.3                              | 21   | 57.8   | 53.9 |
| BRH793196 | 1.5  | 64    | 109.1  | 160.1 | -12.5                             | 13.4 | 40.5   | 83   |
| BRH793197 | 10.5   | 60.9  | 105.5  | 131.1 | 10.5                              | 8.8  | 51     | 44.5 |
| BRH793198 | 22.8   | 93.8  | 127.4  | 173   | 7.4                               | 19   | 54.2   | 57.9 |
| BRH793199 | 37.2   | 59.3  | 127.3  | 135.2 | 8.2                               | 11.4 | 57.8   | 49.9 |
| BRH793200 | 112.9  | 157   | 206.6  | 222.3 | 27.3                              | 28.2 | 79.5   | 70.4 |
| BRH793214 | 71.3   | 139.2 | 151.4  | 182.4 | 38.8                              | 24   | 80.9   | 60.8 |
| BRH793215 | 15.6   | 89.7  | 121.1  | 159.6 | 0.6                               | 14   | 49.1   | 53.2 |
| BRH793216 | 21   | 78.9  | 121.4  | 137.8 | 18.5                              | 13.8 | 61.6   | 52.4 |
| BRH793217 | 27.2   | 62    | 126.4  | 132.4 | 17.3                              | 11   | 57.6   | 49.7 |
| BRH793218 | 16.4   | 75.9  | 118.7  | 140.6 | 12.8                              | 13.8 | 60.8   | 54.3 |
| BRH793219 | 255.7  | 243   | 283.6  | 228.3 | 79.8                              | 70.7 | 94.9   | 85.2 |
| BRH793220 | 49.7   | 169.1 | 150.9  | 208.3 | 26.7                              | 29.5 | 71.8   | 67.4 |
| BRH793221 | 26.4   | 82.7  | 124    | 156.6 | 20.5                              | 11.6 | 65.1   | 49.2 |
| BRH793222 | 23.3   | 96.1  | 106.2  | 161.4 | -4.4                              | 21.4 | 44     | 60.7 |
| BRH793223 | 8.8  | 48.6  | 113.5  | 139.3 | -9.9                              | 10.9 | 36.8   | 51.5 |
| BRH793224 | -0.3   | 55.1  | 103.6  | 141.1 | -11                               | 12.6 | 36.2   | 51.6 |
| BRH793225 | -7   | 38.3  | 98.2*  | 126.6 | -13.8                             | 10.9 | 34.7   | 50.5 |
| *         | Repeat analysis(3/17/2014) response was 110.2 RU |       |        |       |                                   |      |        |      |

### Drug Tolerance Limit:

The assay for potential AMG 416 drug tolerance effects utilized various concentrations of AMG 416 and AMG 416-HSA spiked into pooled serum obtained from ESRD patients with added positive control rabbit anti-AMG 416 antibody, to simulate the effect that residual AMG 416 in the patients' bloodstreams might have in interfering with the SPR assay to detect anti-AMG 416 antibodies. As the LLRD for the AMG 416 SPR assay surface was determined to be 2 µg/ml (see previous section), the drug tolerance for the AMG 416 SPR assay surface was tested for the potential interfering effect of 0 and 2 µg/ml of positive control antibody. Additionally, the LLRD for the AMG 416-HSA SPR assay surface was determined to be 500 ng/ml; drug tolerance for the AMG 416-HSA SPR assay surface was assayed for the potential interfering effects of 0, 500, 1000, and 2000 ng/ml of positive control antibody. The drug tolerance target at the LLRD is 50 ng/ml. The results of these experiments are shown below:

Drug Tolerance for AMG 416 Surface:

| Anti-AMG 416 Concentration | Drug Name | Concentration ng/mL | BRU   | CRU   | IM Status |
|----------------------------|-----------|---------------------|-------|-------|-----------|
| 2000 ng/mL                 | AMG 416   | 200                 | 92.9  | 143.1 | Negative  |
| 2000 ng/mL                 | AMG 416   | 150                 | 94.4  | 143.4 | Negative  |
| 2000 ng/mL                 | AMG 416   | 100                 | 107.2 | 151.1 | Positive  |
| 2000 ng/mL                 | AMG 416   | 50                  | 124.8 | 177.8 | Positive  |
| 2000 ng/mL                 | AMG 416-H | 5000                | 44.6  | 93.3  | Negative  |
| 2000 ng/mL                 | AMG416-H  | 1000                | 108.5 | 152.8 | Positive  |
| 2000 ng/mL                 | AMG416-H  | 200                 | 137.7 | 178.3 | Positive  |
| 2000 ng/mL                 | AMG416-H  | 100                 | 141.8 | 183.5 | Positive  |
| 2000 ng/mL                 | AMG416-H  | 50                  | 147.1 | 187.7 | Positive  |
| 0 ng/mL                    | AMG 416   | 200                 | 21.2  | 80.1  | Negative  |
| 0 ng/mL                    | AMG 416   | 150                 | 9.3   | 59.8  | Negative  |
| 0 ng/mL                    | AMG 416   | 100                 | 19.1  | 77.5  | Negative  |
| 0 ng/mL                    | AMG 416   | 50                  | 7.8   | 55.5  | Negative  |
| 0 ng/mL                    | AMG 416-H | 5000                | 9.7   | 59.4  | Negative  |
| 0 ng/mL                    | AMG416-H  | 1000                | -0.1  | 42.2  | Negative  |
| 0 ng/mL                    | AMG416-H  | 200                 | 9.5   | 56.3  | Negative  |
| 0 ng/mL                    | AMG416-H  | 100                 | 6.6   | 52.8  | Negative  |
| 0 ng/mL                    | AMG416-H  | 50                  | 7.3   | 53.2  | Negative  |

The AMG 416 SPR assay surface was found to be capable of tolerating  $\geq 100$  ng/ml of soluble AMG 416 and  $\geq 1$  µg/ml of AMG 416-HSA at the LLRD concentration of the positive control antibody (2000 ng/ml).

Drug Tolerance for AMG 416-HSA Surface:

| Anti-AMG 416 Concentration | Drug Name | Concentration ng/mL | BRU   | CRU   | IM Status |
|----------------------------|-----------|---------------------|-------|-------|-----------|
| 500 ng/mL                  | AMG 416   | 200                 | 31    | 43.8  | Negative  |
| 500 ng/mL                  | AMG 416   | 150                 | 34.1  | 44.7  | Positive  |
| 500 ng/mL                  | AMG 416   | 100                 | 34.1  | 44.7  | Positive  |
| 500 ng/mL                  | AMG 416   | 50                  | 41.7  | 49.6  | Positive  |
| 500 ng/mL                  | AMG 416-H | 5000                | 9.6   | 22.3  | Negative  |
| 500 ng/mL                  | AMG416-H  | 1000                | 19.7  | 29.3  | Negative  |
| 500 ng/mL                  | AMG416-H  | 200                 | 33.7  | 41.5  | Positive  |
| 500 ng/mL                  | AMG416-H  | 100                 | 38.5  | 44.8  | Positive  |
| 500 ng/mL                  | AMG416-H  | 50                  | 40    | 46.6  | Positive  |
| 1000 ng/mL                 | AMG 416   | 200                 | 58.5  | 63.5  | Positive  |
| 1000 ng/mL                 | AMG 416   | 150                 | 69.6  | 73    | Positive  |
| 1000 ng/mL                 | AMG 416   | 100                 | 66.8  | 71.4  | Positive  |
| 1000 ng/mL                 | AMG 416   | 50                  | 72.1  | 75.6  | Positive  |
| 1000 ng/mL                 | AMG 416-H | 5000                | 15.7  | 26.4  | Negative  |
| 1000 ng/mL                 | AMG416-H  | 1000                | 52.7  | 33    | Positive  |
| 1000 ng/mL                 | AMG416-H  | 200                 | 62.5  | 64.5  | Positive  |
| 1000 ng/mL                 | AMG416-H  | 100                 | 70.1  | 71.9  | Positive  |
| 1000 ng/mL                 | AMG416-H  | 50                  | 75.7  | 77.6  | Positive  |
| 2000 ng/mL                 | AMG 416   | 200                 | 117.1 | 120.2 | Positive  |
| 2000 ng/mL                 | AMG 416   | 150                 | 123.5 | 121.5 | Positive  |
| 2000 ng/mL                 | AMG 416   | 100                 | 129.1 | 124.3 | Positive  |
| 2000 ng/mL                 | AMG 416   | 50                  | 145.6 | 139.4 | Positive  |
| 2000 ng/mL                 | AMG 416-H | 5000                | 48.5  | 45    | Positive  |
| 2000 ng/mL                 | AMG416-H  | 1000                | 122.4 | 119.1 | Positive  |
| 2000 ng/mL                 | AMG416-H  | 200                 | 154.6 | 144.5 | Positive  |
| 2000 ng/mL                 | AMG416-H  | 100                 | 166.3 | 162.7 | Positive  |
| 2000 ng/mL                 | AMG416-H  | 50                  | 158.4 | 147.5 | Positive  |
| 0 ng/mL                    | AMG 416   | 200                 | 21.2  | 80.1  | Negative  |
| 0 ng/mL                    | AMG 416   | 150                 | 9.3   | 59.8  | Negative  |
| 0 ng/mL                    | AMG 416   | 100                 | 19.1  | 77.5  | Negative  |
| 0 ng/mL                    | AMG 416   | 50                  | 7.8   | 55.5  | Negative  |
| 0 ng/mL                    | AMG 416-H | 5000                | 9.7   | 59.4  | Negative  |
| 0 ng/mL                    | AMG416-H  | 1000                | -0.1  | 42.2  | Negative  |
| 0 ng/mL                    | AMG416-H  | 200                 | 9.5   | 56.3  | Negative  |
| 0 ng/mL                    | AMG416-H  | 100                 | 6.6   | 52.8  | Negative  |
| 0 ng/mL                    | AMG416-H  | 50                  | 7.3   | 53.2  | Negative  |

At the LLRD concentration of the positive control antibody (500 ng/ml), the AMG 416-HSA SPR assay surface is capable of tolerating  $\geq 150$  ng/ml of soluble AMG 416 and  $\geq 200$  ng/ml AMG 416-HSA. At a higher concentration of positive control antibody (1000 ng/ml), the AMG 416 SPR assay surface is capable of tolerating  $\geq 200$  ng/ml of soluble AMG 416, and  $\geq 1000$  ng/ml of soluble AMG 416-HSA. At the highest tested concentration of positive control antibody (2000 ng/ml), the AMG 416 SPR assay surface is capable of tolerating  $\geq 200$  ng/ml of soluble AMG 416, and  $\geq 5000$  ng/ml of soluble AMG 416-HSA.

*Reviewers comment: The experimentally determined values for drug tolerance at LLRD are 150 ng/ml for the AMG 416 surface and 200 ng/ml on the AMG 416-HSA surface. Considering all assay validation results indicate the AMG 416-HSA surface is a better test platform than the AMG 416 surface, ADA results from the AMG 416-HSA surface is likely to be more reflective of true results. The analyses of ADA should therefore be based more on results from this surface, and the results from the AMG 416 surface can be used to confirm the AMG 416-HSA results. In this scenario, the 200 ng/ml tolerance is higher than the drug levels in patient sera as shown in pharmacokinetic data (Study 20120229). The tolerance level is therefore suitable for the purpose of the assay.*

**Assay Specificity:**

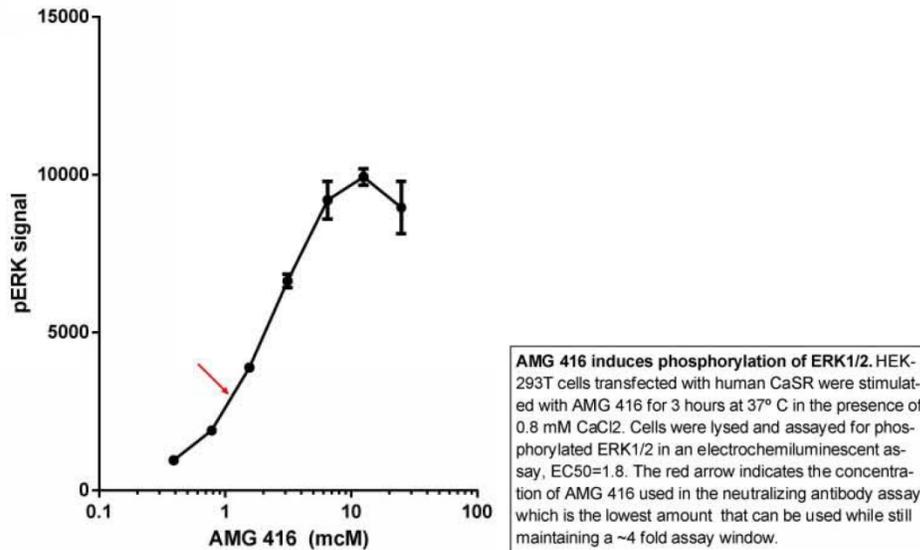
To evaluate the impact of hemoglobin, bilirubin, and lipids in patient serum on the validity of the SPR assay, these serum constituents were spiked into pooled ESRD serum for negative sample analysis, and pooled ESRD serum with the positive control antibody (2 µg/ml and 500 ng/ml) for analysis on AMG 416 and AMG 416-HSA SPR assay surfaces. These experiments showed that the tested interference factors did not negatively influence the assay (see chart below).

*Reviewers comment: These results are adequate to show that such factors as hemoglobin, bilirubin, and lipids, in the concentrations tested by the sponsor, will not interfere with the accuracy of the assay. It is noteworthy that in some cases, the concentrations of interfering factors used by the sponsor in their assay are far in excess to those seen in normal human sera, thus strengthening their assertion that the SPR assay is specific, and can overcome various interfering factors.*

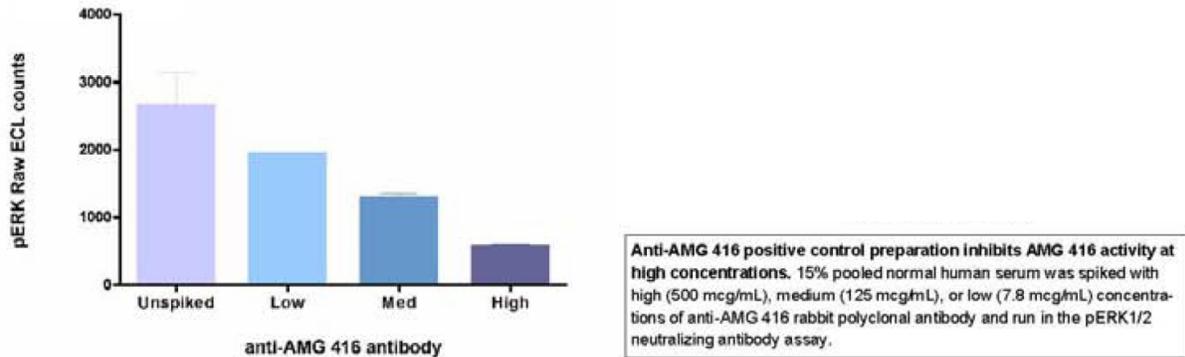
| Anti-AMG 416 Concentration | Serum Interference Factor    | Tested Surface | BRU   | CRU   | IM Status |
|----------------------------|------------------------------|----------------|-------|-------|-----------|
| 2000 ng/mL                 | Hemoglobin- 5mg/mL           | AMG 416        | 147.9 | 212.6 | Positive  |
| 2000 ng/mL                 | Unconj-Bilirubin : 0.2 mg/mL | AMG 416        | 139.7 | 216.1 | Positive  |
| 2000 ng/mL                 | Conj-Bilirubin : 0.2 mg/mL   | AMG 416        | 141.8 | 218.5 | Positive  |
| 2000 ng/mL                 | Intra Lipids : 1.10          | AMG 416        | 145   | 218   | Positive  |
| 2000 ng/mL                 | Intra Lipids : 1.20          | AMG 416        | 152.7 | 228.8 | Positive  |
| 2000 ng/mL                 | Hemoglobin- 5mg/mL           | AMG 416-H      | 200.5 | 177.3 | Positive  |
| 2000 ng/mL                 | Unconj-Bilirubin : 0.2 mg/mL | AMG 416-H      | 181.1 | 177   | Positive  |
| 2000 ng/mL                 | Conj-Bilirubin : 0.2 mg/mL   | AMG 416-H      | 170.7 | 139.4 | Positive  |
| 2000 ng/mL                 | Intra Lipids : 1.10          | AMG 416-H      | 187.8 | 172.1 | Positive  |
| 2000 ng/mL                 | Intra Lipids : 1.20          | AMG 416-H      | 178.1 | 164.8 | Positive  |
| 500 ng/mL                  | Hemoglobin- 5mg/mL           | AMG 416-H      | 58.3  | 50.8  | Positive  |
| 500 ng/mL                  | Unconj-Bilirubin : 0.2 mg/mL | AMG 416-H      | 43.9  | 53    | Positive  |
| 500 ng/mL                  | Conj-Bilirubin : 0.2 mg/mL   | AMG 416-H      | 45.3  | 52.3  | Positive  |
| 500 ng/mL                  | Intra Lipids : 1.10          | AMG 416-H      | 42.3  | 49.6  | Positive  |
| 500 ng/mL                  | Intra Lipids : 1.20          | AMG 416-H      | 43.9  | 50.4  | Positive  |

**5.3.5.3 Section 3.4 – Bioassay for Neutralizing Antibody Activity against AMG 416**

Development of a ligand-binding *in vitro* assay was attempted to detect AMG 416 neutralizing antibodies (see 5.3.5.3 Appendix 3). As a first step, specificity of AMG 416 binding was assayed. HEK293T cells, or HEK293T cells transfected with CaSR, were incubated with biotinylated AMG 416, and then incubated with streptavidin-APC for detection of bound AMG 416. This binding assay was found to lack specificity, as equal binding was detected in both the CaSR-transfected and non-CaSR-transfected cells. In further characterization of this non-specific binding, it was found that biotinylated AMG 416 bound irrelevant proteins as well as the target CaSR; this association was likely charge-based, and distinct from the specific agonistic binding of AMG 416 to CaSR. In light of these results, the Sponsor concluded that a ligand binding assay was not a practicable methodology for the evaluation of AMG 416 binding specificity. Therefore a specific cell-based activity assay was developed, using HEK293T cells expressing transfected CaSR, with phosphorylation of ERK1/2 serving as the assay endpoint, as quantitated by electrochemiluminescent immunoassay readout.



The figure (above) shows the results of an experiment demonstrating the dose-responsive effect of increasing concentrations of AMG 416 on the pERK electrochemiluminescent immunoassay readout in the CaSR-transfected HEK293T cell system.

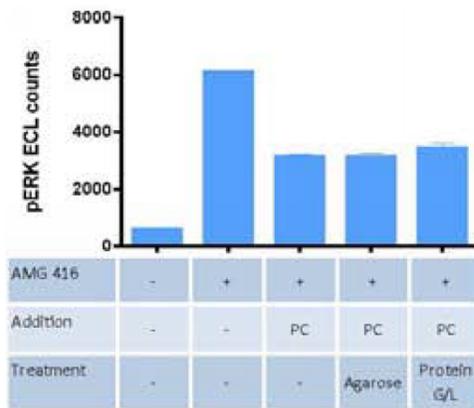


The rabbit-raised polyclonal antibody used as a positive control model (for the blocking ADA that could potentially be present in patient serum) in pooled human serum is a poor neutralizer of AMG 416 activity. A very high antibody concentration of approximately 1mg/ml (in undiluted serum) would be necessary to obtain even 50% inhibition.

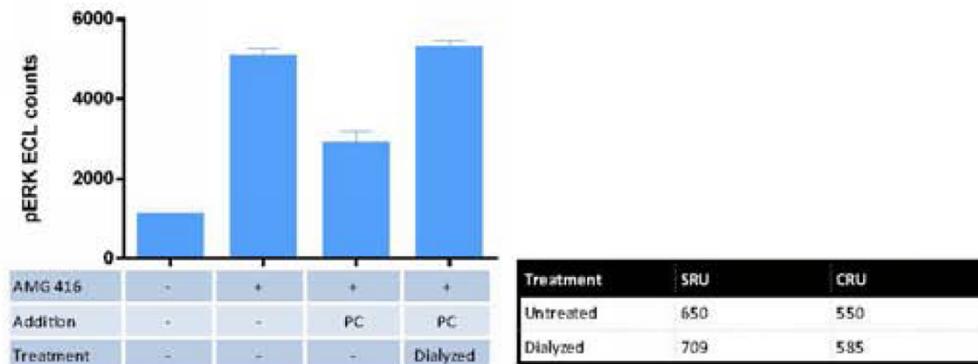
To further test the potential rabbit-raised polyclonal AMG 416 positive control blocking antibody, the pERK electrochemiluminescent immunoassay was conducted using human serum with added rabbit-raised polyclonal antibody against AMG 416 that had been passed through columns of either blank agarose, or protein G/protein L-coupled agarose. As evidenced by the SPR immunoassay data shown below, the protein G/L agarose column was very effective at clearing the rabbit polyclonal anti-AMG 416 binding antibodies from the human serum preparation.

| Treatment   | SRU   | CRU   | % Inhibition |
|-------------|-------|-------|--------------|
| Untreated   | 823.8 | 613.5 | NA           |
| Agarose     | 747.3 | 587.9 | 9.3%         |
| Protein G/L | 23.3  | 24.5  | 97.2%        |

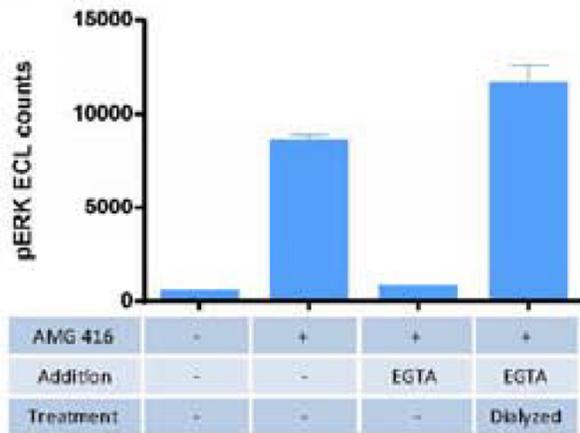
Surprisingly, the depletion of the polyclonal anti-AMG 416 binding antibodies (indicated by “PC” in the figure below) from the human serum preparation by Protein G/L had little effect in restoring the pERK electrochemiluminescent immunoassay readout, shown below.



In contrast, subjecting the human serum and anti-AMG 416 binding antibodies to dialysis with 10kDa cut-off completely removed the inhibitory activity, indicating that neutralization of AMG 416 activity was due to an entity in the antibody preparation with a sub-10kDa molecular weight (ie. most likely not an antibody at all; see graph below). SPR immunoanalysis of the dialyzed human serum with rabbit-raised polyclonal antibody against AMG 416 revealed that the antibody still remained in the dialyzed samples, and was still capable to binding AMG 416 (see chart below), indicating that the neutralization of AMG 416 was most likely due to a small molecular-weight entity of less than 10kDa that was present in the polyclonal antibody preparation, and not the antibody itself.



As an additional control, EGTA (a chelator of calcium ions, which interferes with AMG 416 activity) was tested in a dialyzed or non-dialyzed setting (see graph below), demonstrating that the blocking of AMG 416 activity that was observed by addition of the polyclonal antibody preparation might have been attributable to the presence of EGTA in the antibody preparation. Thus, the sponsor concludes that even high levels of anti-AMG 416 antibodies are not capable of having neutralizing activity by virtue of the antibodies themselves, and thus can find no indication that antibodies elicited against AMG 416 would be able to neutralize the activity of the drug.



*Reviewer comment: The sponsor has conducted sufficient in vitro experiments to show that a cell-based neutralizing antibody (NAb) assay is impractical since even high affinity antibodies raised against AMG 416 do not have blocking ability with regards to the drug activity. This is acceptable from a practical point. The clinical division will have to make a decision on whether the lack of NAb assay impacts approvability.*

### 5.3.5.3 Section 5 – Clinical Study Results

#### 5.3.5.3 Section 5.1 – Pre-existing Antibodies

The AMG 416 clinical trials performed to date examining immunogenicity are listed in Table 3, below. Several trials utilized an indirect-ELISA method, with the incidence of anti-AMG 416 ADA being relatively rare (3.1%, 0.0%, 1.3%, and 0.0%). Trials utilizing the SPR procedure were somewhat more successful in detecting such antibodies, suggesting a higher sensitivity inherent to the methodology (some findings of up to 15.1%). Within these studies, 80.3% of ADA incidences were shown to be pre-existing in the patients before exposure to AMG 416. Additionally, no instances of immunological response boosting of more than two-fold over the pre-existing response were found.

*Reviewer comment: The data chart depicting the SPR assay results measured at various times from patients administered AMG 416 show several incidences of anti-AMG 416 antibody positivity in the collected sera by the SPR method, however these data do show that in many*

*instances, the positivity is pre-existing on Day 1, and in these patients, there is no pronounced rise in the detected levels of anti-AMG 416 antibody over the course of the treatment period that would indicate any boosting effect due to later exposure of an immunogenic antigen.*

#### 5.3.5.3 Section 5.2 – Development of AMG 416-specific ADA in treated patients

The total incidence of anti-AMG 416 ADA found by the SPR method in sHPT patients treated with AMG 416 for up to six months was 7.1% (71/995); out of the total number of patients, only 1.5% developed ADA after exposure to AMG 416 (having been ADA-negative prior to commencement of AMG 416 treatment).

*Reviewer comment: These figures of “de novo” AMG 416-specific antibody development in patients (after beginning treatment) are somewhat modest in comparison to those of the patients with pre-existing AMG 416 ADA; these data are disclosed in the proposed label text, however the label does not mention that the* (b) (4)

#### 5.3.5.3 Section 5.3 – Impact of anti-AMG 416 Antibodies

Among the pooled data combining the two Phase 3, multi-center, randomized, double-blind, placebo-controlled studies (#20120229 and #20120230; Safety Analysis Set) with the highest SPR-analyzed incidences of AMG 416 ADA, 503 subjects received AMG 416. These patients were analyzed for ADA on day 1, week 12, week 27, and at study follow-up. Of these 503 patients, 11.1% (56) were found with anti-AMG 416 antibodies. Of these 56 patients, 43 had pre-existing ADA, and 13 developed ADA only after exposure to AMG 416.

**Table 3. Clinical Immunogenicity of AMG 416**

| Study  | Design   | Assay <sup>a</sup> | Incidence (%)               |
|--|--|--------------------|-----------------------------|
| <a href="#">20130107</a><br>(formerly KAI-4169-001)    | Phase 1, single-center, randomized, double-blind, placebo-controlled, single ascending dose  | ELISA              | 1/32 (3.1%)                 |
| <a href="#">20130139</a><br>(formerly KAI-4169-002)    | Phase 1, multicenter, randomized, double-blind, placebo-controlled, crossover or parallel, single ascending dose                                     | ELISA              | 0/28 (0%)                   |
| <a href="#">20120330</a><br>(formerly KAI-4169-003)    | Phase 2, multicenter, randomized, double-blind, placebo-controlled, multiple-dose, dose escalation   | ELISA              | 1/78 (1.3%)                 |
| <a href="#">20120331</a><br>(formerly KAI-4169-005)    | Phase 2, multicenter, open-label, single-arm, multiple-dose, dose titration  | ELISA              | 0/37 (0%)                   |
| <a href="#">20120334</a><br>(formerly KAI-4169-005-01) | Phase 2, multicenter, open-label, single-arm extension of Study <a href="#">20120331</a>   | SPR                | 3/30 (10%)                  |
| <a href="#">20120229</a>                               | Phase 3, multicenter, randomized, double-blind, placebo-controlled   | SPR                | 38/251 (15.1%) <sup>#</sup> |
| <a href="#">20120230</a>                               | Phase 3, multicenter, randomized, double-blind, placebo-controlled   | SPR                | 18/252 (7.1%) <sup>#</sup>  |
| <a href="#">20120359</a>                               | Phase 3, multicenter, open-label, single-arm, multiple-dose, switch study from oral cinacalcet HCl to IV AMG 416                                     | SPR                | 7/148 (4.7%) <sup>#</sup>   |
| <a href="#">20120360</a>                               | Phase 3, multicenter, 2-arm, active-controlled, double-blind, double-dummy, multiple dose  | SPR                | 8/338 (2.4%) <sup>#</sup>   |
| <a href="#">20130147</a>                               | Phase 1, single-center, open-label, single-arm, single dose  | SPR                | 0/6 (0%) <sup>#</sup>       |
| <a href="#">20120231</a>                               | Phase 3, multicenter, open-label, single-arm extension of Studies <a href="#">20120229</a> , <a href="#">20120230</a> , and <a href="#">20120359</a> | SPR                | 46/832 (5.5%)*              |

<sup>a</sup> Two varieties of anti-AMG 416 immunoassay have been implemented: an indirect-ELISA format assay (GCL-233), and a surface-plasmon resonance (SPR) dual flow cell assay (MET-003428).

<sup>#</sup> - Included in the incidence presented in the executive summary (7.1%; 71 out of 995).

\* - Interim Analysis as of 15 JAN 2015.

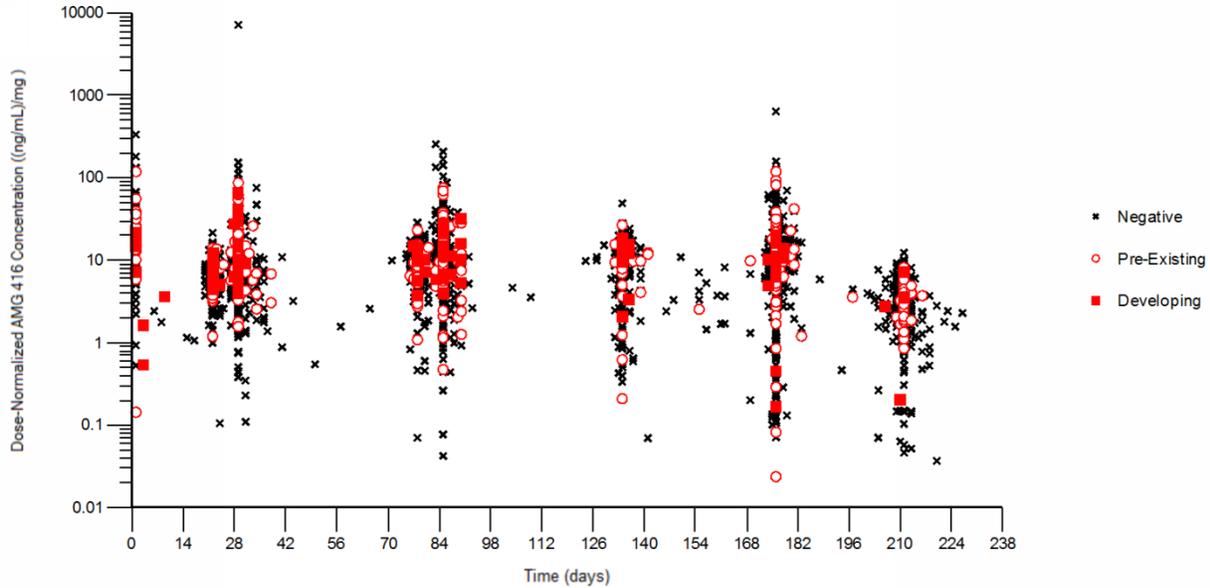
### 5.3.5.3 Section 5.3.1 – Effects of AMG 416-specific ADA on Pharmacokinetics

#### Preamble:

This section only summarizes the clinical findings. The impacts of the appearance of ADA on safety and clinical efficacy are deferred to clinical pharmacology to evaluate.

Dose-normalized plasma concentrations of AMG 416 were studied to assess the effects of immunogenicity on pharmacokinetics (see graph below). There was no significant impact of anti-AMG 416 ADA on the concentration of AMG 416 in the trial subjects over time, irrespective of whether they had pre-existing ADA or developed ADA over the course of the timeframe of the clinical trial.

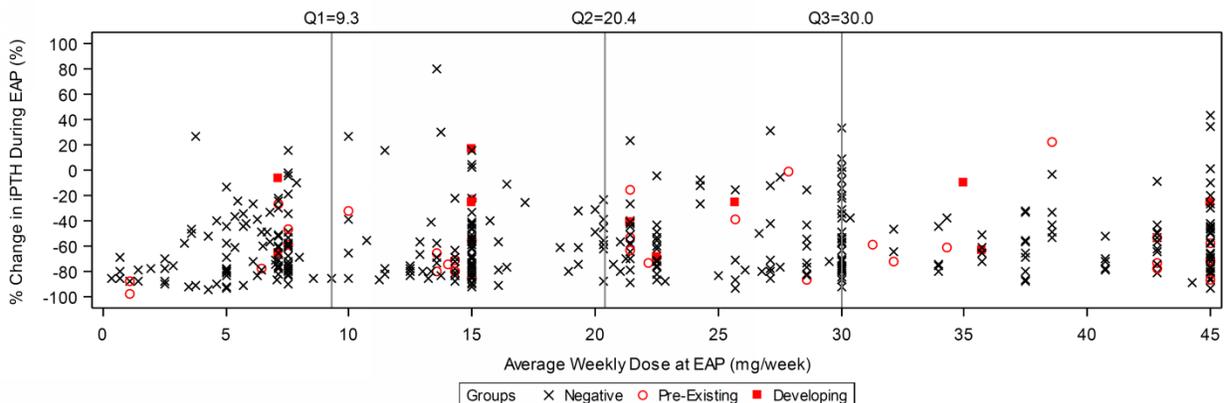
Reviewer comment: These data support the Sponsor’s claim that the presence of AMG 416-specific ADA do not have a significantly detrimental effect on the levels of the drug in the blood of patients receiving it.



5.3.5.3 Section 5.3.2 – Effects of AMG 416-specific ADA on Clinical Efficacy

The change in parathyroid hormone level over the Efficacy Assessment Period (EAP) relative to baseline was compared against the average weekly dose of AMG 416 for each clinical study subject; it was found that there was no impact of anti-AMG 416 ADA on the efficacy of AMG 416, nor were patients receiving high doses of AMG 416 more likely to be positive for anti-AMG 416 antibodies.

Reviewer comment: The data shown below support the assertion of the Sponsor that anti-AMG 416 ADA do not have a significant effect on the efficacy of the drug. It is noteworthy that according to the graph shown below, there are even a significant number of patients that are negative for ADA that do not show the intended iPTH-lowering clinical response to the drug.



### 5.3.5.3 Section 5.3.3 – Effects of AMG 416-specific ADA on Clinical Safety

The safety profiles of clinical trial test subjects (Placebo-controlled studies 20120229 and 20120230) who tested positive for AMG 416-specific ADA were compared against the safety profiles of patients who were ADA-negative, with specific regard to hypersensitivity and infusion reactions (see Section 5.3.5.3.5.3.3, Table 4; not reproduced here). Such immune reactions, where reported, were not attributable to any association with the AMG 416 administration, nor with the observation of anti-AMG-416 antibodies.

*Reviewer comment: The combined clinical trials included 513 patients receiving placebo, and 503 patients receiving AMG 416; among these, 447 were antibody negative, and 56 developed ADA, or had pre-existing ADA. Among the placebo group and the AMG 416 group, the incidents of adverse event were roughly the same. Additionally, within the AMG 416 group, the adverse events could not be associated with the presence of anti-AMG 416 antibodies.*

### 5.3.5.3 Section 6 – Immunogenicity Impact and Risk Management Conclusion

The SPR immunoassay methodology, utilizing AMG 416 and AMG 416-HSA (SAPC) have been shown to be an effective bioanalytical strategy for the detection of developing and mature ADA responses against AMG 416. The assay validation, and observation that instrument responses do not change drastically from the end of the study (week 27) to the safety follow-up timepoint (week 30) indicate that the SPR immunoassay has an acceptable drug tolerance.

The ADA testing strategy by SPR immunoassay demonstrated modest antigenicity of AMG 416, and even the presence of pre-existing ADA. There was little evidence of immunogenicity, however, as pre-existing anti-AMG 416 immune responses were not “boosted” by treatment with AMG 416, and the number of patients receiving AMG 416 that developed immune responses against it were minimal. Additionally, there was no evidence of alterations to pharmacokinetics, clinical response, or safety profile that could be attributable to pre-existing AMG 416 ADA, nor development of AMG 416 ADA.

#### **1.14.1.2 Annotated Draft Labeling Text, Section 6.2 Immunogenicity**

The Label text is as follows:

“6.2 Immunogenicity

(b) (4)  
In clinical studies, 7.1% (71 out of 995) of patients with secondary HPT treated with [TRADENAME] for up to 6 months tested positive for binding antibodies ( (b) (4) [57 out of 71] of these had pre-existing antibodies).

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies. If formation of anti-etelcalcetide binding antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

(b) (4)

*Reviewer comment: The first paragraph of the Immunogenicity Draft Labeling Text is consistent with the results discussed in the Integrated Immunogenicity Report; no edits are needed. We defer review of the second paragraph to clinical pharmacology reviewers.*

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

/s/  
-----

BRUCE K HUANG  
04/08/2016

JUHONG LIU  
04/08/2016



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 4, 2016

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.  
Division Director  
Division of Cardiovascular and Renal Products /CDER

To: Meghna Jairath, RPM  
DMEP

Subject: QT-IRT Consult to NDA 208325

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

This memo responds to your consult to us dated 11/4/2015 regarding the ECG summary and draft labeling in the NDA submission. The QT-IRT received and reviewed the following materials:

- Your consult
- ECG summary report
- Proposed labeling for etelcalcetide

## QT-IRT Comments for DMEP

The ECG summary and the proposed labeling section 6.1 *QTc Prolongation Secondary to Hypocalcemia* are acceptable.

## BACKGROUND

Etelcalcetide is (*KAI-4169*) a calcium-sensing receptor (CaSR) agonist indicated for the treatment of secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD) on hemodialysis.

The QT-IRT has previously reviewed and agreed to a QT waiver request submitted by sponsor under the IND 109773 for the following rationales: "*A thorough QTc study cannot be safely*

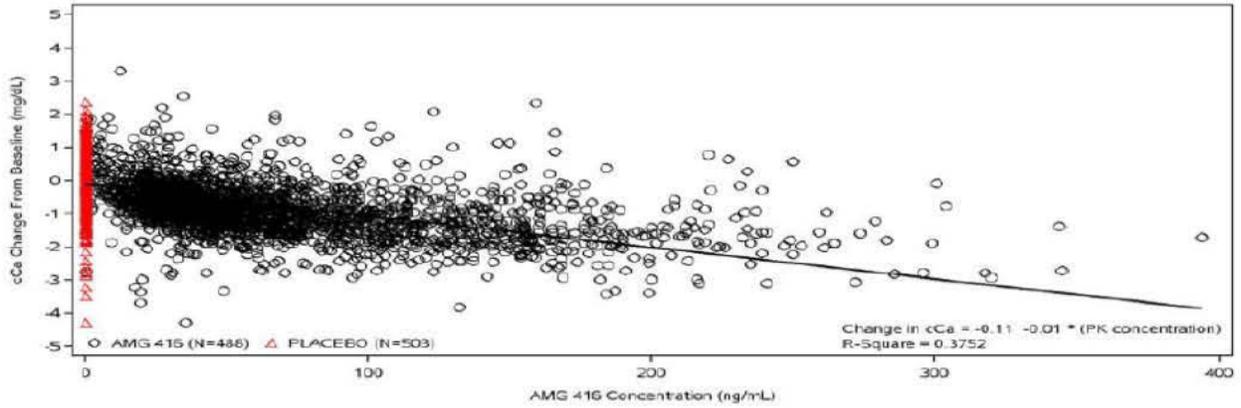
*conducted with KAI-4169 in healthy subjects because hypocalcemia was observed following a single 10 mg dose, limiting the exposure that can be safely achieved in healthy volunteers. In addition, a thorough QTc study in either healthy volunteers or hemodialysis subjects will produce results that are confounded by the direct effect of reductions in serum calcium on QTc, making any meaningful interpretation difficult. Furthermore, a significant number of hemodialysis subjects have prolonged QTc (i.e., > 450 ms) at baseline, so the inclusion of a positive control to assess assay sensitivity may not be acceptable in this population.”*

In the clinical development program, the effects of etelcalcetide on electrocardiogram (ECG) assessments have been characterized during single- and multiple-dose studies in healthy subjects and in subjects with secondary hyperparathyroidism (HPT) receiving maintenance hemodialysis.

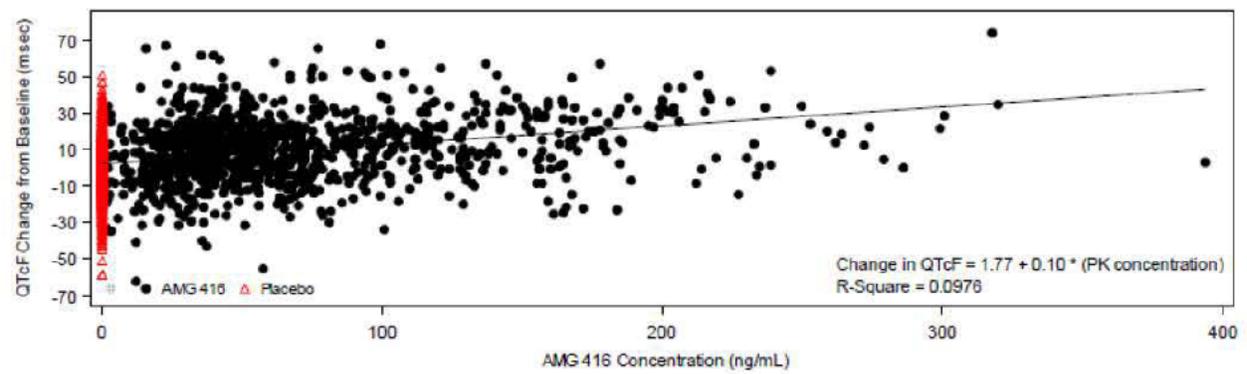
Administration of etelcalcetide was associated with reductions in serum calcium, and a reduction in serum calcium was associated with QTc interval prolongation in both nonclinical and clinical studies. The estimated difference in the mean change from baseline in predialysis QTc interval between etelcalcetide and placebo was above the threshold of regulatory concern for thorough QT studies (ie, mean difference > 5 ms with an upper bound of the 95% confidence interval [CI] of > 10 ms).

**Figure 1: Calcium Change From Baseline vs. Etelcalcetide Concentration (A), QTcF Change From Baseline vs. Etelcalcetide Concentration (B), and QTcF Change From Baseline vs. Calcium Change From Baseline (C)**

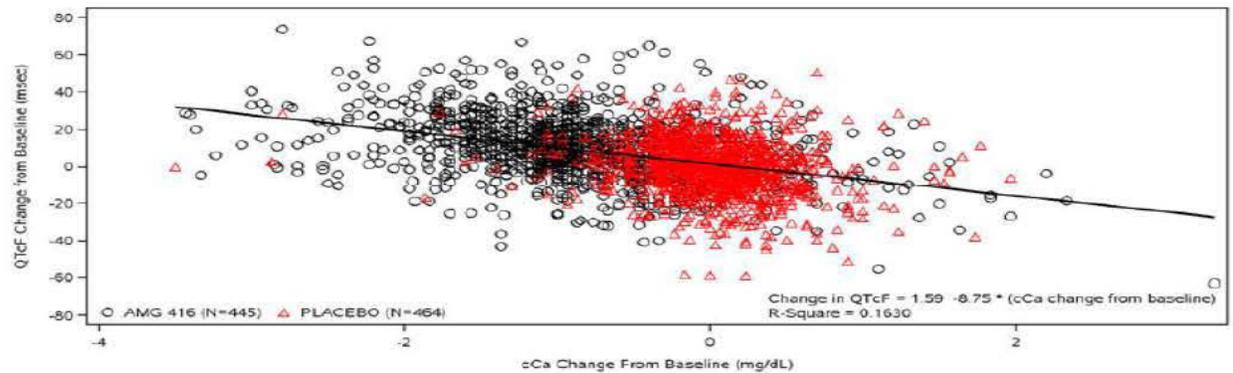
A



B



C



Categorical analyses indicated that the etelcalcetide group had a higher subject incidence of postbaseline increases in QTc interval compared with the placebo group.

**Table 5. Predialysis QTcF Interval Maximum Postbaseline and Maximum Increase From Baseline Categories (6-month Placebo-controlled Pool Safety Analysis Set With On-treatment Approach)**

| QTcF  | 20120229                      |                               | 20120230                      |                               | Total placebo-controlled studies |                               |
|---|-------------------------------|-------------------------------|-------------------------------|-------------------------------|----------------------------------|-------------------------------|
|   | Placebo<br>(N = 254)<br>n (%) | AMG 416<br>(N = 251)<br>n (%) | Placebo<br>(N = 259)<br>n (%) | AMG 416<br>(N = 252)<br>n (%) | Placebo<br>(N = 513)<br>n (%)    | AMG 416<br>(N = 503)<br>n (%) |
| <b>Baseline – n (%)</b>                       |                               |                               |                               |                               |                                  |                               |
| ≤ 450 msec                                    | 210 (82.7)                    | 179 (71.3)                    | 199 (76.8)                    | 198 (78.6)                    | 409 (79.7)                       | 377 (75.0)                    |
| > 450 to 480 msec                             | 25 (9.8)                      | 46 (18.3)                     | 31 (12.0)                     | 36 (14.3)                     | 56 (10.9)                        | 82 (16.3)                     |
| > 480 to 500 msec                             | 6 (2.4)                       | 6 (2.4)                       | 14 (5.4)                      | 7 (2.8)                       | 20 (3.9)                         | 13 (2.6)                      |
| > 500 msec                                    | 4 (1.6)                       | 2 (0.8)                       | 2 (0.8)                       | 0 (0.0)                       | 6 (1.2)                          | 2 (0.4)                       |
| <b>Maximum post-baseline – n (%)</b>          |                               |                               |                               |                               |                                  |                               |
| ≤ 450 msec                                    | 176 (69.3)                    | 123 (49.0)                    | 173 (66.8)                    | 133 (52.8)                    | 349 (68.0)                       | 256 (50.9)                    |
| > 450 to 480 msec                             | 49 (19.3)                     | 72 (28.7)                     | 47 (18.1)                     | 71 (28.2)                     | 96 (18.7)                        | 143 (28.4)                    |
| > 480 to 500 msec                             | 13 (5.1)                      | 14 (5.6)                      | 15 (5.8)                      | 22 (8.7)                      | 28 (5.5)                         | 36 (7.2)                      |
| > 500 msec                                    | 4 (1.6)                       | 14 (5.6)                      | 6 (2.3)                       | 10 (4.0)                      | 10 (1.9)                         | 24 (4.8)                      |
| <b>Maximum increase from baseline – n (%)</b> |                               |                               |                               |                               |                                  |                               |
| ≤ 30 msec                                     | 221 (87.0)                    | 167 (66.5)                    | 223 (86.1)                    | 178 (70.6)                    | 444 (86.5)                       | 345 (68.6)                    |
| > 30 to 60 msec                               | 16 (6.3)                      | 46 (18.3)                     | 13 (5.0)                      | 53 (21.0)                     | 29 (5.7)                         | 99 (19.7)                     |
| > 60 msec                                     | 0 (0.0)                       | 4 (1.6)                       | 0 (0.0)                       | 2 (0.8)                       | 0 (0.0)                          | 6 (1.2)                       |

QTcF = QT interval using Fridericia's correction

This pool includes data from the 2 placebo-controlled Studies 20120229 and 20120230.

On-treatment approach: data collected on or before the last nonmissing dose of investigational product were included.

The observations with the following diagnoses or findings were excluded from the analyses: artificial pacemaker, atrial fibrillation, atrial flutter, left bundle branch block, and right bundle branch block.

Source: Modified from ISS Table 7.44

The sponsor proposed the following labeling language in Section 6.1

*QTc Prolongation Secondary to Hypocalcemia*

(b) (4). In the combined placebo-controlled studies, a higher percentage of patients in the [TRADENAME] group compared with the placebo group had a maximum increase from baseline of > 60 msec in the QTcF interval (1.2% [TRADENAME], 0% placebo). The patient incidence of maximum post-baseline predialysis QTcF > 500 msec in the [TRADENAME] and placebo groups was 4.8% and 1.9%, respectively.

Thank you for requesting our input into the development of this product under NDA 208325. We welcome more discussion with you now and in the future. Please feel free to contact us via email at [cdcrdcrpqt@fda.hhs.gov](mailto:cdcrdcrpqt@fda.hhs.gov)

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

/s/  
-----

JIANG LIU  
01/04/2016

NORMAN L STOCKBRIDGE  
01/04/2016

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

| Application Information  |  |   |
|--|--|---|
| NDA # 208325<br>BLA#   | NDA Supplement #: S-<br>BLA Supplement #: S- | Efficacy Supplement Category:<br><input type="checkbox"/> New Indication (SE1)<br><input type="checkbox"/> New Dosing Regimen (SE2)<br><input type="checkbox"/> New Route Of Administration (SE3)<br><input type="checkbox"/> Comparative Efficacy Claim (SE4)<br><input type="checkbox"/> New Patient Population (SE5)<br><input type="checkbox"/> Rx To OTC Switch (SE6)<br><input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7)<br><input type="checkbox"/> Labeling Change With Clinical Data (SE8)<br><input type="checkbox"/> Manufacturing Change With Clinical Data (SE9)<br><input type="checkbox"/> Animal Rule Confirmatory Study (SE10) |
| Proprietary Name: Under review<br>Established/Proper Name: Etelcalcetide<br>Dosage Form: Intravenous injection<br>Strengths: 2.5, 5, 10 mg/vial at concentration of 5mg/mL   |  |   |
| Applicant: KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen, Inc.<br>Agent for Applicant (if applicable):  |  |   |
| Date of Application: August 24, 2015<br>Date of Receipt: August 24, 2015<br>Date clock started after UN: n/a   |  |   |
| PDUFA/BsUFA Goal Date: August 24, 2016   |  | Action Goal Date (if different):  |
| Filing Date: November 6, 2015  |  | Date of Filing Meeting: October 7, 2015   |
| Chemical Classification (original NDAs only) :<br><input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination<br><input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination<br><input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination<br><input type="checkbox"/> Type 4- New Combination<br><input type="checkbox"/> Type 5- New Formulation or New Manufacturer<br><input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA<br><input type="checkbox"/> Type 8- Partial Rx to OTC Switch |  |   |
| Proposed indication(s)/Proposed change(s): for Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis   |  |   |
| Type of Original NDA:<br>AND (if applicable)<br>Type of NDA Supplement:  |  | <input checked="" type="checkbox"/> 505(b)(1)<br><input type="checkbox"/> 505(b)(2)<br><hr/> <input type="checkbox"/> 505(b)(1)<br><input type="checkbox"/> 505(b)(2)   |
| <b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i></b><br><a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>   |  |   |

|  |   |
|--|---|
| Type of BLA  | <input type="checkbox"/> 351(a)<br><input type="checkbox"/> 351(k)  |
| <b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b>  |   |
| Review Classification:   | <input checked="" type="checkbox"/> Standard<br><input type="checkbox"/> Priority   |
| <b>The application will be a priority review if:</b>   | <input type="checkbox"/> Pediatric WR<br><input type="checkbox"/> QIDP<br><input type="checkbox"/> Tropical Disease Priority Review Voucher<br><input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher  |
| <ul style="list-style-type: none"> <li>• <b>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</b></li> <li>• <b>The product is a Qualified Infectious Disease Product (QIDP)</b></li> <li>• <b>A Tropical Disease Priority Review Voucher was submitted</b></li> <li>• <b>A Pediatric Rare Disease Priority Review Voucher was submitted</b></li> </ul> |   |
| Resubmission after withdrawal? <input type="checkbox"/>  | Resubmission after refuse to file? <input type="checkbox"/>   |
| Part 3 Combination Product? <input type="checkbox"/>   | <input type="checkbox"/> Convenience kit/Co-package<br><input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.)<br><input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.)<br><input type="checkbox"/> Device coated/impregnated/combined with drug<br><input type="checkbox"/> Device coated/impregnated/combined with biologic<br><input type="checkbox"/> Separate products requiring cross-labeling<br><input type="checkbox"/> Drug/Biologic<br><input type="checkbox"/> Possible combination based on cross-labeling of separate products<br><input type="checkbox"/> Other (drug/device/biological product) |
| <b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b>   |   |

|  |  |
|--|--|
| <input type="checkbox"/> Fast Track Designation<br><input type="checkbox"/> Breakthrough Therapy Designation<br><i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i><br><input type="checkbox"/> Rolling Review<br><input type="checkbox"/> Orphan Designation<br><br><input type="checkbox"/> Rx-to-OTC switch, Full<br><input type="checkbox"/> Rx-to-OTC switch, Partial<br><input type="checkbox"/> Direct-to-OTC<br><br>Other: | <input type="checkbox"/> PMC response<br><input type="checkbox"/> PMR response:<br><input type="checkbox"/> FDAAA [505(o)]<br><input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B)<br><input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)<br><input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) |
|--|--|

Collaborative Review Division (if OTC product): n/a

List referenced IND Number(s): 109773

| Goal Dates/Product Names/Classification Properties  | YES                                 | NO                       | NA | Comment |
|---|-------------------------------------|--------------------------|----|---------|
| PDUFA/BsUFA and Action Goal dates correct in tracking system?<br><br><b>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</b>                    | <input checked="" type="checkbox"/> | <input type="checkbox"/> |    |         |
| Are the established/proper and applicant names correct in tracking system?<br><br><b>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</b> | <input checked="" type="checkbox"/> | <input type="checkbox"/> |    |         |

|   |  |                                     |                          |   |
|---|--|-------------------------------------|--------------------------|---|
| <i>to the supporting IND(s) if not already entered into tracking system.</i>  |  |                                     |                          |   |
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i><br><a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a><br><i>If no, ask the document room staff to make the appropriate entries.</i> | <input checked="" type="checkbox"/>  | <input type="checkbox"/>            | <input type="checkbox"/> | NME PDUFA V under Program. Standard Review. |
| <b>Application Integrity Policy</b>   | <b>YES</b>   | <b>NO</b>                           | <b>NA</b>                | <b>Comment</b>                              |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i><br><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a><br><b>If yes, explain in comment column.</b>  | <input type="checkbox"/>   | <input checked="" type="checkbox"/> |                          |   |
| <b>If affected by AIP, has OC been notified of the submission? If yes, date notified:</b>   | <input type="checkbox"/>   | <input type="checkbox"/>            |                          |   |
| <b>User Fees</b>  | <b>YES</b>   | <b>NO</b>                           | <b>NA</b>                | <b>Comment</b>                              |
| Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?   | <input checked="" type="checkbox"/>  | <input type="checkbox"/>            |                          |   |
| <u>User Fee Status</u><br><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>   | Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ):<br><input checked="" type="checkbox"/> Paid<br><input type="checkbox"/> Exempt (orphan, government)<br><input type="checkbox"/> Waived (e.g., small business, public health)<br><input type="checkbox"/> Not required |                                     |                          |   |
| <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>   | Payment of other user fees:<br><input checked="" type="checkbox"/> Not in arrears<br><input type="checkbox"/> In arrears   |                                     |                          |   |
| <u>User Fee Bundling Policy</u><br><i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i><br><a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>   | Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i><br><input type="checkbox"/> Yes<br><input type="checkbox"/> No<br>n/a  |                                     |                          |   |
| <b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>   | <b>YES</b>   | <b>NO</b>                           | <b>NA</b>                | <b>Comment</b>                              |
| Is the application a 505(b)(2) NDA? ( <i>Check the 356h form,</i>   | <input type="checkbox"/>   | <input type="checkbox"/>            | X                        |   |

|  |                                     |                          |                                     |                |  |
|--|-------------------------------------|--------------------------|-------------------------------------|----------------|--|
| cover letter, and annotated labeling). <b>If yes</b> , answer the bulleted questions below:  |                                     |                          |                                     |                |  |
| <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> </ul>   |                                     | <input type="checkbox"/> | <input type="checkbox"/>            |                |  |
| <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</li> </ul>  |                                     | <input type="checkbox"/> | <input type="checkbox"/>            |                |  |
| <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</li> </ul> <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>                    |                                     | <input type="checkbox"/> | <input type="checkbox"/>            |                |  |
| <ul style="list-style-type: none"> <li>Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</li> </ul> <p><b>Check the Electronic Orange Book at:</b><br/> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p>  |                                     | <input type="checkbox"/> | <input type="checkbox"/>            |                |  |
| <b>If yes</b> , please list below:   |                                     |                          |                                     |                |  |
| Application No.  | Drug Name                           | Exclusivity Code         | Exclusivity Expiration              |                |  |
|  |                                     |                          |                                     |                |  |
|  |                                     |                          |                                     |                |  |
|  |                                     |                          |                                     |                |  |
| <p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p> |                                     |                          |                                     |                |  |
| <b>Exclusivity</b>   | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b> |  |
| Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b><br><a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>   | <input type="checkbox"/>            | <input type="checkbox"/> | x                                   |                |  |
| <b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?   | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                |  |
| <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>   |                                     |                          |                                     |                |  |
| <b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?  | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            |                |  |
| <b>If yes</b> , # years requested: 5 years   |                                     |                          |                                     |                |  |
| <i>Note: An applicant can receive exclusivity without requesting it;</i>   |                                     |                          |                                     |                |  |

|  |                          |                          |                                     |  |
|--|--------------------------|--------------------------|-------------------------------------|--|
| <i>therefore, requesting exclusivity is not required.</i>  |                          |                          |                                     |  |
| <b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?   | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> |  |
| <b>If yes,</b> did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?<br><br><i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            |  |
| <b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?<br><br><i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i><br><br><i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> |  |

| <b>Format and Content</b>   |  |                          |                          |                |
|---|--|--------------------------|--------------------------|----------------|
| <i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>   | <input type="checkbox"/> All paper (except for COL)<br><input checked="" type="checkbox"/> All electronic<br><input type="checkbox"/> Mixed (paper/electronic) |                          |                          |                |
|   | <input type="checkbox"/> CTD<br><input type="checkbox"/> Non-CTD<br><input type="checkbox"/> Mixed (CTD/non-CTD)   |                          |                          |                |
| <b>If mixed (paper/electronic) submission,</b> which parts of the application are submitted in electronic format?   |  |                          |                          |                |
| <b>Overall Format/Content</b>   | <b>YES</b>   | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
| <b>If electronic submission,</b> does it follow the eCTD guidance? <sup>1</sup><br><b>If not,</b> explain (e.g., waiver granted).                           | <input checked="" type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <b>Index:</b> Does the submission contain an accurate comprehensive index?  | <input checked="" type="checkbox"/>  | <input type="checkbox"/> |                          |                |
| Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: | <input checked="" type="checkbox"/>  | <input type="checkbox"/> |                          |                |

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

|  |                                     |                          |                                     |   |
|--|-------------------------------------|--------------------------|-------------------------------------|---|
| <input checked="" type="checkbox"/> legible<br><input type="checkbox"/> English (or translated into English)<br><input type="checkbox"/> pagination<br><input type="checkbox"/> navigable hyperlinks (electronic submissions only)   |                                     |                          |                                     |   |
| <b>If no</b> , explain.  |                                     |                          |                                     |   |
| <b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?   | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |   |
| <b>If yes</b> , BLA #  |                                     |                          |                                     |   |
|  |                                     |                          |                                     |   |
|  |                                     |                          |                                     |   |
|  |                                     |                          |                                     |   |
|  |                                     |                          |                                     |   |
| <b>Forms and Certifications</b>  |                                     |                          |                                     |   |
| <i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i> |                                     |                          |                                     |   |
| <b>Application Form</b>  | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b>  |
| Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                                     |   |
| <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>  |                                     |                          |                                     |   |
| Are all establishments and their registration numbers listed on the form/attached to the form?   | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            |   |
| <b>Patent Information (NDAs/NDA efficacy supplements only)</b>   | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b>  |
| Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?  | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            |   |
| <b>Financial Disclosure</b>  | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b>  |
| Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                                     | Sponsor confirmed that the signer is authorized to sign as applicant. |
| <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>   |                                     |                          |                                     |   |
| <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>  |                                     |                          |                                     |   |
| <b>Clinical Trials Database</b>  | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b>  |
| Is form FDA 3674 included with authorized signature?   | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                                     |   |
| <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>   |                                     |                          |                                     |   |

|   |                                     |                          |                                     |                            |
|---|-------------------------------------|--------------------------|-------------------------------------|----------------------------|
| <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>  |                                     |                          |                                     |                            |
| <b>Debarment Certification</b>  | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b>             |
| Is a correctly worded Debarment Certification included with authorized signature?<br><br><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i><br><br><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            |                            |
| <b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>  | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b>             |
| <b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?<br><br><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i><br><br><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>  | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> | All electronic submission. |
| <b>Controlled Substance/Product with Abuse Potential</b>  | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b>             |
| <u>For NMEs:</u><br>Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?<br><br><i>If yes, date consult sent to the Controlled Substance Staff:</i><br><br><u>For non-NMEs:</u><br><i>Date of consult sent to Controlled Substance Staff :</i>  | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                            |
| <b>Pediatrics</b>   | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b>             |
| <b><u>PREA</u></b><br><br>Does the application trigger PREA?<br><br><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i><br><br><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>  | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                                     | PERC date<br>June 1, 2016  |

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

Version: 7/10/2015

7

|  |  |                                     |                          |   |
|--|--|-------------------------------------|--------------------------|---|
| <i>forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i> |  |                                     |                          |   |
| <b>If the application triggers PREA</b> , is there an agreed Initial Pediatric Study Plan (iPSP)?<br><br><i>If no, may be an RTF issue - contact DPMH for advice.</i>  | <input checked="" type="checkbox"/>  | <input type="checkbox"/>            | <input type="checkbox"/> | December 11, 2014   |
| <b>If required by the agreed iPSP</b> , are the pediatric studies outlined in the agreed iPSP completed and included in the application?<br><br><i>If no, may be an RTF issue - contact DPMH for advice.</i>                                     | <input type="checkbox"/>   | <input checked="" type="checkbox"/> | <input type="checkbox"/> | Request for waiver for preterm and newborn infants (0 to (b) (4) days) and partial deferral for infants (1 month to < 2 years), children (2 to 11 years) and adolescents (12 to < 18 years) until safety and efficacy profile in adults has been established. |
| <b><u>BPCA:</u></b><br><br>Is this submission a complete response to a pediatric Written Request?<br><br><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>                     | <input type="checkbox"/>   | <input checked="" type="checkbox"/> |                          |   |
| <b>Proprietary Name</b>  | <b>YES</b>   | <b>NO</b>                           | <b>NA</b>                | <b>Comment</b>  |
| Is a proposed proprietary name submitted?<br><br><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>  | <input checked="" type="checkbox"/>  | <input type="checkbox"/>            | <input type="checkbox"/> | Submission date August 25, 2015. Under review for second time.  |
| <b>REMS</b>  | <b>YES</b>   | <b>NO</b>                           | <b>NA</b>                | <b>Comment</b>  |
| Is a REMS submitted?<br><br><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>   | <input type="checkbox"/>   | <input checked="" type="checkbox"/> | <input type="checkbox"/> |   |
| <b>Prescription Labeling</b>   | <input type="checkbox"/> <b>Not applicable</b>   |                                     |                          |   |
| Check all types of labeling submitted.   | <input checked="" type="checkbox"/> Package Insert (PI)<br><input type="checkbox"/> Patient Package Insert (PPI)<br><input type="checkbox"/> Instructions for Use (IFU)<br><input type="checkbox"/> Medication Guide (MedGuide)<br><input checked="" type="checkbox"/> Carton labels<br><input checked="" type="checkbox"/> Immediate container labels |                                     |                          |   |

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

|  |   |                          |                                     |                |
|--|---|--------------------------|-------------------------------------|----------------|
|  | <input type="checkbox"/> Diluent<br><input type="checkbox"/> Other (specify)  |                          |                                     |                |
|  | <b>YES</b>  | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b> |
| Is Electronic Content of Labeling (COL) submitted in SPL format?<br><br><i>If no, request applicant to submit SPL before the filing date.</i>  | <input checked="" type="checkbox"/>   | <input type="checkbox"/> |                                     |                |
| Is the PI submitted in PLR format? <sup>4</sup>  | <input checked="" type="checkbox"/>   | <input type="checkbox"/> |                                     |                |
| <b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?<br><br><i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>   | <input type="checkbox"/>  | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                |
| <b>For applications submitted on or after June 30, 2015:</b><br>Is the PI submitted in PLLR format? <sup>5</sup>   | <input checked="" type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/>            |                |
| Has a review of the available pregnancy and lactation data been included?  | <input checked="" type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/>            |                |
| <b>For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?<br><br><i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i> | <input type="checkbox"/>  | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?  | <input checked="" type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/>            |                |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)  | <input checked="" type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/>            |                |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?   | <input checked="" type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/>            |                |
| <b>OTC Labeling</b>  | <input checked="" type="checkbox"/> <b>Not Applicable</b>   |                          |                                     |                |
| Check all types of labeling submitted.   | <input type="checkbox"/> Outer carton label<br><input type="checkbox"/> Immediate container label<br><input type="checkbox"/> Blister card<br><input type="checkbox"/> Blister backing label<br><input type="checkbox"/> Consumer Information Leaflet (CIL) |                          |                                     |                |

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

5

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

|  |   |                          |                          |  |
|--|---|--------------------------|--------------------------|--|
|  | <input type="checkbox"/> Physician sample<br><input type="checkbox"/> Consumer sample<br><input type="checkbox"/> Other (specify) |                          |                          |  |
|  | <b>YES</b>  | <b>NO</b>                | <b>NA</b>                | <b>Comment</b>   |
| Is electronic content of labeling (COL) submitted?<br><br><i>If no, request in 74-day letter.</i>  | <input type="checkbox"/>  | <input type="checkbox"/> |                          |  |
| Are annotated specifications submitted for all stock keeping units (SKUs)?<br><br><i>If no, request in 74-day letter.</i>  | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> |  |
| If representative labeling is submitted, are all represented SKUs defined?<br><br><i>If no, request in 74-day letter.</i>  | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> |  |
| All labeling/package sent to OSE/DMEPA?  | <input type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/> |  |
| <b>Other Consults</b>  | <b>YES</b>  | <b>NO</b>                | <b>NA</b>                | <b>Comment</b>   |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)<br><br><i>If yes, specify consult(s) and date(s) sent: both consults send on November 5, 2015</i> | <input checked="" type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> | QT and immunogenicity  |
| <b>Meeting Minutes/SPAs</b>  | <b>YES</b>  | <b>NO</b>                | <b>NA</b>                | <b>Comment</b>   |
| End-of Phase 2 meeting(s)?<br><b>Date(s):</b><br><br><i>If yes, distribute minutes before filing meeting</i>   | <input checked="" type="checkbox"/>   | <input type="checkbox"/> |                          | July 2, 2012   |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?<br><b>Date(s):</b><br><br><i>If yes, distribute minutes before filing meeting</i>   | <input checked="" type="checkbox"/>   | <input type="checkbox"/> |                          | May 13, 2015<br>Sponsor cancelled the meeting upon receiving the preliminary comments. |
| Any Special Protocol Assessments (SPAs)?<br><b>Date(s):</b><br><br><i>If yes, distribute letter and/or relevant minutes before filing meeting</i>  | <input checked="" type="checkbox"/>   | <input type="checkbox"/> |                          | April 18, 2012 and May 8, 2013   |

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** October 7, 2015

**BACKGROUND:**

NDA 208325

Drug Name: etelcalcetide injection

MOA: calcium-sensing receptor agonist

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.

Regulatory: NME

PDUFA (Program standard-12 months): August 24, 2016

Previous interactions under IND 109773: EOP2 meeting (June 9, 2012) and Pre NDA meeting (May 13, 2015)

Submission: all electronic

PDUFA Fees: paid

Proprietary name: under review second time

PSP: Agreement (December 11, 2014)

**REVIEW TEAM:**

| Discipline/Organization                             | Names              |                      | Present at filing meeting? (Y or N) |
|---|--------------------|----------------------|-------------------------------------|
| Regulatory Project Management                       | RPM:               | Meghna M. Jairath    | Y                                   |
|   | CPMS/TL:           | Pamela Lucarelli     | Y                                   |
| Cross-Discipline Team Leader (CDTL)                 |                    |                      |                                     |
| Division Director/Deputy                            | Jean-Marc Guettier |                      | N                                   |
| Office Director/Deputy                              | Curt Rosebraugh    |                      | N                                   |
| Clinical  | Reviewer:          | William (Bill) Lubas | Y                                   |
|   | TL:                | Marina Zemskova      | Y                                   |
| Social Scientist Review ( <i>for OTC products</i> ) | Reviewer:          |                      |                                     |
|   | TL:                |                      |                                     |
| OTC Labeling Review ( <i>for OTC products</i> )     | Reviewer:          |                      |                                     |
|   | TL:                |                      |                                     |

|   |           |                                |         |
|---|-----------|--------------------------------|---------|
|   |           |                                |         |
| Clinical Microbiology ( <i>for antimicrobial products</i> ) | Reviewer: |                                |         |
|   | TL:       |                                |         |
| Clinical Pharmacology                                       | Reviewer: | Ritesh Jain                    | Y       |
|   | TL:       | Jaya Vaidyanathan              | Y       |
| • Genomics  | Reviewer: |                                |         |
| • Pharmacometrics   | Reviewer: | Nitin Mehrotra and Jee Eun Lee | N and Y |
| Biostatistics   | Reviewer: | Alex Cambon                    | Y       |
|   | TL:       | Mark Rothman                   | Y       |

|  |           |                       |   |
|--|-----------|-----------------------|---|
| Nonclinical<br>(Pharmacology/Toxicology)                                 | Reviewer: | Miyun Tsai-Turton     | Y |
|  | TL:       | David Carlson         | Y |
| Statistics (carcinogenicity)   | Reviewer: |                       |   |
|  | TL:       |                       |   |
| Product Quality (CMC) Review Team:                                       | ATL:      | Suong Tran            | Y |
|  | RBPM:     | Anika Lalmansingh     | N |
| • Drug Substance   | Reviewer: | <u>Joseph Leginus</u> | N |
| • Drug Product   | Reviewer: | <u>John Amartey</u>   | N |
| • Process  | Reviewer: | <u>Derek Smith</u>    | N |
| • Microbiology   | Reviewer: | <u>Vinayak Pawar</u>  | N |
| • Facility   | Reviewer: | <u>Hansong Chen</u>   | N |
| • Biopharmaceutics   | Reviewer: | <u>Derek Smith</u>    | N |
| • Immunogenicity   | Reviewer: |                       |   |
| • Labeling (BLAs only)   | Reviewer: |                       |   |
| • Other (e.g., Branch Chiefs, EA Reviewer)                               |           |                       |   |
| OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)                           | Reviewer: |                       |   |
|  | TL:       |                       |   |
| OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels) | Reviewer: |                       |   |
|  | TL:       |                       |   |
| OSE/DMEPA (proprietary name, carton/container labels)                    | Reviewer: | Leeza Rahimi          | Y |
|  | TL:       | Yelena Maslov         | N |
| OSE/DRISK (REMS)   | Reviewer: |                       |   |
|  | TL:       |                       |   |
| OC/OSI/DSC/PMSB (REMS)   | Reviewer: |                       |   |
|  | TL:       |                       |   |

|  |   |  |                        |
|--|---|--|------------------------|
| Bioresearch Monitoring (OSI)                                 | Reviewer:                                     | Cynthia Kleppiner  | Y                      |
|  | TL:   | Janice Pohlman   | N                      |
| Controlled Substance Staff (CSS)                             | Reviewer:                                     |  |                        |
|  | TL:   |  |                        |
| Other reviewers/disciplines                                  |   |  |                        |
| <ul style="list-style-type: none"> <li>Discipline</li> </ul> | Reviewer:                                     | DPV- Margee Webster/Christian Cao<br>DRISK- Mona Patel/Naomi Redd/Ali Niak | Y and Y<br>Y, N, and Y |
|  | TL:   |  |                        |
| Other attendees  | Associate Director of Labeling-Monika Houston |  | Y                      |

**FILING MEETING DISCUSSION:**

|   |  |
|---|--|
| <p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505 b)(2) filing issues: <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES <input type="checkbox"/> NO<br><input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no</b>, explain:</p>   | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> No comments   |

|   |  |
|---|--|
| <p><b>CLINICAL</b></p> <p><b>Comments:</b></p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter                           |
| <ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>   | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul> | <input type="checkbox"/> YES<br>Date if known:<br><input checked="" type="checkbox"/> NO<br><input type="checkbox"/> To be determined<br><br>Reason: the application did not raise significant safety or efficacy issues |
| <ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>   | <input type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO  |
| <p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>  | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter                           |
| <p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter                           |

|  |   |
|--|---|
| <p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter            |
| <ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>   | <input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO  |
| <p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter            |
| <p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter            |
| <p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input checked="" type="checkbox"/> Review issues for 74-day letter |
| <p><b><u>New Molecular Entity (NDAs only)</u></b></p> <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>   | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no,</b> was a complete EA submitted?</p> <p><b>Comments:</b></p> | <input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO<br><br><input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <p><b>Comments:</b></p>  | <input type="checkbox"/> Not Applicable<br><br><input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO   |

|  |  |
|--|--|
| <p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>  | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input type="checkbox"/> Review issues for 74-day letter |
| <p><b><u>CMC Labeling Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>   | <input type="checkbox"/> Review issues for 74-day letter   |
| <p><b>APPLICATIONS IN THE PROGRAM (PDUFA V)<br/>(NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul> | <input type="checkbox"/> N/A<br><br><input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO<br><br><input type="checkbox"/> YES<br><input type="checkbox"/> NO              |
| <ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>  |  |
| <ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>  | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>   | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>   | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO   |

| <b>REGULATORY PROJECT MANAGEMENT</b>  |   |
|---|---|
| <b>Signatory Authority:</b> Curt Rosebraugh, M.D.   |   |
| <b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V):<br>January 25, 2016                        |   |
| <b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional): |   |
| <b>Comments:</b>  |   |
| <b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>  |   |
| <input type="checkbox"/>  | The application is unsuitable for filing. Explain why:  |
| <input checked="" type="checkbox"/>   | The application, on its face, appears to be suitable for filing.<br><br><u>Review Issues:</u><br><br><input type="checkbox"/> No review issues have been identified for the 74-day letter.<br><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.<br><br><u>Review Classification:</u><br><br><input checked="" type="checkbox"/> Standard Review<br><input type="checkbox"/> Priority Review |
| <b>ACTION ITEMS</b>   |   |
| <input checked="" type="checkbox"/>   | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).  |
| <input type="checkbox"/>  | If RTF, notify everyone who already received a consult request, OSE PM, and RBPM  |
| <input type="checkbox"/>  | If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.   |
| <input type="checkbox"/>  | If priority review, notify applicant in writing by day 60 (see CST for choices)   |
| <input checked="" type="checkbox"/>   | Send review issues/no review issues by day 74   |
| <input checked="" type="checkbox"/>   | Conduct a PLR format labeling review and include labeling issues in the 74-day letter   |
| <input checked="" type="checkbox"/>   | Update the PDUFA V DARRTS page (for applications in the Program)  |
| <input type="checkbox"/>  | Other   |

Annual review of template by OND ADRAAs completed: September 2014

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

/s/  
-----

MEGHNA M JAIRATH  
11/06/2015

**REGULATORY PROJECT MANAGER  
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW  
OF THE PRESCRIBING INFORMATION**

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 208325

**Application Type:** New NDA

**Drug Name(s)/Dosage Form(s):** etelcalcetide injection

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

**Receipt Date:** August 24, 2015

**Goal Date:**

### **1. Regulatory History and Applicant's Main Proposals**

KAI pharmaceuticals submitted NDA 208325 for etelcalcetide injection for the proposed indication to treat secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis. The NDA will undergo standard review under the PDUFA V "the program". The PDUFA date is August 24, 2016.

### **2. Review of the Prescribing Information**

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

### **3. Conclusions/Recommendations**

No SRPI format deficiencies were identified in the review of this PI.

---

### **4. Selected Requirements of Prescribing Information**

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

# Selected Requirements of Prescribing Information

## Highlights

See Appendix for a sample tool illustrating Highlights format.

### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

**Comment:**

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
  - TOC from the Full Prescribing Information (FPI).

**Comment:**

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Headings in HL must be presented in the following order:

| Heading                                  | Required/Optional                         |
|--|---|
| • <b>Highlights Heading</b>              | Required                                  |
| • <b>Highlights Limitation Statement</b> | Required                                  |
| • <b>Product Title</b>                   | Required                                  |
| • <b>Initial U.S. Approval</b>           | Required                                  |
| • <b>Boxed Warning</b>                   | Required if a BOXED WARNING is in the FPI |
| • <b>Recent Major Changes</b>            | Required for only certain changes to PI*  |
| • <b>Indications and Usage</b>           | Required                                  |
| • <b>Dosage and Administration</b>       | Required                                  |

## Selected Requirements of Prescribing Information

|   |   |
|---|---|
| • <b>Dosage Forms and Strengths</b>               | Required  |
| • <b>Contraindications</b>                        | Required (if no contraindications must state “None.”) |
| • <b>Warnings and Precautions</b>                 | Not required by regulation, but should be present     |
| • <b>Adverse Reactions</b>                        | Required  |
| • <b>Drug Interactions</b>                        | Optional  |
| • <b>Use in Specific Populations</b>              | Optional  |
| • <b>Patient Counseling Information Statement</b> | Required  |
| • <b>Revision Date</b>                            | Required  |

\* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

**Comment:**

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

**Comment:**

**N/A**

## Selected Requirements of Prescribing Information

14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

### Recent Major Changes (RMC) in Highlights

- N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

### Dosage Forms and Strengths in Highlights

- YES 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

### Contraindications in Highlights

- YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

### Adverse Reactions in Highlights

- YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at**

## Selected Requirements of Prescribing Information

(insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).”

Comment:

### Patient Counseling Information Statement in Highlights

**YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION** and **FDA-approved patient labeling**
- See 17 for **PATIENT COUNSELING INFORMATION** and **Medication Guide**

Comment:

### Revision Date in Highlights

**YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment:

## Selected Requirements of Prescribing Information

---

### Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.  
*Comment:*
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- NO** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].  
*Comment:* Has "from" under 2.3 and "with" under 5.3 in lower case. This is acceptable.
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS\***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

|   |
|---|
| <b>BOXED WARNING</b>  |
| <b>1 INDICATIONS AND USAGE</b>  |
| <b>2 DOSAGE AND ADMINISTRATION</b>  |
| <b>3 DOSAGE FORMS AND STRENGTHS</b>   |
| <b>4 CONTRAINDICATIONS</b>  |
| <b>5 WARNINGS AND PRECAUTIONS</b>   |
| <b>6 ADVERSE REACTIONS</b>  |
| <b>7 DRUG INTERACTIONS</b>  |
| <b>8 USE IN SPECIFIC POPULATIONS</b>  |
| <b>8.1 Pregnancy</b>  |
| <b>8.2 Lactation</b> (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery") |
| <b>8.3 Females and Males of Reproductive Potential</b> (if not required to be in PLLR format, use "Nursing Mothers")          |
| <b>8.4 Pediatric Use</b>  |
| <b>8.5 Geriatric Use</b>  |
| <b>9 DRUG ABUSE AND DEPENDENCE</b>  |
| <b>9.1 Controlled Substance</b>   |
| <b>9.2 Abuse</b>  |
| <b>9.3 Dependence</b>   |
| <b>10 OVERDOSAGE</b>  |
| <b>11 DESCRIPTION</b>   |
| <b>12 CLINICAL PHARMACOLOGY</b>   |
| <b>12.1 Mechanism of Action</b>   |
| <b>12.2 Pharmacodynamics</b>  |
| <b>12.3 Pharmacokinetics</b>  |
| <b>12.4 Microbiology (by guidance)</b>  |
| <b>12.5 Pharmacogenomics (by guidance)</b>  |
| <b>13 NONCLINICAL TOXICOLOGY</b>  |
| <b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>  |
| <b>13.2 Animal Toxicology and/or Pharmacology</b>   |
| <b>14 CLINICAL STUDIES</b>  |
| <b>15 REFERENCES</b>  |
| <b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>   |
| <b>17 PATIENT COUNSELING INFORMATION</b>  |

**Comment:**

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[*see Warnings and Precautions (5.2)*]."

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

#### BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

#### CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment: *Has contraindications listed*

#### ADVERSE REACTIONS Section in the FPI

- NO** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment: *Sponsor added "clinical" ...rates observed in "clinical" practice. This is acceptable.*

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

## Selected Requirements of Prescribing Information

### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
  - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

**Comment:**

- N/A** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix: Highlights and Table of Contents Format

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol  
Initial U.S. Approval: YYYY

#### WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

#### RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y  
Section Title, Subsection Title (x.x) M/201Y

#### INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

#### DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

#### DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

#### CONTRAINDICATIONS

- Text (4)
- Text (4)

#### WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

#### USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

### FULL PRESCRIBING INFORMATION: CONTENTS\*

#### WARNING: TITLE OF WARNING

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

#### 6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

#### 7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/  
-----

MEGHNA M JAIRATH  
11/05/2015