

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208743Orig1s000**

**OTHER REVIEW(S)**

## 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 #                      208743, Abaloparatide  
Product Name:

---

PMR/PMC Description:    #3189-1 Enhanced Assessment of Immunogenicity in Patients Treated with Abaloparatide-SC

Part 1: Analyze all collected serum samples from subjects enrolled in the BA058-05-003 study not previously tested for appearance of abaloparatide binding antibodies. Test the confirmed positive samples for abaloparatide binding ADA titer, and abaloparatide drug neutralization.

---

Part 2: Test all confirmed anti-abaloparatide positive serum samples from patients enrolled in the BA058-05-003 study for antibodies able to cross-react with or neutralize endogenous PTH or PTHrP.

---

|                              |                            |                   |
|------------------------------|----------------------------|-------------------|
| PMR/PMC Schedule Milestones: | Final Protocol Submission: | <u>07/31/2017</u> |
|                              | Study/Trial Completion:    | <u>03/31/2018</u> |
|                              | Final Report Submission:   | <u>07/31/2018</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

Review of safety data did not reveal safety concerns directly related to immunogenicity of Abaloparatide. However, immunogenicity responses as described in Section 6.2 Immunogenicity of the Package Insert were only based on studies performed with serum samples from a portion of patients. To provide a more accurate description of immune response to Abaloparatide, the sponsor needs to test serum samples not included in its initial study and revise the Package Insert if necessary. The studies are intended to facilitate a more accurate description of the immune response to Abaloparatide and to its endogenous counterparts in the labeling, and thus do not directly arise from a safety issue.

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 objective is to more completely assess the immunogenicity and cross-reactivity in patients who participated in Study BA058-003.

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.

The agreed upon studies involve analysis of existing samples collected during the sponsor's Phase 3 study BA058-05-003 for antibodies against the study drug and those which are cross-reactive against endogenous counterparts. Immunogenicity incidence data reported to the Agency are limited with respect to the analysis of available subject sera samples. Data necessary to verify the total incidence and establish the course of development of antidrug antibodies (ADA), including ADA cross-reactive with endogenous peptides, over the full duration of the Phase 3 trial are not currently available from all subjects.

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  
Analysis of existing clinical samples from Phase 3 study BA058-05-003 which were not previously analyzed for immunogenicity against the study drug BA058 due to incomplete sponsor sample analysis plan which was not previously reviewed by the immunogenicity consult team.

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/  
-----

CHRISTINE P NGUYEN  
04/27/2017

---

## 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:** April 10, 2017

**Requesting Office or Division:** Division of Bone, Reproductive, and Urologic Products (DBRUP)

**Application Type and Number:** NDA 208743

**Product Name and Strength:** Tymlos (abaloparatide) Injection 80 mcg/40 mL

**Submission Date:** February 8, 2017

**Applicant/Sponsor Name:** Radius

**OSE RCM #:** 2016-1715-1

**DMEPA Primary Reviewer:** Walter Fava, RPh., MEd.

**DMEPA Team Leader:** Lolita White, PharmD

**DMEPA Associate Director for Human Factors:** QuynhNhu Nguyen, MS

---

#### 1 PURPOSE OF MEMO

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that we review the revised Instructions for Use for Tymlos (abaloparatide) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that were discussed as part of review of HF validation study results during the late cycle meeting and later conveyed to Radius as meeting responses.<sup>a</sup>

#### 2 BACKGROUND

On September 22, 2016 during the mid-cycle communication<sup>b</sup> with Radius, we communicated our concerns with the HF validation study results of study participants who either failed to prime the pen prior to use, who unnecessarily re-primed the pen upon subsequent use, and

---

<sup>a</sup> Late cycle meeting for Tymlos (NDA 208743) December 20, 2016. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research.

<sup>b</sup> Mid cycle meeting for Tymlos (NDA 208743) September 22, 2016. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research

participants who received needlestick injuries as reported in their summary of study results. As a result of our discussion, Radius agreed to make revisions to the IFU and conduct another validation study.

On November 1, 2016 Radius submitted a revised HF validation protocol and IFU for our review. We found the revisions acceptable<sup>c</sup>.

On December 12, 2016, Radius submitted the HF validation study results which focused on the two identified areas of concern (e.g. priming, needlesticks). The results from the December 12, 2016 submission continue to identify failures and difficulties removing the needle from the device resulting in needlestick injury and also identified failures related to the priming step.

During the late cycle meeting with Radius on December 20, 2016, we communicated the following concerns:

- Study participants failed to prime the device properly. Subjective feedback suggests misinterpretation of the (b) (4) to mean skip the priming step.
- Study participants failed to safely remove the needle from the device which resulted in needlestick injury. Subjective feedback suggests difficulty understanding the graphics and language for the needle removal step.

Based on our feedback and discussion, Radius revised the IFU to address the failures. The revised IFU and an updated Use Related Risk Analysis (URRA) were submitted by Radius for Agency review on February 8, 2017 (See Appendix A).

### 3 ASSESSMENT

Tymlos (abaloparatide) is a human parathyroid hormone related peptide (PTHrP1-34) analog indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture. It will be available in a multiple dose prefilled pen that delivers 30 daily doses of 80 mcg abaloparatide in 40 mL.

We reviewed the revised IFU submitted to the Agency on February 8, 2017 for risk of medication error. The following paragraphs provide our review of the IFU:

#### Priming

We reviewed the revised IFU to determine if the instructions for the priming step poses risk of medication error. In the previous study, participants who failed to prime the pen or who were confused at the priming step verbalized confusion with the (b) (4) in the IFU, which may lead to dose omission or underdose. Our review of the revised IFU notes that Radius revised the language of the IFU and provided clarity for the critical task of priming the pen prior to use. More specifically, Radius replaced the (b) (4) sign with an 'Attention' sign. We find this

---

<sup>c</sup> Fava W Human Factors Review Memo for Tymlos (NDA 208743). 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 NOV 4. 3 p. OSE RCM No.: 2016-1715

revision clarifies the intent of the instructions and also increases the understanding of the need to prime only with first use. We find this revision acceptable

#### Needle removal

We reviewed of the revised IFU to determine if modifications have been made to clarify the proper instructions to remove the pen needle. In the previous study, participants who failed to safely remove the needle from the device without injury verbalized confusion with the instructions specifically with the graphics of (b) (4) arrows and the use of the terminology (b) (4). Our review of the revised IFU notes that Radius has added clarity to the graphics and simplified language surrounding the removal of the pen needle. Radius replaced the word (b) (4) with the more simplified language 'like (b) (4) a cap from a bottle' and also made the arrows simpler to understand with one concise arrow instead of the (b) (4) presentation. We find this revision acceptable.

In addition, we also reviewed the updated Use Related Risk Analysis (URRA) based on the modifications to the IFU to ensure that there are no new risks being introduced by the modifications. We found the URRA acceptable and do not have any recommendations at this time.

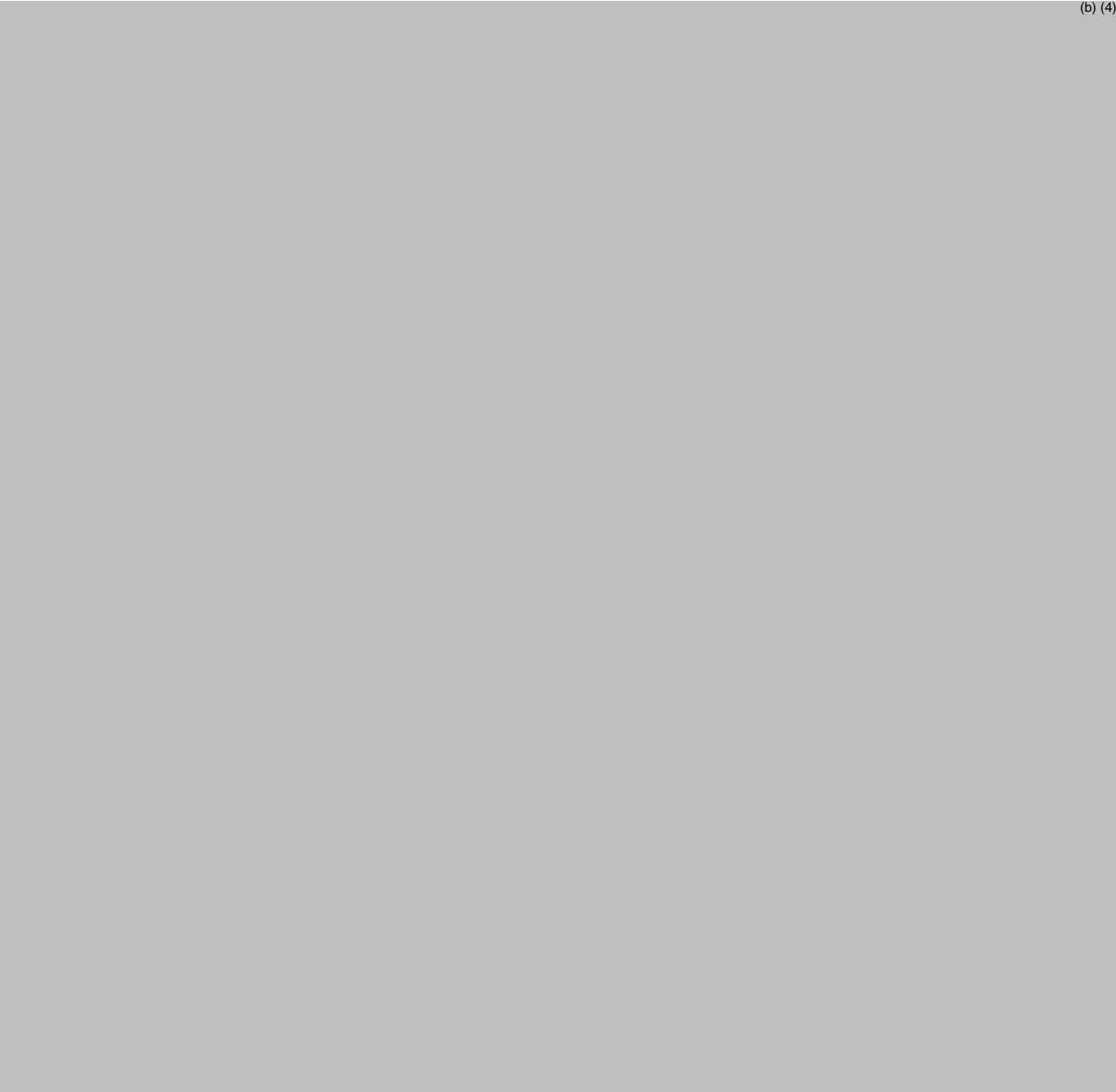
#### **4 CONCLUSION**

The revisions to the IFU are acceptable from a medication error perspective. The revisions are supported by the updated use related risk analysis. We determined that the revisions do not require additional validation testing. We have no further recommendations at this time.

**APPENDIX A. LABELING AND USE RELATED RISK ANALYSIS  
EXCERPTED FROM THE FEBRUARY 8, 2017 SUBMISSION**

**A. REVISED IFU**

(b) (4)



## B. UPDATED USE RELATED RISK ANALYSIS

### 5. ANALYSIS OF HAZARDS AND RISKS ASSOCIATED WITH THE USE OF THE DEVICE.

A risk assessment using a FMEA methodology was prepared for the abaloparatide pen. The following table provides the tasks which were included in this supplemental study.

| Use Risk and Task Priority |                                                   |                                                                              |               |
|----------------------------|---------------------------------------------------|------------------------------------------------------------------------------|---------------|
| Task                       | Potential Use Error                               | Potential User harm                                                          | Risk Priority |
| One time setup             | Skip priming process                              | Potential for under dose on first injection                                  | High          |
| Normal Use                 | Repeating of Priming                              | Waste of drug and potential to run out of product in the pen before intended | High          |
| Needle Removal             | Unable to remove needle<br>Potential needle stick | Pen unusable – delay in treatment<br>Minimal injury with needle              | Medium        |

No changes to the use risk assessment were identified.

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

/s/  
-----

LOLITA G WHITE on behalf of WALTER L FAVA  
04/10/2017

LOLITA G WHITE  
04/10/2017

QUYNHNHU T NGUYEN  
04/10/2017

## IMMUNOGENICITY CONSULT REVIEW MEMORANDUM

**DATE:** March 13, 2017  
**NDA:** 208743  
**CONSULT DATE:** December 5, 2016  
**PRIMARY REVIEW:** Bruce Huang, PhD; Product Quality Reviewer  
**THROUGH:** Harold Dickensheets, PhD; Chemist (Secondary Reviewer)  
**PRODUCT:** Abaloparatide (BA058, BIM-44058)  
**ROUTE OF ADMIN:** subcutaneous injection (disposable pen system)  
**INDICATION:** Treatment of osteoporosis in postmenopausal women  
**SPONSOR:** Radius Health, Inc.  
**CLINICAL DIVISION:** CDER/ODEIII/DBRUP; RPM – Samantha Bell

### RECOMMENDATION:

Abaloparatide contains a 14 amino acid sequence in the N-terminal that is non-identical to any known primate proteins. Consequently, this unique region of the peptide has the potential to be efficiently distinguished as a foreign antigen by patient immune systems, and trigger a substantial humoral immune response. Effective monitoring by the Sponsor to detect antidrug antibodies (ADA) to protect patient safety in clinical studies and to aid in determining the risk of ADA development upon abaloparatide treatment was initiated. The sponsor has developed validated abaloparatide ADA assays for total ADA binding, ADA confirmation, ADA titer, and abaloparatide neutralizing ADA. Because the abaloparatide peptide amino acid sequence is identical to that of the endogenous PTHrP in its 21 C-terminal amino acids, the possibility of cross-reactivity of ADA specific for abaloparatide with endogenous PTHrP or PTH is also conceivable. The Sponsor has additionally developed validated assays to investigate ADA cross-reactivity and potential neutralization of endogenous PTHrP and PTH. This is crucial as it appears that among 610 patients who received abaloparatide for eighteen months, a relatively high incidence of ADA positivity (300; ~49%) was confirmed, with 68% (201/297 evaluable ADA positives) of those patients confirmed as ADA positive demonstrating the presence of abaloparatide neutralizing ADA. Treatment-emergent ADA cross-reactivity was not confirmed against endogenous PTH, yet was confirmed against endogenous PTHrP in 2.4% (7/297) of evaluable ADA positive subjects at 18 months. Among the PTHrP cross-reactive subjects, 43% of the PTHrP positive subjects (3 of the 7), or 1.0% (3/297) of evaluable ADA positive subjects demonstrated the presence of low-titer (1:6 titer) endogenous PTHrP neutralizing antibodies.

The recommendation of the immunogenicity review team is that the sponsor has demonstrated acceptable validation of their various immunogenicity assay methods. Data arising from use of these methods may reliably be used to report abaloparatide ADA incidence, titer, NAb incidence and the incidence of ADA cross-reactive with endogenous PTHrP and PTH, and neutralizing ADA against endogenous PTHrP from clinical immunogenicity samples.

**PROPOSED COMMENTS TO FILE (as sent to Clinical RPM 03-04-17):**

Pending concurrence from the Medical Officer and application approval, the immunogenicity review team recommends the following (b) (4) post-marketing commitments to be included in action letter. Please send the following rationale and proposed PMC language to the sponsor and request the sponsor to revise as necessary and propose completion date for each PMC:

Immunogenicity incidence data reported in your submission are limited with respect to the analysis of available subject sera samples. Data necessary to verify the total incidence and establish the course of development of antidrug antibodies (ADA), including ADA cross-reactive with endogenous peptides, over the full duration of your Phase 3 trial are not currently available from all subjects. We recommend the following (b) (4) post-marketing commitments to ensure all samples collected from your Phase 3 study are analyzed with regard to anti-abaloparatide antibodies.

- **Rationale for PMC1:**

Subjects in your Phase 3 study BA058-05-003 were classified as ADA negative based on their ADA status at Visit 9 (18 months). Samples collected prior to Visit 9 from subjects scored as ADA negative at Visit 9 were not analyzed for abaloparatide ADA, resulting in an incomplete abaloparatide ADA profile and potential under reporting of ADA incidence. All available samples collected during the Phase 3 study BA058-05-003 from subjects reported as ADA negative at Visit 9 should be assayed for abaloparatide binding. Samples confirmed positive for abaloparatide binding ADA should be subsequently tested for ADA titer, and abaloparatide drug neutralization.

Proposed PMC1:

Analyze all collected serum samples from subjects enrolled in the BA058-05-003 study not previously tested for appearance of abaloparatide binding antibodies. Test the confirmed positive samples for abaloparatide binding ADA titer, and abaloparatide drug neutralization. Results from these studies should be submitted to the Agency by ....

- **Rationale for PMC2:**

Analysis of the development of ADA cross-reactivity against endogenous PTH and PTHrP has only been performed on immunogenicity samples collected at the Visit 9 (18 month) time point. Abaloparatide ADA positive samples prior to Visit 9 have not been assayed for endogenous peptide cross-reactivity or neutralization. These data are necessary to determine the progression of cross-reactive ADA development over the course of the Phase 3 study duration, in order to understand both the incidence and titers of cross-reactive ADA. All available ADA positive samples retained from the Phase 3 study BA058-05-003 should be assayed for PTH and PTHrP cross-reactivity, titer and neutralization.

Proposed PMC2:

Test all confirmed anti-abaloparatide positive serum samples from patients enrolled in the BA058-05-003 study for antibodies able to cross-react with or neutralize endogenous PTH or PTHrP. Results from these studies should be submitted to the Agency by ....

**TABLE OF CONTENTS:**

[Summary of drug and use in proposed indication.....4](#)

[Summary of Immunogenicity data from Phase 3 trials \(BA058-005-003; ACTIVE\) and \(BA058-005-05; ACTIVEExtend\).....5](#)

[Validation of RIA for Detection of Anti-Abaloparatide Antibodies in Normal Human Serum \(Report \(b\) \(4\)-MTQ2, Nov. 2007\).....7](#)

[Validation of Assay Cut-point Using Disease-State Samples for Method \(b\) \(4\) - RIA for Detection of Anti-Abaloparatide Antibodies in Human Serum \(Report \(b\) \(4\) MTQ3, Feb. 2010\).....16](#)

[Validation Report of a Cell-Based Assay to Detect Neutralizing Antibodies to Abaloparatide Using \(b\) \(4\), Jul. 2015\).....22](#)

[Review of anti-abaloparatide cross-reactivity with endogenous human PTH and PTHrP.....32](#)

[Anti-PTH Antibody Detection Assay Validation \(\(b\) \(4\) Method #50289\).....32](#)

[Anti-PTH Neutralizing Antibody Detection Assay Validation PROTOCOL \(\(b\) \(4\) Study \(b\) \(4\)-15-227-013\).....45](#)

[Anti-PTHrP Antibody Detection Assay Validation \(b\) \(4\) Method #50322\).....49](#)

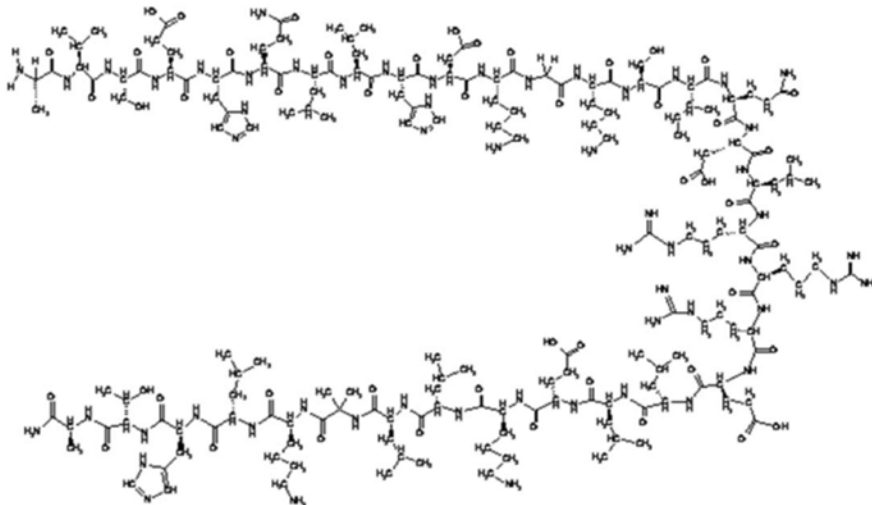
[Anti-PTHrP NAb Detection Assay Validation \(\(b\) \(4\) Study # \(b\) \(4\)-15-227-027\).....62](#)

## REVIEW MEMORANDUM

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

Abaloparatide (BA058, BIM-44058) is a 34 amino acid (3960.6 MW) synthetic peptide analog of human parathyroid hormone-related protein (PTHrP), administered by subcutaneous injection for the reduction of fracture risk in vertebral and non-vertebral bones. The peptide formula and structure are shown below:

Ala-Val-Ser-Glu-His-Gln-Leu-Leu-His-Asp-Lys-Gly-Lys-Ser-Ile-Gln-Asp-Leu-Arg-Arg-Arg-Glu-Leu-Leu-Glu-Lys-Leu-Leu-Aib-Lys-Leu-His-Thr-Al



The 21 C-terminal amino acids are identical to PTHrP, with the remaining 13 N-terminal amino acids containing 8 stability-improving substitutions (see Hattersley G, *et al*; 2016). The MOA for abaloparatide is reported by the sponsor to occur through binding the RG conformation (and, to a lesser extent, the R0 conformation) of the PTH1R receptor, thus stimulating the rapid increase of bone mineral density and anabolic bone markers, resulting in selective stimulation of bone formation. PTH1R is principally expressed in bone and kidney. Due to the homology with PTH in the first 36 amino acids, PTHrP binds to PTH1R, having effects on the regulation of calcium ion homeostasis through activation of adenylate cyclase and phospholipase C. Endogenously, PTHrP is necessary for bone development; its paracrine/autocrine signaling is involved in regulation of cellular growth, differentiation, development, and death. Additionally, PTHrP regulates transport of calcium in bones, cartilage, and mammary glands. The abaloparatide peptide sequence is optimized to retain the anabolic activity of PTHrP, but with decreased bone resorption and reduced calcium-mobilizing potential, which result in a net anabolic effect for bones.

### Summary of Immunogenicity data from Phase 3 trials (BA058-005-003; ACTIVE) and (BA058-005-05; ACTIVEextend)

The Phase 3 ACTIVE clinical trial comparing subcutaneous (SC) abaloparatide versus placebo and versus teriparatide in the treatment of otherwise healthy osteoporotic postmenopausal

women, was designed as a randomized, multi-center, multinational, double-blind, placebo-controlled study to evaluate efficacy and safety of a daily 80µg dose of abaloparatide (BA058)-SC for 18 months in the prevention of new vertebral and nonvertebral fractures. Samples for immunogenicity analysis were collected at baseline (prior to treatment at Visit 3) and at months 1, 3, 6, 12 and 18. Any patients who were confirmed positive for binding ADA (using the validated RIA assay described below) at the End-of-Treatment (Visit 9) had their previous time points analyzed for the presence of ADA and to examine the time-course of ADA development. Subsequent to ADA detection and confirmation by competition, antibody titers were determined and NAb assessed by the cell-based method described below. Patients subsequently enrolled in the ACTIVEExtend study received no further abaloparatide study drug and were to be tested for ADA every 6 months until they returned to their baseline ADA levels, following a similar testing regimen. The summarized immunogenicity data from the combined Phase 3 studies are presented below in “Table 1. Incidence of Antibody Formation in Study BA058-05-003 and Study BA058-05-005 in Patients Treated with Abaloparatide-SC Followed by Alendronate (Antibody Population\*)”, reproduced from the sponsor’s 17-Jan-2017 submission, “*Interim 37 Month Report Anti-Abaloparatide Antibody Immunogenicity Testing Summar, BA058-005-003 (ACTIVE) and BA058-005-005 (ACTIVEExtend) September 12, 2016*”, (page 7 of 19):

**Table 1: Incidence of Antibody Formation in Study BA058-05-003 and Study BA058-05-005 in Patients Treated with Abaloparatide-SC Followed by Alendronate (Antibody Population\*)**

| Visit                | ACTIVE Study<br>(Abaloparatide-SC) |      |      |                | ACTIVEExtend Study<br>(Abaloparatide-SC/ALN) |      |      |    |
|----------------------|------------------------------------|------|------|----------------|----------------------------------------------|------|------|----|
|                      | 3                                  | 6    | 8    | 9              | 3                                            | 4    | 6    |    |
| Months               | Baseline                           | 6    | 12   | 18             | 6                                            | 12   | 18   |    |
| % positive*          | <0.01                              | 18.9 | 40.0 | 49.2           | 26.8                                         | 14.8 | 13.2 |    |
| # Confirmed Positive | 2                                  | 115  | 244  | 300**          | 148                                          | 82^  | 73^  |    |
| Titer                | <1:1                               | 1    | 10   | 18             | 18                                           | 10   | 6    | 6  |
|                      | 1:1                                | 1    | 71   | 147            | 179                                          | 88   | 59   | 49 |
|                      | 1:10                               | 0    | 33   | 62             | 78                                           | 44   | 14   | 15 |
|                      | 1:100                              | 0    | 1    | 12             | 23                                           | 6    | 2    | 2  |
|                      | 1:1000                             | 0    | 0    | 0              | 1***                                         | 0    | 0    | 0  |
| NAb Positive* (%)    |                                    |      |      | 201<br>(33.0%) | 124<br>(22.4%)                               |      |      |    |

\* BA058-05-003 study antibody population n=610; Study BA058-05-005 antibody population n=553.

^One patient confirmed ADA positive but titer not determined.

\*\* Includes 2 patients that screened positive at Visit 9, but serum volume was insufficient for confirmation; these patients were confirmed ADA+ based on Visit 8 results

NAb=neutralizing antibody.

\*\*\*Patient number 1430033

Source: Adapted from Section 14.3.6, Table 14.3.6.1a., Table 14.3.6.1b

**Reviewer Comments:** *The data presented in Table 1 indicates that abaloparatide exhibits an overall ADA incidence in these studies of 49.2% (300 ADA<sup>+</sup> per 610 study subjects evaluated) at Visit 9 (18 months of treatment). Of these 300 patients, 298 were evaluable for NAb testing at 18 months; 201 (67%) of them tested positive for abaloparatide NAb, an overall NAb incidence of 33% (201/610). This indicates that abaloparatide is highly immunogenic (potentially due to low homology of the N-terminal portion of the abaloparatide peptide to the endogenous PTHrP peptide). Indeed, the “foreign” amino acid sequence that constitutes the N-terminal portion of the abaloparatide protein contains no detected putative conserved domains, and has no identical sequences to any known primate proteins. Among the top 100 hits recovered from a BLAST search of the N-terminal abaloparatide sequence, the only mammalian matches were obtained from the “Large Subunit GTPase-1-like proteins or homologs” from the deer mouse (83% identity), and Damara mole rat (77% identity). Notably, it is conceivable that this N-terminal region of completely “foreign” protein structure may provide sufficient immunogenic stimulus to break immunologic tolerance to the remaining C-terminal portion of the protein (which is identical to 21 amino acids of the endogenous PTHrP).*

*In addition to the increased incidence of ADA across the trial, there was an overall increase in the number of patients with evaluable ADA titers observed with longer treatment duration. However, for the 6, 12 and 18 month assay timepoints, the percentage of evaluated subjects with low ADA titers (<1:1 and 1:1) and high titers (1:10, 1:100, 1:1000) remained relatively constant, at ~70% and ~30%, respectively. Regardless, the substantial immunogenic response included the development of NAb; the presence of high titer ADA and NAb has the potential to affect the efficacy of the product.*

*The sponsor evaluation noted that a correlation was seen between anti-abaloparatide antibody formation and decreased PK exposure (AUC) and a corresponding (drug) clearance. However, it is unclear if the PK assessments included acid treatment of the samples to allow for detection of Ab-bound drug which could interfere with drug detection, therefore potentially leading to apparent reductions in drug content when there are anti-drug Ab:drug complexes present. The sponsor performed analysis of patient PK exposures by NAb<sup>+</sup> status (data not found in submission) and reported that there was no impact on either AUC or clearance parameters, and no apparent clinical associations of NAb<sup>+</sup> with safety and efficacy endpoints, or treatment emergent adverse events (TEAEs). Thus, the sponsor concluded that the presence of anti-abaloparatide antibodies had no apparent effect on efficacy or safety of abaloparatide treatment over 18 months, even with the evidence of NAb and differences in PK exposure and clearance effects previously noted.*

#### **Potential risks of anti-abaloparatide antibody development**

*ADA specific for abaloparatide in patients have the potential to bind to and neutralize the drug during treatment, which could affect drug half-life and result in diminished clinical efficacy. More worrying from an immunogenicity perspective however, is the potential risk of abaloparatide ADA to cross-react with and neutralize the endogenous PTHrP of patients. As previously discussed, abaloparatide contains both a human and a novel foreign peptide*

*sequence. Therefore, the foreign sequence may conceivably have the potential to act as an effective adjuvant in the generation of a humoral immune response against not only the novel portion of the abaloparatide protein, but also the more conserved “endogenous” (self) portion as well, through an epitope spreading process. In such a case, an anti-self response of this nature might impact not just the efficacy of the abaloparatide drug, but also the patient’s own PTHrP, and possibly other endogenous proteins sharing similar sequences or structural motifs to PTHrP, including PTH. The clinical significance of such an auto-immune reaction would likely be the onset of a deficiency-like syndrome with resulting inability to stimulate PTH receptors, and thus dysregulation of serum calcium and phosphorous could occur. Consequently, low blood calcium may lead to loss of muscle control, disruption of nerve conduction, and increased bone fragility.*

*In my opinion, there are potential concerns, noted above, regarding abaloparatide ADA with respect to both ADA interfering with abaloparatide efficacy and ADA cross-reactive with endogenous peptides. However, these concerns have been largely addressed by the validated ADA assays and the validated cross-reactivity assessments for endogenous PTHrP and PTH included in the sponsor’s immunogenicity program. Appropriate assays for monitoring the development of abaloparatide ADA and their ability to interact with endogenous PTH receptor agonist peptides have been implemented; additional post-marketing studies to fully characterize ADA responses across all immunogenicity sampling time points collected have been recommended, as noted above.*

(b) (4)

**Table 1: Validation parameters for ADA method MTQ2 (normal serum)**

| Validation parameter                                         | Value                                                |
|--------------------------------------------------------------|------------------------------------------------------|
| Minimum required dilution                                    | 1:4                                                  |
| Normal assay cut-point (% binding)                           | 7.81%                                                |
| Normalization factor                                         | 1.276                                                |
| Inter -assay precision of the positive controls              | ≤ 37.4%                                              |
| Inter -assay precision of the negative controls              | ≤ 18.5%                                              |
| Intra -assay precision of the positive and negative controls | ≤ 12.7%                                              |
| Sensitivity (rabbit anti-abaloparatide antibody dilution)    | 1:100,000                                            |
| Specificity (abaloparatide)                                  | 500 pg/mL produce ≥ 30% inhibition                   |
| Recovery                                                     | Consistent CVs through all 10 individual sera tested |
| Freeze-thaw stability                                        | ≤ 20 % after 5 cycles                                |
| Thawed matrix stability                                      | 24 hours, stored on ice                              |



**Reviewer Comment:** Per our 03-Feb-2017 IR comment 5, the sponsor has provided an assay sensitivity estimate of 0.235-0.118 ng/mL rather than the 1:100000 PC antiserum dilution sensitivity data provided originally – indicated above by the reviewer-annotated red arrow.

Assay Cut Point determination: Rabbit anti-abaloparatide antibodies (Batch 7362 3, Radius Health, Inc.), spiked in pooled normal human serum, were used as a surrogate positive control for patient anti-abaloparatide antibodies in competitive RIA detection assays using 50 normal human serum samples. The minimum required dilutions (MRD) 1:4 and 1:8 were tested; 1:4 was found to produce good sensitivity with tolerable interference, and was chosen for use in analysis of samples.

Fifty human serum samples were analyzed at the 1:4 MRD in three validation runs for determination of inter-assay non-specific binding, in order to establish the assay cut point (ACP, see Table below, copied from the submission):

**Table 1a. Assay Cut Point Determination MRD 1:4**

| Lot | 1MTQ2 | 2MTQ2 | 3MTQ2 | Mean | SD    | %CV  | Lot | 1MTQ2 | 2MTQ2 | 3MTQ2 | Mean | SD     | %CV   |
|-----|-------|-------|-------|------|-------|------|-----|-------|-------|-------|------|--------|-------|
| 1   | 4.42  | 5.71  | 6.54  | 5.56 | 1.07  | 19.2 | 26  | 6.56  | 7.41  | 8.86  | 7.61 | 1.16   | 15.3  |
| 2   | 5.14  | 7.54  | 7.83  | 6.84 | 1.48  | 21.6 | 27  | 5.88  | 7.00  | 6.97  | 6.62 | 0.634  | 9.59  |
| 3   | 5.23  | 5.83  | 6.68  | 5.91 | 0.729 | 12.3 | 28  | 4.90  | 6.13  | 6.17  | 5.73 | 0.718  | 12.5  |
| 4   | RCV   | 7.11  | 7.58  | 7.35 | 0.335 | 4.55 | 29  | 6.50  | 8.52  | 8.39  | 7.80 | 1.13   | 14.4  |
| 5   | 6.07  | 6.65  | 7.61  | 6.77 | 0.781 | 11.5 | 30  | 6.37  | 6.98  | 7.07  | 6.81 | 0.379  | 5.56  |
| 6   | 4.34  | 5.45  | 7.00  | 5.60 | 1.34  | 23.9 | 31  | 5.73  | 7.20  | 7.52  | 6.82 | 0.956  | 14.0  |
| 7   | 4.81  | 6.58  | 8.12  | 6.50 | 1.66  | 25.5 | 32  | 5.08  | 5.68  | 6.74  | 5.83 | 0.841  | 14.4  |
| 8   | 4.90  | 7.38  | 8.86  | 7.04 | 2.00  | 28.4 | 33  | 5.89  | 6.33  | 6.96  | 6.39 | 0.535  | 8.36  |
| 9   | 4.50  | 5.97  | 7.20  | 5.89 | 1.36  | 23.0 | 34  | 5.82  | 7.71  | 7.28  | 6.94 | 0.991  | 14.3  |
| 10  | 4.86  | 5.98  | 7.13  | 5.99 | 1.13  | 18.9 | 35  | 5.29  | 7.66  | 7.13  | 6.69 | 1.24   | 18.6  |
| 11  | 5.06  | 6.07  | 6.53  | 5.89 | 0.752 | 12.8 | 36  | RCV   | 6.87  | 6.66  | 6.77 | 0.144  | 2.13  |
| 12  | 6.37  | 7.77  | 8.45  | 7.53 | 1.06  | 14.0 | 37  | 5.57  | 6.60  | 7.33  | 6.50 | 0.884  | 13.6  |
| 13  | 5.48  | 8.47  | 8.22  | 7.39 | 1.66  | 22.4 | 38  | 5.21  | 6.51  | 8.19  | 6.64 | 1.50   | 22.5  |
| 14  | 6.66  | 9.06  | 9.12  | 8.28 | 1.41  | 17.0 | 39  | 6.74  | 7.45  | 7.37  | 7.19 | 0.385  | 5.36  |
| 15  | 5.77  | 7.62  | 7.56  | 6.98 | 1.05  | 15.0 | 40  | 6.86  | 7.24  | 6.65  | 6.92 | 0.302  | 4.37  |
| 16  | 5.77  | 7.12  | 7.42  | 6.77 | 0.876 | 12.9 | 41  | 7.40  | 8.05  | 7.77  | 7.74 | 0.326  | 4.21  |
| 17  | 5.23  | 6.39  | 7.00  | 6.21 | 0.900 | 14.5 | 42  | 6.20  | 7.21  | 6.91  | 6.77 | 0.518  | 7.64  |
| 18  | 4.98  | 6.83  | 7.72  | 6.51 | 1.40  | 21.5 | 43  | 6.08  | 7.48  | 7.16  | 6.91 | 0.734  | 10.6  |
| 19  | 5.39  | 9.04  | 7.95  | 7.46 | 1.88  | 25.1 | 44  | 5.65  | 7.51  | 6.69  | 6.62 | 0.928  | 14.0  |
| 20  | 4.80  | 6.88  | 7.25  | 6.31 | 1.32  | 20.9 | 45  | 5.40  | 5.37  | 6.00  | 5.59 | 0.355  | 6.34  |
| 21  | 5.94  | 7.03  | 7.18  | 6.72 | 0.678 | 10.1 | 46  | 6.26  | 6.44  | 6.96  | 6.55 | 0.361  | 5.51  |
| 22  | 5.27  | 6.65  | 6.48  | 6.14 | 0.751 | 12.2 | 47  | 5.15  | 5.75  | 5.37  | 5.42 | 0.304  | 5.80  |
| 23  | 5.48  | 6.85  | 6.67  | 6.33 | 0.748 | 11.8 | 48  | 6.35  | 6.38  | 6.45  | 6.39 | 0.0523 | 0.817 |
| 24  | 6.12  | 8.70  | 8.13  | 7.65 | 1.36  | 17.8 | 49  | 6.45  | 6.85  | 7.18  | 6.83 | 0.366  | 5.36  |
| 25  | 7.08  | 8.90  | 8.69  | 8.22 | 1.00  | 12.2 | 50  | 6.09  | 8.13  | 6.61  | 6.94 | 1.06   | 15.3  |

Legend: RCV- replicate coefficient of variation > 25%

The mean % binding data for each run was ordered from lowest to highest, for application of 95% prediction interval (mean + SD\*1.645), see red box annotated below by the reviewer on Table 2a below, copied from the submission (below):

| Run 1MTQ2 |                          | Run 2MTQ2 |                          | Run 3MTQ2 |                          | All Runs          |                          |
|-----------|--------------------------|-----------|--------------------------|-----------|--------------------------|-------------------|--------------------------|
| Lot       | Mean<br>(Mean % Binding) | Lot       | Mean<br>(Mean % Binding) | Lot       | Mean<br>(Mean % Binding) | Lot               | Mean<br>(Mean % Binding) |
| 6         | 4.34                     | 45        | 5.37                     | 47        | 5.37                     | 47                | 5.42                     |
| 1         | 4.42                     | 6         | 5.45                     | 45        | 6.00                     | 1                 | 5.56                     |
| 9         | 4.50                     | 32        | 5.68                     | 28        | 6.17                     | 45                | 5.59                     |
| 20        | 4.80                     | 1         | 5.71                     | 48        | 6.45                     | 6                 | 5.60                     |
| 7         | 4.81                     | 47        | 5.75                     | 22        | 6.48                     | 28                | 5.73                     |
| 10        | 4.86                     | 3         | 5.83                     | 11        | 6.53                     | 32                | 5.83                     |
| 8         | 4.90                     | 9         | 5.97                     | 1         | 6.54                     | 11                | 5.89                     |
| 28        | 4.90                     | 10        | 5.98                     | 50        | 6.61                     | 9                 | 5.89                     |
| 18        | 4.98                     | 11        | 6.07                     | 40        | 6.65                     | 3                 | 5.91                     |
| 11        | 5.06                     | 28        | 6.13                     | 36        | 6.66                     | 10                | 5.99                     |
| 32        | 5.08                     | 33        | 6.33                     | 23        | 6.67                     | 22                | 6.14                     |
| 2         | 5.14                     | 48        | 6.38                     | 3         | 6.68                     | 17                | 6.21                     |
| 47        | 5.15                     | 17        | 6.39                     | 44        | 6.69                     | 20                | 6.31                     |
| 38        | 5.21                     | 46        | 6.44                     | 32        | 6.74                     | 23                | 6.33                     |
| 3         | 5.23                     | 38        | 6.51                     | 42        | 6.91                     | 48                | 6.39                     |
| 17        | 5.23                     | 7         | 6.58                     | 33        | 6.96                     | 33                | 6.39                     |
| 22        | 5.27                     | 37        | 6.60                     | 46        | 6.96                     | 37                | 6.50                     |
| 35        | 5.29                     | 5         | 6.65                     | 27        | 6.97                     | 7                 | 6.50                     |
| 19        | 5.39                     | 22        | 6.65                     | 6         | 7.00                     | 18                | 6.51                     |
| 45        | 5.40                     | 18        | 6.83                     | 17        | 7.00                     | 46                | 6.55                     |
| 23        | 5.48                     | 49        | 6.85                     | 30        | 7.07                     | 27                | 6.62                     |
| 13        | 5.48                     | 23        | 6.85                     | 10        | 7.13                     | 44                | 6.62                     |
| 37        | 5.57                     | 36        | 6.87                     | 35        | 7.13                     | 38                | 6.64                     |
| 44        | 5.65                     | 20        | 6.88                     | 43        | 7.16                     | 35                | 6.69                     |
| 31        | 5.73                     | 30        | 6.98                     | 21        | 7.18                     | 21                | 6.72                     |
| 15        | 5.77                     | 27        | 7.00                     | 49        | 7.18                     | 36                | 6.77                     |
| 16        | 5.77                     | 21        | 7.03                     | 9         | 7.20                     | 16                | 6.77                     |
| 34        | 5.82                     | 4         | 7.11                     | 20        | 7.25                     | 42                | 6.77                     |
| 27        | 5.88                     | 16        | 7.12                     | 34        | 7.28                     | 5                 | 6.77                     |
| 33        | 5.89                     | 31        | 7.20                     | 37        | 7.33                     | 30                | 6.81                     |
| 21        | 5.94                     | 42        | 7.21                     | 39        | 7.37                     | 31                | 6.82                     |
| 5         | 6.07                     | 40        | 7.24                     | 16        | 7.42                     | 49                | 6.83                     |
| 43        | 6.08                     | 8         | 7.38                     | 31        | 7.52                     | 2                 | 6.84                     |
| 50        | 6.09                     | 26        | 7.41                     | 15        | 7.56                     | 43                | 6.91                     |
| 24        | 6.12                     | 39        | 7.45                     | 4         | 7.58                     | 40                | 6.92                     |
| 42        | 6.20                     | 43        | 7.48                     | 5         | 7.61                     | 34                | 6.94                     |
| 46        | 6.26                     | 44        | 7.51                     | 18        | 7.72                     | 50                | 6.94                     |
| 48        | 6.35                     | 2         | 7.54                     | 41        | 7.77                     | 15                | 6.98                     |
| 12        | 6.37                     | 15        | 7.62                     | 2         | 7.83                     | 8                 | 7.04                     |
| 30        | 6.37                     | 35        | 7.66                     | 19        | 7.95                     | 39                | 7.19                     |
| 49        | 6.45                     | 34        | 7.71                     | 7         | 8.12                     | 4                 | 7.35                     |
| 29        | 6.50                     | 12        | 7.77                     | 24        | 8.13                     | 13                | 7.39                     |
| 26        | 6.56                     | 41        | 8.05                     | 38        | 8.19                     | 19                | 7.46                     |
| 14        | 6.66                     | 50        | 8.13                     | 13        | 8.22                     | 12                | 7.53                     |
| 39        | 6.74                     | 13        | 8.47                     | 29        | 8.39                     | 26                | 7.61                     |
| 40        | 6.86                     | 29        | 8.52                     | 12        | 8.45                     | 24                | 7.65                     |
| 25        | 7.08                     | 24        | 8.70                     | 25        | 8.69                     | 41                | 7.74                     |
| 41        | 7.40                     | 25        | 8.90                     | 8         | 8.86                     | 29                | 7.80                     |
| 4         | RCV                      | 19        | 9.04                     | 26        | 8.86                     | 25                | 8.22                     |
| 36        | RCV                      | 14        | 9.06                     | 14        | 9.12                     | 14                | 8.28                     |
|           |                          |           |                          |           |                          | mean              | 6.70                     |
|           |                          |           |                          |           |                          | SD                | 0.676                    |
|           |                          |           |                          |           |                          | SD x 1.645        | 1.11                     |
|           |                          |           |                          |           |                          | SD x 1.645 + mean | 7.81                     |

Legend:  
  Results Outside the 95% confidence limit

The ACP for the 1:4 MRD was determined to be 7.81. Cut point normalization was performed to account for daily variability in signal response of the assay, using the ratio of the “Mean % binding of blank serum + SD\*1.645” to the “Mean % binding of the negative control values (NC2)” (green box, see Table 3a, below, copied from the submission and annotated in color by

the reviewer). The Normalization Factor for MRD 1:4 dilution was calculated to be 1.276 (see blue box annotated in color by the reviewer, below).

**Reviewer comment:** *The ACP calculation for the RIA is acceptable; a sufficient number of treatment-naïve patients were sampled, and having an upper negative limit with 95% confidence interval allows a theoretical 5% false-positive rate. The “mean+1.645 SD” calculation method is an appropriate computational formula. The normalization factor that was calculated will allow the Sponsor to acceptably account for inter-assay variability.*

Table 3a. Normalization Determination MRD 1:4

| Lot | Run         | Run   | Run   |
|-----|-------------|-------|-------|
|     | 1MTQ2       | 2MTQ2 | 3MTQ2 |
|     | (% Binding) |       |       |
| 1   | 4.42        | 5.71  | 6.54  |
| 2   | 5.14        | 7.54  | 7.83  |
| 3   | 5.23        | 5.83  | 6.68  |
| 4   | RCV         | 7.11  | 7.58  |
| 5   | 6.07        | 6.65  | 7.61  |
| 6   | 4.34        | 5.45  | 7.00  |
| 7   | 4.81        | 6.58  | 8.12  |
| 8   | 4.90        | 7.38  | 8.88  |
| 9   | 4.50        | 5.97  | 7.20  |
| 10  | 4.86        | 5.98  | 7.13  |
| 11  | 5.06        | 6.07  | 6.53  |
| 12  | 6.37        | 7.77  | 8.45  |
| 13  | 5.48        | 8.47  | 8.22  |
| 14  | 6.66        | 9.06  | 9.12  |
| 15  | 5.77        | 7.62  | 7.56  |
| 16  | 5.77        | 7.12  | 7.42  |
| 17  | 5.23        | 6.39  | 7.00  |
| 18  | 4.98        | 6.83  | 7.72  |
| 19  | 5.39        | 9.04  | 7.95  |
| 20  | 4.80        | 6.88  | 7.25  |
| 21  | 5.94        | 7.03  | 7.18  |
| 22  | 5.27        | 6.65  | 6.48  |
| 23  | 5.48        | 6.85  | 6.67  |
| 24  | 6.12        | 8.70  | 8.13  |
| 25  | 7.08        | 8.90  | 8.89  |
| 26  | 6.56        | 7.41  | 8.86  |
| 27  | 5.88        | 7.00  | 6.97  |
| 28  | 4.90        | 6.13  | 6.17  |
| 29  | 6.50        | 8.52  | 8.39  |
| 30  | 6.37        | 6.98  | 7.07  |
| 31  | 5.73        | 7.20  | 7.52  |
| 32  | 5.08        | 5.68  | 6.74  |
| 33  | 5.89        | 6.33  | 6.96  |
| 34  | 5.82        | 7.71  | 7.28  |
| 35  | 5.29        | 7.66  | 7.13  |
| 36  | RCV         | 6.87  | 6.68  |
| 37  | 5.57        | 6.60  | 7.33  |
| 38  | 5.21        | 6.51  | 6.19  |
| 39  | 6.74        | 7.45  | 7.37  |
| 40  | 6.86        | 7.24  | 6.65  |
| 41  | 7.40        | 8.05  | 7.77  |
| 42  | 6.20        | 7.21  | 6.91  |
| 43  | 6.08        | 7.48  | 7.16  |
| 44  | 5.65        | 7.51  | 6.89  |
| 45  | 5.40        | 5.37  | 6.00  |
| 46  | 6.26        | 6.44  | 6.96  |
| 47  | 5.15        | 5.75  | 5.37  |
| 48  | 6.35        | 6.38  | 6.45  |
| 49  | 6.45        | 6.85  | 7.18  |
| 50  | 6.09        | 8.13  | 6.61  |

| Individual Normalization Factors           |       |
|--------------------------------------------|-------|
| F1=                                        | 1.476 |
| F2=                                        | 1.216 |
| F3=                                        | 1.136 |
| mean                                       | 1.276 |
| SD                                         | 0.178 |
| %CV                                        | 13.9  |
| Normalization Factor for MRD 1:4 dilutions |       |
| 1.276                                      |       |

|                       |       |       |       |
|-----------------------|-------|-------|-------|
| Mean of ACP Samples   | 5.69  | 7.04  | 7.31  |
| SD of ACP Samples     | 0.722 | 0.933 | 0.781 |
| SD of Samples x 1.645 | 1.19  | 1.53  | 1.28  |
| Mean + SD x 1.645     | 6.88  | 8.58  | 8.59  |
| Mean of NC2           | 4.66  | 7.05  | 7.56  |

Legend: RCV- CV > 25%, values are not used to calculate overall mean

The NC2 negative control was prepared by pooling 44-48 individual human serum units used during assay development. The surrogate positive control that was used for assay validation consisted of rabbit anti-abaloparatide antibody diluted in pooled negative control human serum.

**NOTE:** The Sponsor chose to base acceptance criteria for all validation runs on the condition that the mean values recorded with the NC and dilutions of the PC have the following relationship: NC<PC1<PC2<PC3<PC4 (see chart below for PC definitions, copied from the submission), and the %CV≤25% for all controls:

- NC = Negative control used for validation data tables
- NC2 = Negative control used during assay cut point runs only
- PC1 = Low surrogate positive control (1:50,000 dilution)
- PC2 = Back-up low surrogate positive control (1:40,000 dilution)
- PC3 = Middle surrogate positive control (1:5000 dilution)
- PC4 = High surrogate positive control (1:1000 dilution)

**Reviewer Comment:** Based on information obtained from the Sponsor from their Response to IR (Feb. 3, 2017), the approximate concentration of the anti-abaloparatide antibody is 47 µg/ml, therefore the following PC concentrations were calculated by the reviewer:

- PC1 (low positive control) = 0.94 ng/ml
- PC2 (back-up low positive control) = 1.175 ng/ml
- PC3 (middle positive control) = 9.4 ng/ml
- PC4 (high positive control) = 47 ng/ml

**Inter-assay Precision:** Six validation runs were performed using the NC and dilutions of the surrogate positive control in triplicate; the %CV of binding for the surrogate positive controls was found to be ≤18.5%, while the %CV of binding for the NC was 37.4% (see Table 4a, below, copied from the submission and annotated by the reviewer):

|     | Run 4 MTQ2 |      |      | Run 6 MTQ2 |      |      | Run 7 MTQ2 |      |      | Run 8 MTQ2 |      |      |
|-----|------------|------|------|------------|------|------|------------|------|------|------------|------|------|
| NC  | 7.59       | 6.74 | 6.28 | 4.29       | 4.61 | 4.65 | 8.05       | 9.31 | 7.90 | 3.21       | 3.67 | 3.07 |
| PC1 | 12.3       | 10.5 | 10.7 | 9.33       | 8.60 | 8.83 | 13.4       | 13.7 | 13.2 | 8.31       | 8.58 | 9.21 |
| PC2 | 13.6       | 12.2 | 11.3 | 10.1       | 9.89 | 10.2 | 14.8       | 14.3 | 13.9 | 10.0       | 9.96 | 10.6 |
| PC3 | 42.4       | 41.3 | 41.2 | 41.3       | 41.7 | 39.9 | 48.8       | 48.8 | 42.9 | 43.2       | 42.5 | 43.3 |
| PC4 | 80.8       | 79.0 | 77.6 | 80.5       | 79.2 | 81.3 | 87.0       | 87.3 | 87.5 | 80.0       | 80.4 | 80.6 |

|     | Run 9 MTQ2 |      |      | Run 10 MTQ2 |      |      |
|-----|------------|------|------|-------------|------|------|
| NC  | 3.07       | 3.13 | 3.13 | 5.91        | 6.30 | 6.20 |
| PC1 | 8.41       | 8.42 | 8.60 | 10.9        | 11.9 | 11.4 |
| PC2 | 9.94       | 9.56 | 10.1 | 12.2        | 12.5 | 12.1 |
| PC3 | 43.3       | 42.7 | 43.3 | 45.2        | 45.9 | 44.5 |
| PC4 | 80.0       | 80.0 | 79.1 | 85.2        | 84.9 | 84.2 |

| Legend: |                                                            |
|---------|------------------------------------------------------------|
| NC      | Negative Control                                           |
| PC1     | Low surrogate positive control (1:50,000 dilution)         |
| PC2     | Back-up low surrogate positive control (1:40,000 dilution) |
| PC3     | Middle surrogate positive control (1:5000 dilution)        |
| PC4     | High surrogate positive control (1:1000 dilution)          |

| Inter Assay Results |             |           | Normalized |         |                             |
|---------------------|-------------|-----------|------------|---------|-----------------------------|
|                     | Global mean | Global SD | Global %CV | Mean NC | ACP                         |
| NC                  | 5.39        | 2.02      | 37.4       | 6.87    | 8.76                        |
| PC1                 | 10.35       | 1.91      | 18.5       | 4.52    | 5.77                        |
| PC2                 | 11.50       | 1.73      | 15.0       | 8.42    | 10.7                        |
| PC3                 | 43.45       | 2.42      | 5.57       | 8 MTQ2  | 4.23                        |
| PC4                 | 81.92       | 3.18      | 3.89       | 9 MTQ2  | 3.97                        |
|                     |             |           |            | 10 MTQ2 | 7.83                        |
|                     |             |           |            |         | Normalization factor= 1.276 |

**Reviewer comment:** The testing for Inter-assay Precision showed that the ADA method MTQ2 met the acceptance criteria in the mean for NC<PC1<PC2<PC3<PC4, and the %CV of binding for the surrogate positive control is ≤25% for all dilutions tested. The testing for the NC resulted in a higher %CV (37.5%), however it consistently produced results lower than that of the Low surrogate positive control. This is an acceptable result.

**Intra-assay Precision:** The negative control and surrogate positive controls were analyzed in six preparations for analysis, by three separate assays, each. The intra-assay precision (%CV of any run for any control sample) was found to be ≤12.7%, which was recorded from a reading of NC, which appeared to generally yield greater variability than any of the positive control samples (see Table 5a, below, copied from the submission).

Table 5a. Intra Assay Analysis of the NC and PCs MRD 1:4

| Run ID | NC    | Low PC | Backup | Backup  | High PC |
|--------|-------|--------|--------|---------|---------|
|        |       |        | Low PC | High PC |         |
| 4 MTQ2 | 7.29  | 11.5   | 12.8   | 42.0    | 81.6    |
|        | 7.63  | 11.6   | 13.1   | 41.9    | 80.5    |
|        | 7.16  | 11.3   | 13.0   | 42.1    | 77.4    |
|        | 7.01  | 11.7   | 12.2   | 40.8    | 79.4    |
|        | 6.32  | 11.4   | 12.3   | 40.1    | 78.8    |
|        | 6.96  | 11.5   | 12.5   | 41.5    | 79.8    |
| N=     | 6     | 6      | 6      | 6       | 6       |
| Mean   | 7.06  | 11.5   | 12.7   | 41.4    | 79.6    |
| SD     | 0.435 | 0.141  | 0.373  | 0.795   | 1.44    |
| %CV    | 6.17  | 1.23   | 2.95   | 1.92    | 1.81    |

| Run ID | NC    | Low PC | Backup | Backup  | High PC |
|--------|-------|--------|--------|---------|---------|
|        |       |        | Low PC | High PC |         |
| 8 MTQ2 | 3.12  | 8.47   | 9.84   | 43.4    | 79.3    |
|        | 2.94  | 8.46   | 10.0   | 44.0    | 80.1    |
|        | 3.56  | 7.82   | 10.4   | 43.7    | 80.5    |
|        | 3.05  | 8.35   | 9.36   | 43.3    | 79.7    |
|        | 3.27  | 8.34   | 9.80   | 41.9    | 80.2    |
|        | 2.49  | 8.07   | 8.74   | 43.4    | 80.7    |
| N=     | 6     | 6      | 6      | 6       | 6       |
| Mean   | 3.07  | 8.25   | 9.69   | 43.3    | 80.1    |
| SD     | 0.356 | 0.258  | 0.579  | 0.731   | 0.499   |
| %CV    | 11.6  | 3.13   | 5.98   | 1.69    | 0.623   |

| Run ID | NC    | Low PC | Backup | Backup  | High PC |
|--------|-------|--------|--------|---------|---------|
|        |       |        | Low PC | High PC |         |
| 9 MTQ2 | 3.04  | 7.92   | 10.0   | 43.3    | 79.9    |
|        | 3.03  | 8.24   | 9.86   | 42.3    | 79.7    |
|        | 3.63  | 8.60   | 9.85   | 43.1    | 80.2    |
|        | 2.89  | 8.03   | 9.16   | 43.0    | 78.8    |
|        | 2.98  | 7.91   | 9.80   | 41.7    | 79.5    |
|        | 2.44  | 7.65   | 8.98   | 42.9    | 80.4    |
| N=     | 6     | 6      | 6      | 6       | 6       |
| Mean   | 3.00  | 8.06   | 9.62   | 42.7    | 79.7    |
| SD     | 0.381 | 0.328  | 0.434  | 0.595   | 0.561   |
| %CV    | 12.7  | 4.08   | 4.51   | 1.39    | 0.703   |

**Legend:** NC Negative Control  
 Low PC Low surrogate positive control (1:50,000 dilution)  
 Backup Low PC Back-up low surrogate positive control (1:40,000 dilution)  
 Backup High PC Middle surrogate positive control (1:5000 dilution)  
 High PC High surrogate positive control (1:1000 dilution)

**Review comment:** The conduct of validation for Intra-assay Precision is consistent with the recommendations of the Agency Draft Guidance, and all calculated %CV were found to be within the range of the ≤25% acceptance criteria. This supports the acceptability of the RIA assay validation.

**Assay Sensitivity:** Dilutions of the rabbit anti-abaloparatide PC antibody in pooled human serum (1:100 to 1:100,000) were assayed to evaluate the sensitivity of the assay. For the 1:4 MRD, the sensitivity (dilution of the PC that resulted in % binding just above the normalized assay CP) was found to be greater than 1:100,000, as the results of the assay were never below the NACP, even at the greatest 1:100,000 dilution; see Table 6a, below, copied from the submission:

| Dilution of Neat Ab | CPM  | Mean | SD   | %CV    | % Binding | Mean of Each Dilution |
|---------------------|------|------|------|--------|-----------|-----------------------|
| 100,000             | 1249 | 1238 | 16.3 | 1.31   | 8.70      |                       |
| 100,000             | 1226 |      |      |        |           |                       |
| 100,000             | 1248 | 1233 | 21.2 | 1.72   | 8.65      | 8.73                  |
| 100,000             | 1218 |      |      |        |           |                       |
| 100,000             | 1258 | 1252 | 8.49 | 0.678  | 8.84      |                       |
| 100,000             | 1246 |      |      |        |           |                       |
| 80,000              | 1328 | 1337 | 12.0 | 0.899  | 9.70      |                       |
| 80,000              | 1345 |      |      |        |           |                       |
| 80,000              | 1319 | 1289 | 42.4 | 3.29   | 9.22      | 9.42                  |
| 80,000              | 1259 |      |      |        |           |                       |
| 80,000              | 1311 | 1301 | 14.1 | 1.09   | 9.34      |                       |
| 80,000              | 1291 |      |      |        |           |                       |
| 70,000              | 1318 | 1330 | 16.3 | 1.22   | 9.63      |                       |
| 70,000              | 1341 |      |      |        |           |                       |
| 70,000              | 1334 | 1332 | 2.83 | 0.212  | 9.65      | 9.58                  |
| 70,000              | 1330 |      |      |        |           |                       |
| 70,000              | 1295 | 1312 | 23.3 | 1.78   | 9.45      |                       |
| 70,000              | 1328 |      |      |        |           |                       |
| 60,000              | 1369 | 1360 | 12.7 | 0.936  | 9.94      |                       |
| 60,000              | 1351 |      |      |        |           |                       |
| 60,000              | 1327 | 1355 | 39.6 | 2.92   | 9.89      | 9.76                  |
| 60,000              | 1383 |      |      |        |           |                       |
| 60,000              | 1342 | 1313 | 41.0 | 3.12   | 9.46      |                       |
| 60,000              | 1284 |      |      |        |           |                       |
| 50,000              | 1474 | 1450 | 34.6 | 2.39   | 10.8      |                       |
| 50,000              | 1425 |      |      |        |           |                       |
| 50,000              | 1476 | 1498 | 30.4 | 2.03   | 11.3      | 11.04                 |
| 50,000              | 1519 |      |      |        |           |                       |
| 50,000              | 1417 | 1458 | 57.3 | 3.93   | 10.9      |                       |
| 50,000              | 1498 |      |      |        |           |                       |
| 10,000              | 3245 | 3250 | 7.07 | 0.218  | 29.1      |                       |
| 10,000              | 3255 |      |      |        |           |                       |
| 10,000              | 3152 | 3230 | 110  | 3.39   | 28.9      | 29.0                  |
| 10,000              | 3307 |      |      |        |           |                       |
| 10,000              | 3304 | 3251 | 75.7 | 2.33   | 29.1      |                       |
| 10,000              | 3197 |      |      |        |           |                       |
| 1,000               | 8578 | 8561 | 24.7 | 0.289  | 83.0      |                       |
| 1,000               | 8543 |      |      |        |           |                       |
| 1,000               | 8578 | 8582 | 5.86 | 0.0659 | 83.2      | 83.4                  |
| 1,000               | 8586 |      |      |        |           |                       |
| 1,000               | 8713 | 8656 | 80.6 | 0.931  | 83.9      |                       |
| 1,000               | 8599 |      |      |        |           |                       |
| 100                 | 9494 | 9496 | 2.83 | 0.0298 | 92.4      |                       |
| 100                 | 9498 |      |      |        |           |                       |
| 100                 | 9475 | 9444 | 43.8 | 0.464  | 91.9      | 92.3                  |
| 100                 | 9413 |      |      |        |           |                       |
| 100                 | 9492 | 9513 | 29.0 | 0.305  | 92.6      |                       |
| 100                 | 9533 |      |      |        |           |                       |

Run ID 10MTQ2

Negative Control % Binding for this run = 6.14%

Normalized Assay Cut Point (NACP) = 7.83%

**Review Comment:** It was noted that the Sponsor's use of antibody titers in describing the Sensitivity of their screening assay was not consistent with the 2016 FDA Draft Guidance on Assay Development and Validation. Therefore, an IR was sent on Feb. 3, 2017, requesting that sensitivity levels for immunogenicity assays be expressed as mass units/volume. Subsequently, the Sponsor responded on Feb. 8, 2017, to inform us that the anti-abaloparatide antibody that was used as a positive control for ADA screening assay validation was estimated to have an IgG concentration of 47µg/ml. Therefore, based on the sponsor-selected 1:4 MRD and a 1:100,000 dilution of the antibody, the approximate sensitivity was back-calculated by the Sponsor as between 0.235 and 0.118 ng/ml (see 08-Feb-2017 Sponsor Response to IR Question 5) which is more sensitive than the 100 ng/ml limit articulated in the Guidance, and is thus acceptable.

On the other hand, using the 1:8 MRD, the dilution of the PC that resulted in % binding just above the normalized assay CP (sensitivity) was found to be approximately 1:80,000, which resulted in a mean binding assay result of 5.06%, while the MRD 1:8 assay NACP is 5.07% (from Project MTQ2 Validation Report, Method ICDIM 25, Table 6b - not shown here for brevity). The approximate sensitivity of the assay using 1:8 MRD, assuming the ~47 µg/ml concentration of the anti-abaloparatide antibody, is therefore back-calculated by the reviewer to be 0.073 ng/ml.

**Review comment:** *As the Sponsor has decided to use the MRD 1:4, it may not seem that the results of the MRD 1:8 assay are relevant to the final sensitivity determination, however it is significant that an upper level of sensitivity was observed in the MRD 1:8 assays, as it confirms that there does exist a level of dilution beyond which the assay will not read positive.*

Freeze/Thaw Stability of the NC and Surrogate PC: Six cycles of freezing at -80°C, then thawing at ambient temperature (≥12 hours each), were performed using the NC and surrogate PC in pooled human serum. Analysis of binding assay results for each cycle were compared against the same control samples that had undergone only one freeze/thaw cycle, which revealed no difference between frozen/thawed samples and reference controls (relative differences ≥20%, from Project MTQ2 Validation Report, Method ICDIM 25 Table 7a, 7b, not reproduced here).

**Review comment:** *The absence of significant difference in assay outcome respective to freezing and thawing demonstrates a measure of robustness inherent to the assay; this is an acceptable finding that supports validation. In a realistic sense, it allows a certain degree of flexibility in the timing of sample analysis, while limiting the uncertainty of changes in the readout that might be attributable to storage of samples or controls.*

Room Temperature Stability of NC and Surrogate PC: NC and PC samples in pooled human serum were kept at RT for ≥24hr, then analyzed in hexuplicate, in comparison to same-level control pools warmed from -80°C just prior to analysis. No significant difference was observed in assay readings comparing samples stored at RT for ≥24hr with samples stored at -80°C (relative % difference ≥20%; see Table 8a, not reproduced here).

**Review comment:** *The assay appears to be resistant to storage at RT for at least 24 hours; the significance of this short-term temperature stability benefit is discussed in the previous section.*

Assay Specificity/Inhibition: Samples of NC and surrogate PC were diluted to 1:4 MRD in assay buffer, and spiked with abaloparatide (concentrations from 0-10,000 pg/ml), then assayed to determine the concentration resulting in ≥30% inhibition of the low surrogate PC1 (see Table 9a, below, copied from the submission).

Table 9a. Assay Inhibition with BIM 44058 MRD 1:4

| Run ID | (% Binding)   |         |         |         |         |         |         |         |         |         |
|--------|---------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|        | Not Inhibited | 10.0    | 25.0    | 50.0    | 100     | 200     | 500     | 1000    | 5000    | 10000   |
| 7MTQ2  | (pg/mL)       | (pg/mL) | (pg/mL) | (pg/mL) | (pg/mL) | (pg/mL) | (pg/mL) | (pg/mL) | (pg/mL) | (pg/mL) |
| NC     | 8.42          | 8.46    | 8.16    | 8.36    | 8.90    | 8.72    | 8.36    | 8.56    | 7.95    | 7.61    |
| PC 1   | 13.4          | 13.2    | 13.1    | 11.9    | 12.1    | 10.9    | 8.82    | 8.80    | 8.01    | 7.75    |
| PC 2   | 14.3          | 14.3    | 14.2    | 12.9    | 11.8    | 11.3    | 9.30    | 9.72    | 8.26    | 7.62    |
| PC 3   | 46.8          | 48.0    | 45.4    | 42.3    | 38.0    | 29.8    | 18.3    | 15.0    | 9.87    | 8.79    |
| PC 4   | 87.3          | 87.3    | 88.5    | 84.1    | 84.0    | 84.2    | 70.5    | 40.1    | 15.4    | 11.9    |

|      | (% Inhibited) |         |         |         |         |         |         |         |         |  |
|------|---------------|---------|---------|---------|---------|---------|---------|---------|---------|--|
|      | 10.0          | 25.0    | 50.0    | 100     | 200     | 500     | 1000    | 5000    | 10000   |  |
|      | (pg/mL)       | (pg/mL) | (pg/mL) | (pg/mL) | (pg/mL) | (pg/mL) | (pg/mL) | (pg/mL) | (pg/mL) |  |
| NC   | -0.503        | 3.12    | 0.765   | -5.69   | -3.52   | 0.704   | -1.59   | 5.59    | 9.70    |  |
| PC 1 | 1.85          | 2.27    | 11.6    | 9.70    | 18.8    | 34.2    | 34.3    | 40.2    | 42.1    |  |
| PC 2 | 0.261         | 0.936   | 9.58    | 17.2    | 20.9    | 35.0    | 32.0    | 42.3    | 46.7    |  |
| PC 3 | -2.67         | 2.88    | 9.50    | 18.7    | 36.4    | 61.0    | 68.0    | 78.9    | 81.2    |  |
| PC 4 | -0.0952       | -1.44   | 3.66    | 3.76    | 3.46    | 19.2    | 54.0    | 82.4    | 86.4    |  |

**Legend:**

- NC Negative Control
- PC1 Low surrogate positive control (1:50,000 dilution)
- PC2 Back-up low surrogate positive control (1:40,000 dilution)
- PC3 Middle surrogate positive control (1:5000 dilution)
- PC4 High surrogate positive control (1:1000 dilution)

The abaloparatide (alternately named BIM 44058 in the chart above) concentration found to produce inhibition of at least 30% in the low surrogate PC was 500 pg/ml (in red box, drawn by reviewer, above), which is the concentration that will be used for Tier 2 confirmation during sample analysis (see Method Validation Report Addendum 2: Report ICDIM 25, Project MTQ5, Nov. 2015, reviewed below).

**Review comment:** *This is an acceptable finding; the observation that addition of the abaloparatide drug to the RIA ADA detection assay results in inhibition of assay signal is reflective of the specificity of the PC antibody for the drug.*

**Recovery:** To confirm the consistent recovery of the surrogate PC antibody from human serum as compared to assay buffer, the PC antibody was spiked into ten different human sera, and demonstrated consistent recovery from all ten, as compared to the spike into assay buffer. Furthermore, the % Binding results obtained from the assay showed NC<PC1<PC2<PC3<PC4, confirming consistent recovery (See Table 10a, copied from the submission, below).

Table 10a. Assay Recovery MRD 1:4  
(% Binding)

| Run ID   | Assay  | Lot 1 | Lot 2             | Lot 3             | Lot 4             | Lot 5             | Lot 6 | Lot 7 | Lot 8 | Lot 9 | Lot 10 |      |
|----------|--------|-------|-------------------|-------------------|-------------------|-------------------|-------|-------|-------|-------|--------|------|
| 6MTQ2    | Buffer |       |                   |                   |                   |                   |       |       |       |       |        |      |
| Unspiked |        | -2.54 | 4.31              | 5.54              | 4.42              | 3.33              | 5.26  | 5.29  | 5.12  | 3.02  | 4.63   | 3.99 |
| PC 1     |        | 3.44  | 9.82              | 10.7              | 9.56              | 8.93              | 10.1  | 9.38  | 10.2  | 8.31  | 8.49   | 9.15 |
| PC 2     |        | 5.16  | 11.1              | 11.8              | 10.9              | 10.9              | 11.2  | 11.2  | 11.4  | 9.79  | 9.94   | 10.1 |
| PC 3     |        | 38.2  | 41.9              | 42.0              | 42.2              | 44.7              | 42.0  | 41.3  | 41.5  | 40.7  | 39.9   | 42.6 |
| PC 4     |        | 78.7  | 81.9              | 79.7              | 79.9              | 82.1              | 79.0  | 78.7  | 82.4  | 83.2  | 79.5   | 81.6 |
|          |        |       | <u>PC 1 level</u> | <u>PC 2 level</u> | <u>PC 3 level</u> | <u>PC 4 level</u> |       |       |       |       |        |      |
|          | mean   |       | 9.46              | 10.8              | 41.9              | 80.8              |       |       |       |       |        |      |
|          | SD     |       | 0.766             | 0.671             | 1.25              | 1.61              |       |       |       |       |        |      |
|          | %CV    |       | 8.09              | 6.20              | 2.99              | 1.99              |       |       |       |       |        |      |

**Legend:**  
PC1 Low surrogate positive control (1:50,000 dilution)  
PC2 Back-up low surrogate positive control (1:40,000 dilution)  
PC3 Middle surrogate positive control (1:5000 dilution)  
PC4 High surrogate positive control (1:1000 dilution)

**Review comment:** The recovery of the PC antibody is consistent, as the detection appears quite reproducible, with low %CV ( $\leq 25\%$ ) despite dilution to several degrees in many different lots of human serum matrix. This is an acceptable outcome, consistent with successful assay validation.

**Validation Run Acceptance Criteria:** Validation of runs was based on meeting the criteria of the mean readout for the negative control  $NC < PC1 < PC2 < PC3 < PC4$ , and the %CV for all controls (based on CPM)  $\leq 25\%$ .

**Review comment:** This is an appropriate setting of acceptance criteria for an ADA detection assay.

**Linearity:** Linearity could not be accurately assessed due to the quasi-quantitative nature of the assay. However, a correlation is readily apparent between the various tested dilution levels of the surrogate PC (PC1-PC4), and the signal output achieved in %Binding.

**Review comment:** The Sponsor claims that conclusion of linearity is difficult to achieve in such assays, as the immune reaction is not directly quantitative. However, the observation of an approximate correlation between dilution levels of the tested controls with the resulting assay signal output is significant in showing that within the range of control concentrations that were tested, the relationship between the concentration and assay signal output is maintained. To reinforce this relationship, the Sponsor could apply the calculation of Pearson Correlation Coefficient.

**B. Validation of Assay Cut-point Using Disease-State Samples for Method (b) (4) - RIA for Detection of Anti-Abaloparatide Antibodies in Human Serum (Report (b) (4) -MTQ3, Feb. 2010)**

**Population-relevant ACP determination:** The NACP was initially validated in 2007 using normal human serum samples ((b) (4) -Study MTQ2, reviewed above). In 2010, the NACP

was re-established using **disease-state** serum samples collected from 49 postmenopausal abaloparatide treatment-naïve osteoporosis patients.

Inter-assay non-specific binding was evaluated by subjecting disease-samples to the 1:4 MRD and using them for three cut-point determination assay runs (1MTQ3-3MTQ3). The mean % binding, %CV, and SD were calculated for each run, and the cut-point for each assay was established using the 95% prediction interval (mean+SD\*1.645), see Table 1, below, copied from the submission. The average ACP (% binding) for the three assay runs is 7.96%.

**Table 1. Assay Cut Point Determination**

| % Binding |            |       |       |
|-----------|------------|-------|-------|
| Sample ID | 1MTQ3      | 2MTQ3 | 3MTQ3 |
| 3         | 4.15       | 5.44  | 8.28  |
| 10        | 4.84       | 6.39  | 9.92  |
| 15        | 4.83       | 5.40  | 5.93  |
| 16        | 3.97       | 4.60  | 7.16  |
| 19        | 4.28       | 4.15  | 5.18  |
| 21        | 4.11       | 5.14  | 8.69  |
| 38        | 4.96       | 4.72  | 5.14  |
| 41        | 5.09       | 4.92  | 7.56  |
| 113       | 4.04       | 4.74  | 4.52  |
| 134       | 4.77       | 6.80  | 8.93  |
| 167       | 4.50       | 6.16  | 7.74  |
| 188       | 3.91       | 4.46  | 5.98  |
| 236       | 5.94       | 8.35  | 12.4  |
| 239       | 5.23       | 6.18  | 9.07  |
| 243       | 4.23       | 4.86  | 7.14  |
| 247       | <i>rcv</i> | 5.46  | 8.72  |
| 255       | 4.38       | 5.59  | 6.45  |
| 281       | 4.56       | 6.54  | 9.24  |
| 291       | 4.28       | 4.62  | 6.16  |
| 311       | 4.13       | 4.67  | 7.62  |
| 391       | 4.40       | 4.56  | 6.25  |
| 394       | 4.60       | 4.88  | 5.95  |
| 410       | 4.75       | 5.70  | 7.60  |
| 412       | 3.66       | 4.16  | 5.78  |
| 417       | 4.79       | 5.29  | 7.33  |
| 436       | 4.05       | 3.89  | 7.14  |
| 465       | 4.87       | 5.71  | 9.69  |
| 468       | 5.74       | 6.21  | 8.09  |

| % Binding |       |       |       |
|-----------|-------|-------|-------|
| Sample ID | 1MTQ3 | 2MTQ3 | 3MTQ3 |
| 516       | 4.85  | 5.97  | 8.12  |
| 522       | 4.31  | 4.65  | 7.01  |
| 552       | 5.99  | 8.07  | 9.92  |
| 610       | 6.40  | 5.64  | 6.14  |
| 637       | 5.77  | 4.97  | 7.99  |
| 666       | 5.90  | 5.19  | 8.36  |
| 685       | 6.77  | 6.41  | 7.68  |
| 710       | 6.04  | 5.51  | 6.17  |
| 764       | 6.02  | 4.84  | 7.02  |
| 771       | 5.80  | 3.91  | 6.67  |
| 772       | 7.94  | 6.49  | 9.34  |
| 809       | 6.80  | 4.82  | 7.13  |
| 862       | 5.78  | 3.88  | 5.41  |
| 863       | 5.15  | 4.31  | 6.59  |
| 917       | 6.08  | 5.24  | 6.37  |
| 918       | 7.01  | 6.27  | 8.13  |
| 941       | 6.78  | 6.10  | 9.67  |
| 963       | 7.15  | 5.50  | 8.22  |
| 965       | 6.57  | 4.44  | 7.32  |
| 969       | 5.18  | 3.48  | 4.39  |
| 974       | 5.73  | 4.55  | 6.16  |
|           |       |       |       |
| n         | 48    | 49    | 49    |
| Mean      | 5.23  | 5.30  | 7.42  |
| SD        | 1.03  | 1.01  | 1.58  |
| %CV       | 19.64 | 18.97 | 21.26 |
|           |       |       |       |
| ACP       | 6.92  | 6.96  | 10.01 |

Normalization of the disease-state ACP values determined in Table 1 was performed by calculation of the Normalization Factor: the ACP value determined in each of the three runs was divided by the average binding values determined for the NCs. The mean of the three calculated NFs was calculated to determine the overall ACP normalization factor (see Table 2, below, copied from the submission). The NF will be used for normalization of the ACP for each run during the sample analysis, using the formula:

$$\text{NACP} = \text{mean \% binding of run NC} * \text{NF}$$

**Table 2. Calculation of Normalization Factor**

|                           | 1MTQ3 | 2MTQ3        | 3MTQ3 |
|---------------------------|-------|--------------|-------|
| <b>Mean</b>               | 6.92  | 6.96         | 10.0  |
| <b>MEAN NC</b>            | 4.21  | 4.09         | 4.50  |
| <b>ACPF</b>               | 1.64  | 1.70         | 2.22  |
| <b>Overall ACP Factor</b> |       | <b>1.857</b> |       |
| SD                        |       | 0.32         |       |
| %CV                       |       | 17.25        |       |

**Review comment:** The calculation of the ACP for Disease-State Samples, and the Normalization Factor appears adequate, both in the number of samples that were considered, and in the overall methodology.

**Validation Run Acceptance Criteria:** Acceptance of assay runs will require  $\geq 4$  of six PC measurements to meet the criteria of  $NC < NACP < low\ PC < high\ PC$ , and  $\%CV \leq 25\%$  for all controls; see Table 3, below, copied from the submission.

**Table 3. Assay Controls**

| Run ID      | %binding |      |      |
|-------------|----------|------|------|
|             | NC       | PC 1 | PC 2 |
| 1MTQ3       | 4.19     | RCV  | 32.5 |
| <b>NACP</b> | 3.84     | 7.71 | 33.3 |
| <b>5.37</b> | 4.59     | 8.58 | 31.8 |
| <b>Mean</b> | 4.21     | 8.14 | 32.5 |
| 2MTQ3       | 4.29     | 7.94 | 33.2 |
| <b>NACP</b> | 4.34     | 7.95 | 34.2 |
| <b>5.22</b> | 3.65     | 7.60 | 33.5 |
| <b>Mean</b> | 4.09     | 7.83 | 33.6 |
| 3MTQ3       | 4.63     | 7.87 | 32.0 |
| <b>NACP</b> | 4.32     | 7.76 | 33.0 |
| <b>5.75</b> | 4.57     | 8.27 | 31.7 |
| <b>Mean</b> | 4.50     | 7.96 | 32.3 |

Note: For the purposes of determining run acceptance, the normalization factor determined in validation MTQ2 and defined in method ICDIM 25 V 1.01 (1.276) was applied to the mean NC for each run to determine each Normalized Assay Cutpoint.

**Review comment:** The analysis of the NC and PC yielded results consistent with validation of the assay; this is an acceptable outcome supporting assay validation.

The ADA CP determination for disease state human serum (described in Project (b) (4)-Study MTQ3) is summarized in the table below, copied from the submission:

| Validation parameter                            | Value          |
|-------------------------------------------------|----------------|
| Minimum required dilution                       | 1:4            |
| Assay cut-point (% binding)                     | 7.96 %         |
| Normalisation factor                            | 1.857          |
| Inter -assay precision of the positive controls | $\leq 7.93\%$  |
| Inter -assay precision of the negative controls | $\leq 17.25\%$ |

The plan for sample analysis is shown below (see Appendix D, Section 8):

- Tier 1: Screen pre-dose and post-dose samples at 1:4 MRD in the same run; results below NACP are negative, results above NACP are potentially positive and progressed to Tier 2. NACP utilizes an appropriate 95% confidence interval, allowing a 5% false-positive rate. To account for variability across assay runs, a floating cut point and normalization factor based on assay of a pooled set of 50 negative control samples run in triplicate was employed.
- Tier 2: Potentially positive samples from Tier 1 are analyzed in assay buffer (1:4), or in inhibition solution containing cold competitor abaloparatide (1:4). Results showing <30% inhibition are confirmed negative, and results showing  $\geq 30\%$  inhibition are confirmed positive and progressed to Tier 3. Confirmatory assay cut point was defined originally using an arbitrary 30% inhibition; later this inhibitory level was statistically verified (see below) by the sponsor to correlate approximately with a 1% false positive rate, and so was retained.
- Samples confirmed positive by Tier 2 testing are tested for titer by the RIA for % binding, at multiple dilution levels in NC (1:10, 1:20, 1:50, 1:100, etc), to find the dilution where the RIA reading is below the NACP. The reported titer is the most dilute sample to read above the NACP. Samples confirmed positive in Tier 2 are also tested for the presence of abaloparatide neutralizing antibodies, as described below.

*Review comment: The sample analysis testing strategy for disease state human serum samples is reasonable and acceptable.*

**C. Radioimmunoassay (RIA) for Detection of Anti-Abaloparatide Antibodies in Human Serum (Disease State Confirmatory Cut-Point) (Report (b) (4)-MTQ5, Nov. 2015):**

The 500 pg/ml concentration of abaloparatide study drug reagent that was used in past drug interference experiments (see above: ICDIM-MTQ2, Nov. 2007) was found to not correlate with the abaloparatide reagent concentration used for analysis of patient serum samples in Tier 2 confirmation assays (500 ng/ml is used). Therefore, the Sponsor desired to define a confirmatory cut-point based on data from disease-state samples, and obtain % inhibition data from Tier 2 positive control samples using abaloparatide drug concentrations relevant to current use, for detection of abaloparatide ADA in patients.

CCP Evaluation Using Study Samples: Fifty serum samples obtained from placebo-treated patients were analyzed in three independent assays (MRD 1:4) uninhibited, or with 125 ng/ml final abaloparatide concentration (see Table 2, below, copied from the submission).

[NOTE: (b) (4) Addendum 2, Experimental Design (pg. 22) had a typographical error, stating that the final abaloparatide concentration is 375 ng/ml, which was inconsistent with the Assay Cut-point Experiments section (pg. 13). An Information Request (03-Feb-2017) was sent to the Sponsor for clarification, and they responded on 08-Feb-2017 with a corrected Method

Validation Report Addendum 2 ICDIM 25, Project MTQ5 reissued on 07-Feb-2017, stating that the 375 ng/ml figure was incorrect; the final abaloparatide inhibitor concentration in each reaction is 125 ng/ml (representing the 1:4 dilution of the 500 ng/ml abaloparatide stock). Table 2 from the report reissue, copied below, provides the design of the validation experiment;

**Table 2**  
Experimental Design

| Assay Run | Plan Panel # | Plan Plate # | Run ID | Analyst | Samples Tested |
|-----------|--------------|--------------|--------|---------|----------------|
| 1         | 1            | 1            | 1MTQ5  | 1       | 1-25           |
| 2         | 1            | 2            | 2MTQ5  | 2       | 26-50          |
| 3         | 2            | 3            | 3MTQ5  | 1       | 1-25           |
| 4         | 2            | 4            | 4MTQ5  | 2       | 26-50          |
| 5         | 3            | 5            | 5MTQ5  | 1       | 1-25           |
| 6         | 3            | 6            | 6MTQ5  | 2       | 26-50          |

For analysis, the ratio of % binding response of inhibited samples as compared to uninhibited samples was calculated as:

$$\text{Ratio} = (\text{Mean inhibited \%binding}) \div (\text{Mean uninhibited \%binding})$$

% Inhibition =  $100 \times (1 - \text{Ratio})$  (see Table below, copied from the 08-Feb-2017 submission)

Tukey's outlier filter was used to remove outliers from the data:

Any value less than  $(Q1 + 1.5 \times IQR)$  or greater than  $(Q3 + 1.5 \times IQR)$  is defined as an outlier.

Q1=First quartile (25<sup>th</sup> percentile) value, middle value between the median and smallest value

Q3=Third quartile (75<sup>th</sup> percentile) value, middle value between the median and largest value

IQR=Interquartile range,  $Q3 - Q1$

## Individual Percent Inhibition Estimates

| Sample | % Inhibition |         |         |
|--------|--------------|---------|---------|
|        | Panel 1      | Panel 2 | Panel 3 |
| 1      | 19.2%        | 4.86%   | 2.37%   |
| 2      | 24.7%        | 2.47%   | -15.8%  |
| 3      | -26.0%       | -6.34%  | 3.96%   |
| 4      | 5.85%        | 6.52%   | 10.6%   |
| 5      | 41.7%        | -8.45%  | 10.7%   |
| 6      | -0.40%       | -3.03%  | 5.22%   |
| 7      | -35.9%       | 6.29%   | 10.4%   |
| 8      | -7.70%       | -15.4%  | 2.65%   |
| 9      | -5.93%       | 8.78%   | 1.64%   |
| 10     | -30.9%       | 2.85%   | 2.12%   |
| 11     | -18.9%       | 7.37%   | -10.5%  |
| 12     | 13.6%        | 10.1%   | -13.4%  |
| 13     | 11.4%        | 6.30%   | 2.72%   |
| 14     | -0.29%       | 10.1%   | -2.72%  |
| 15     | -17.1%       | -4.44%  | -11.2%  |
| 16     | -9.38%       | -12.5%  | -7.74%  |
| 17     | 32.6%        | 0.44%   | -7.83%  |
| 18     | 21.2%        | -7.70%  | 9.21%   |
| 19     | -51.8%       | 2.04%   | -0.34%  |
| 20     | 11.9%        | 1.79%   | -0.79%  |
| 21     | 14.8%        | 6.75%   | 6.08%   |
| 22     | -2.16%       | 14.0%   | 3.65%   |
| 23     | rcv          | 19.7%   | 24.7%   |
| 24     | 25.0%        | 10.3%   | 5.44%   |
| 25     | 20.7%        | 14.8%   | 10.5%   |
| 26     | -21.4%       | 7.84%   | -5.44%  |
| 27     | -8.15%       | 9.14%   | -9.15%  |
| 28     | -18.5%       | 11.7%   | -12.8%  |
| 29     | -16.9%       | 25.3%   | 11.5%   |
| 30     | -6.07%       | 2.94%   | 1.95%   |
| 31     | 8.69%        | 9.54%   | -6.92%  |
| 32     | -0.76%       | 4.92%   | 1.45%   |
| 33     | -15.9%       | 11.2%   | 4.46%   |
| 34     | -11.3%       | 4.71%   | 3.39%   |
| 35     | -1.40%       | 10.5%   | 11.6%   |
| 36     | -19.8%       | 4.90%   | 21.4%   |
| 37     | 3.40%        | -0.65%  | -0.33%  |
| 38     | -0.79%       | -89.8%  | 10.1%   |
| 39     | 23.8%        | -4.61%  | 6.88%   |
| 40     | 0.60%        | -9.52%  | 6.96%   |
| 41     | 1.19%        | -9.68%  | 2.82%   |
| 42     | 0.46%        | 3.49%   | rcv     |
| 43     | -17.2%       | -19.0%  | 0.31%   |
| 44     | -4.14%       | -14.2%  | 0.87%   |
| 45     | -4.11%       | -16.8%  | -4.79%  |
| 46     | -18.3%       | -33.3%  | 0.76%   |
| 47     | 14.6%        | -13.1%  | 2.88%   |
| 48     | -10.8%       | -75.8%  | 4.72%   |
| 49     | -7.16%       | -41.6%  | 7.94%   |
| 50     | 18.2%        | -27.7%  | 1.77%   |

rcv - Duplicate results with >25% CV.

The following formulas were applied to the Inhibition data:

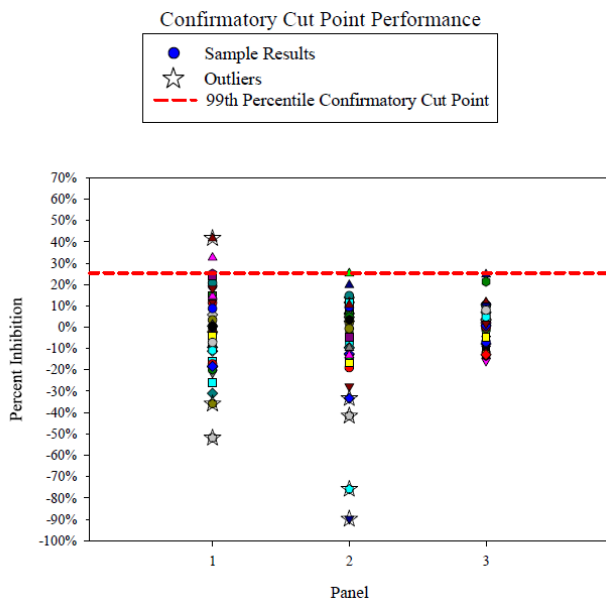
- **Ratio = (Mean inhibited % binding) / (Mean uninhibited % binding)**
- **% Inhibition = 100 x (1-Ratio)**

The Confirmatory Cut Points were calculated by estimating the upper percentiles of the pooled data ratios (see Table below, copied from the submission):

Table 1  
Confirmatory Cut Points

| Confirmatory Cut Point Estimates for Different Upper Percentiles |              |                  |              |                    |              |
|------------------------------------------------------------------|--------------|------------------|--------------|--------------------|--------------|
| 95 <sup>th</sup>                                                 |              | 99 <sup>th</sup> |              | 99.9 <sup>th</sup> |              |
| Ratio                                                            | % Inhibition | Ratio            | % Inhibition | Ratio              | % Inhibition |
| 0.788                                                            | 21.2%        | 0.747            | 25.3%        | 0.674              | 32.6%        |

The Confirmatory Cut Point associated with the 99<sup>th</sup> percentile was applied to the tested samples (shown graphically below, in a figure from the submission).



**Review comment:** The calculation of the Confirmatory Cut Point appears to be appropriately conducted. The data from these experimental assays supports the 30% Confirmatory Cut Point that had previously been arbitrarily assigned, and represents an upper percentile between the 99<sup>th</sup> and 99.9<sup>th</sup> percentile.

#### D. Validation Report of a Cell-Based Assay to Detect Neutralizing Antibodies to Abaloparatide Using ECL Detection of cAMP : BAL-15-227-003-REP (BioAgilytix Labs, Jul.-Aug. 2015)

A cell-based assay (BAL-15-227-003) was developed to detect the presence of antibodies with neutralizing capabilities against the abaloparatide drug in the serum of post-menopausal women. The assay uses UMR-106 cells, which express PTHR1 (parathyroid hormone 1 receptor), which activates PKC upon binding by abaloparatide, resulting in elevation of cAMP. The change of cAMP levels in UMR-106 cells is detected by a competitive ECL immunoassay kit, in which increased levels of expressed cAMP displace the labeled cAMP detector, resulting in decreased luminescence. Therefore, neutralization of abaloparatide by ADA present in the sample would result in blockade of abaloparatide binding to PTHR1, and thus abrogation of the cAMP elevation, and consequently increased electrochemiluminescence response relative to ADA-negative samples (see [Attachment 1](#) at the end of this review for a diagrammatic overview of

the cAMP assay). For assay validation, the positive control (PC) consisted of rabbit antiserum containing anti-abaloparatide nAb (estimated by the Sponsor to contain 47 µg/ml, see Assay Sensitivity Section for (b) (4)-MTQ2, above). The MRD that was established during qualification of the assay in human serum was 1:4.

**Reviewer Note:** The abaloparatide drug concentration used by BioAgilytix Labs (BAL) in these NAb assays was incorrectly labeled as being 2.16 mg/ml; their re-examining of the reagent label revealed the actual concentration to be 174 mg/ml (this information is detailed in a BioAgilytix Labs internal memorandum dated Oct. 22, 2015, which was included in the Response to FDA Information Request document sent to the Agency on Feb. 8, 2017; see pages 14-15). The implications of this error are discussed in relevant sections below.

**Assay Cut Point:** Serum samples from 150 individual placebo-treated women were analyzed two times by three analysts over six runs. According to the submission, normalization of data was performed by dividing each sample RLU (relative light units) by the mean RLU of the Negative Control samples as shown in the calculation method copied below:

$$\text{Normalized Value} = \frac{\text{RLU of Sample}}{\text{Mean RLU of Negative Control}}$$

From the data collected, 4 outliers were identified for exclusion by being >1.5 times the interquartile range from the 1st and 3rd quartiles. Figure 3 from the NAb Validation Report submission is included below:

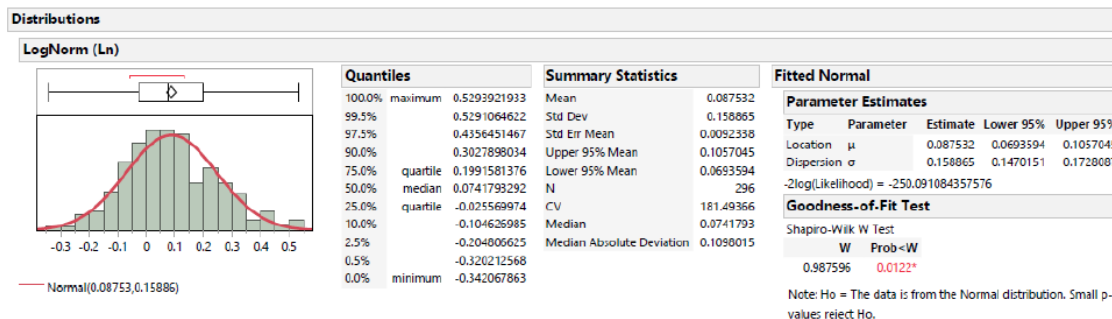


**Figure 3. Final Distribution after Removal of Outliers.**

*Distribution Analysis of LogNorm data results showing Median of 0.074 and Median Absolute Deviation of 0.110*

The remaining data was used to establish the 99<sup>th</sup> quantile (for a 1% false positive rate):

$$\text{LogNorm Median} + 1.483 * Z * \text{LogNorm Median Absolute Deviation (where the Z factor}=2.33 \text{ is appropriate for the 99}^{\text{th}} \text{ quantile)}$$

From the chart above, the following calculation is made by the sponsor:

$$0.074 + 1.483 * 2.33 * 0.110 = 0.454$$

Transformation by the exponential function yields the ACP value:  $e^{0.454} = 1.57$

Therefore, any sample or control was declared negative if the normalized assay results were less than 1.57, and positive if they are greater than or equal to 1.57. Analysis of the placebo samples resulted in a false positive rate of 1.01%.

**Review comment:** *The calculation of the Assay Cut Point with placebo-treated samples results in a false positive rate of 1.01%, which is acceptably close to that advised in the Agency Guidance (1% false positive) for NAb assay validation as a Tier 2 test.*

**Assay Sensitivity:** The evaluation of Sensitivity was conducted by serially diluting the surrogate antibody positive control and performing assay runs at the MRD of 1:4 in the presence of abaloparatide drug. The concentration of abaloparatide had originally been recorded as 3 pg/ml, but a subsequent Immunogenicity IR (03-Feb-2017) elicited a response by the Sponsor (Feb. 8, 2017) detailing an erroneous concentration listing: the 3 pg/ml concentration should be corrected to 248 pg/ml. The Sensitivity was calculated as the lowest antibody dilution that could be consistently read above the cut point. As shown in Table 6 (below, copied from the submission), in the presence of 248 pg/ml abaloparatide used for cell stimulation, the 1:6000 concentration of the Positive Control antibody read consistently positive in all three assay runs. From the ~47 µg/ml estimated concentration of the PC (see (b) (4) -MTQ2, above), the Assay Sensitivity of the NAb assay was calculated by the Reviewer to be approximately 7.83ng/ml:

$$47\mu\text{g/mL} \div 6000 \text{ MRD Adj SPC dilution} = 0.007833 \mu\text{g/mL}$$

**Table 6. Antibody Sensitivity**

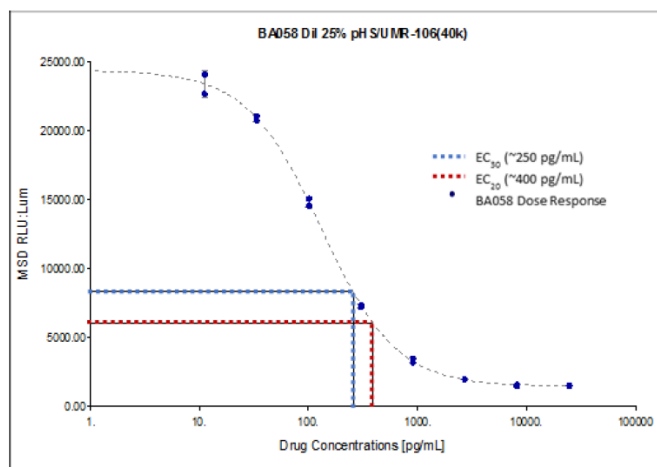
| MRD Adjusted SPC Dilution | *SPC Dilution | Run 1           |           | Run 2           |           | Run 3           |           |
|---------------------------|---------------|-----------------|-----------|-----------------|-----------|-----------------|-----------|
|                           |               | Mean Normalized | **Results | Mean Normalized | **Results | Mean Normalized | **Results |
| 3000                      | 12000         | 3.0781          | Positive  | 3.3247          | Positive  | 2.7475          | Positive  |
| 6000                      | 24000         | 2.0125          | Positive  | 2.3374          | Positive  | 2.5021          | Positive  |
| 12,000                    | 48000         | 1.4683          | Negative  | 1.6431          | Positive  | 1.8122          | Positive  |
| 24,000                    | 96000         | 1.2552          | Negative  | 1.3574          | Negative  | 1.5004          | Negative  |
| 48,000                    | 192000        | 1.0672          | Negative  | 1.2567          | Negative  | 1.3910          | Negative  |
| 96,000                    | 384000        | 1.0476          | Negative  | 1.1622          | Negative  | 1.2873          | Negative  |
| 192,000                   | 768000        | 0.99603         | Negative  | 1.1406          | Negative  | 1.2616          | Negative  |
| 384,000                   | 1536000       | 1.0261          | Negative  | 1.0932          | Negative  | 1.1455          | Negative  |

\*Actual dilution of positive control antibody in the assay plate. Final Sensitivity was calculated based on the assay MRD of 4-fold.

\*\*Result is based on the mean of 2 replicates relative to the assay cut point of 1.57.

**Review comment:** *The Sensitivity of the assay appears adequate for the detection of abaloparatide neutralizing antibody. The amount of abaloparatide drug present in the assay as tested (248 pg/ml) is acceptable (near the EC<sub>50</sub> for the dose-response curve, as shown in Figure 5 from the 08-Feb-2017 Immunogenicity IR Response document, copied below). Also from the same response document, the concentration of abaloparatide study drug from a single-dose PK study was measured (see [Attachment 2](#), at the end of this review). The amount of drug that is expected to be in circulation at the time of blood draw for testing will be very low, since abaloparatide has a t<sub>1/2</sub> of 2 hours; it is rapidly degraded by proteases and is largely cleared from systemic circulation by renal elimination within 6-7 hours.*

**Figure 5: Abaloparatide Dose Response Standard Curve**



**Assay Specificity:** The evaluation of Specificity was analyzed by performing the NAb assay with three concentrations of human IgG (10.0, 1.0, 0.1 µg/ml) spiked into the negative control human serum pool, in the presence of 248 pg/ml of abaloparatide drug. The baseline control consisted of the assay with 248 pg/ml of abaloparatide drug, but without IgG. No cross-reactivity was detected between the assay and the non-specific human IgG, all assay readouts were measured below the 1.57 ACP, and were considered negative:

**Table 7. Specificity Results**

| Condition             | Normalized Mean | CV (%) | % of NC | Results  |
|-----------------------|-----------------|--------|---------|----------|
| IgG 10 mg/mL          | 0.974           | 8.4    | 97.4    | Negative |
| IgG 1.0 mg/mL         | 1.019           | 11.0   | 101.9   | Negative |
| IgG 0.1 mg/mL         | 1.109           | 3.7    | 110.9   | Negative |
| Negative Control (NC) | 1.000           | 7.2    | 100.0   | Negative |

**Review comment:** The results of the Specificity Assay are acceptable in demonstrating the lack of any false positivity in the reading that would be caused by non-specific antibodies in the assay media.

**Drug Tolerance:** The tolerance of the NAb assay was evaluated in the presence of various concentrations of the abaloparatide drug (see Table 8, below, revised by the reviewer from the submission to include updated abaloparatide concentrations and notations). As noted previously (see IR Response of Feb. 8, 2017), the concentration of abaloparatide previously reported is incorrect; consequently, the concentrations listed in the table should be read as: 248 pg/ml, 372 pg/ml, 496 pg/ml, and 992 pg/ml. Additionally, the HPC, LPC1, and LPC2 concentrations of the positive control antibody are: 47 ng/ml, 0.94 ng/ml, and 1.175 ng/ml, respectively, calculated from the antibody concentration information also provided in the IR Response.

**Table 8 Drug Tolerance Results**

| Name                | Revised [Drug] | Mean     | SD     | CV (%) | Result   |
|---------------------|----------------|----------|--------|--------|----------|
| HPC 3 pg/mL Drug    | 248 pg/mL      | 3.4486   | 0.0352 | 1.0    | Positive |
| HPC 4.5 pg/mL Drug  | 372 pg/mL      | 3.2196   | 0.0503 | 1.6    | Positive |
| HPC 6 pg/mL Drug    | 496 pg/mL      | 2.7940   | 0.1695 | 6.1    | Positive |
| HPC 12 pg/mL Drug   | 992 pg/mL      | *1.4762  | 0.1384 | 9.4    | Negative |
| LPC1 3 pg/mL Drug   | 248 pg/mL      | 1.9925   | 0.0116 | 0.6    | Positive |
| LPC1 4.5 pg/mL Drug | 372 pg/mL      | *1.4630  | 0.1582 | 10.8   | Negative |
| LPC 6 pg/mL Drug    | 496 pg/mL      | *0.97872 | 0.0073 | 0.7    | Negative |
| LPC1 12 pg/mL Drug  | 992 pg/mL      | *0.50081 | 0.0020 | 0.4    | Negative |
| LPC2 3 pg/mL Drug   | 248 pg/mL      | 1.6895   | 0.1694 | 10.0   | Positive |
| LPC2 4.5 pg/mL Drug | 372 pg/mL      | *1.2197  | 0.0031 | 0.3    | Negative |
| LPC2_6 pg/mL Drug   | 496 pg/mL      | *0.94614 | 0.0166 | 1.8    | Negative |
| LPC2 12 pg/mL Drug  | 992 pg/mL      | *0.44379 | 0.0432 | 9.7    | Negative |

\*Below the cut point of 1.57

The HPC remains positive (above, highlighted yellow by the reviewer) even in the presence of 496 pg/ml of drug, while the LPC can tolerate up to 248 pg/ml of drug.

**Review comment:** *The tolerance of the NAb assay is acceptable. Given the PK profile, and relatively short half-life of abaloparatide, it is likely that blood samples collected 24 hours after administration would contain almost no remaining drug, and would pose little potential for exceeding the tolerance limits of the NAb assay.*

**Selectivity:** Ten placebo-treated human serum samples were tested with, or without a spike of PC antibody at 1:1800 or 1:7200 dilutions (26.1 ng/ml and 6.5 ng/ml, respectively, assuming ~47 µg/ml concentration of the PC antibody stock). As shown in Table 9, copied below from the submission, all samples tested were read within the 30% range of the normalized value of the respective controls:

**Table 9. Selectivity Results**

| Validation Run 5 |              |                 |          |            | Validation Run 6 |              |                 |          |            |
|------------------|--------------|-----------------|----------|------------|------------------|--------------|-----------------|----------|------------|
| Sample ID        | *SPC Content | Normalized Mean | **CV (%) | % Recovery | Sample ID        | *SPC Content | Normalized Mean | **CV (%) | % Recovery |
| NC               | 0            | 1.000           | 8.7      | 100.0      | NC               | 0            | 1.000           | 8.0      | 100.0      |
| HPC              | 1:7200       | 3.417           | 4.7      | 100.0      | HPC              | 1:7200       | 3.673           | 7.4      | 100.0      |
| LPC1             | 1:28,800     | 1.866           | 11.4     | 100.0      | LPC1             | 1:28,800     | 1.851           | 8.6      | 100.0      |
| 22A200565        | 0            | 1.2350          | N/A      | 123.5      | 22A209180        | 0            | 1.2753          | N/A      | 127.5      |
|                  | 1:7200       | 3.374           | 2.2      | 98.7       |                  | 1:7200       | 4.1806          | 3.8      | 113.8      |
|                  | 1:28,800     | 2.050           | 6.2      | 109.9      |                  | 1:28,800     | 2.0458          | 1.9      | 110.5      |
| 22A203018        | 0            | 1.2381          | N/A      | 123.8      | 22A209181        | 0            | 1.1998          | N/A      | 120.0      |
|                  | 1:7200       | 3.466           | 8.2      | 101.4      |                  | 1:7200       | 3.4958          | 1.6      | 95.2       |
|                  | 1:28,800     | 2.056           | 7.5      | 110.2      |                  | 1:28,800     | 2.0227          | 7.7      | 109.3      |
| 22A203019        | 0            | 1.0735          | N/A      | 107.4      | 22A209165        | 0            | 1.0921          | N/A      | 109.2      |
|                  | 1:7200       | 3.002           | 3.5      | 87.8       |                  | 1:7200       | 4.1947          | 3.2      | 114.2      |
|                  | 1:28,800     | 1.982           | 8.5      | 106.2      |                  | 1:28,800     | 1.9309          | 2        | 104.3      |
| 22A202500        | 0            | 1.2519          | N/A      | 125.2      | 22A208806        | 0            | 1.6273          | N/A      | 162.7      |
|                  | 1:7200       | 3.189           | 1.2      | 93.3       |                  | 1:7200       | 3.3915          | 1.5      | 92.3       |
|                  | 1:28,800     | 2.222           | 4.6      | 119.1      |                  | 1:28,800     | 2.0861          | 2.9      | 112.7      |
| 22A202870        | 0            | 1.1392          | N/A      | 113.9      | 22A206806        | 0            | 1.3100          | N/A      | 131.0      |
|                  | 1:7200       | 2.984           | 6.0      | 87.3       |                  | 1:7200       | 4.2528          | 2.5      | 115.8      |
|                  | 1:28,800     | 2.214           | 0.2      | 118.6      |                  | 1:28,800     | 2.0215          | 5        | 109.2      |

\*Actual dilution of positive control antibody in the assay plate.

\*\* Baseline values from single wells

%Recovery = (normalized mean signal for spiked sample/normalized mean signal for respective positive control) x 100

**Review comment:** The selectivity of the NAb assay is acceptable. The experimental evidence that is shown demonstrates consistency of the readings that is within the 30% range of the expected normalized values.

**Intra-assay Precision:** Each assay had two or more determinations of each PC concentration in duplicate wells; each plate contained 8 to 10 replicates wells of the NC to establish a plate cut point. All results were shown to range over 1.5%-20.1% CV (all ≤30%), with signals ranking as expected: HPC>MPC>LPC>NC (see Table 10, not reproduced here). Results of assays reading replicates of the NC similarly met the observation of CV≤30% (7.2%-19.1%), shown in Table 11 (not reproduced here).

**Review comment:** The experiments performed to test the Inter-assay Precision for the NAb assay are acceptable, as are the results that were obtained.

**Inter-assay Precision:** Inter-assay precision was evaluated by seven validation runs by 3 analysts over 2 days using various concentrations of the PC: HPC, MPC, LPC(1,2) and NC in at least duplicate wells; all values were found to rank as expected (HPC>MPC>LPC>NC), with CVs ≤30%. The inter-assay precision of the NC were similarly found to have CV≤30%. The results of the experiments are shown in Tables 12 & 13 from the submission, copied below:

**Table 12. Inter-assay evaluation of antibody controls**

| Validation Run #       | Analyst | HPC Normalized Mean | MPC Normalized Mean | LPC1 Normalized Mean | **LPC2 Normalized Mean |
|------------------------|---------|---------------------|---------------------|----------------------|------------------------|
| 1                      | 1       | 3.6892              | 2.6762              | 1.7693               | 1.3166                 |
| 2                      | 2       | 3.6032              | 2.7555              | 1.8500               | 1.6300                 |
| 3                      | 3       | 2.7365              | 2.4099              | 1.8383               | 1.5858                 |
| 4                      | 2       | 3.5076              | 2.5490              | 1.9243               | 1.6487                 |
| 5                      | 3       | 3.4926              | 2.5284              | 1.7094               | 1.5305                 |
| 6                      | 1       | 3.8995              | 2.4661              | 1.7297               | 1.4765                 |
| 7                      | 2       | 4.1968              | 2.7445              | 1.8372               | 1.8866                 |
| *Inter-Assay Precision | Mean    | 3.5893              | 2.5899              | 1.8083               | 1.5821                 |
|                        | SD      | 0.451               | 0.137               | 0.076                | 0.175                  |
|                        | CV (%)  | 12.6                | 5.3                 | 4.2                  | 11.1                   |

\*The first set of replicates from each intra-assay determination was used as a value for the determination of inter-assay precision.

\*\*The Highlighted LPC2 Normalized means were below the cut point of 1.57.

**Table 13. Inter-assay evaluation of negative controls**

| Validation Run #     | Analyst | *Mean RLU (n=10) | SD   | CV (%) |
|----------------------|---------|------------------|------|--------|
| 1                    | 1       | 5824             | 1112 | 19.1   |
| 2                    | 2       | 6344             | 566  | 8.9    |
| 3                    | 3       | 8603             | 807  | 9.4    |
| *4                   | 2       | 6814             | 488  | 7.2    |
| 5                    | 3       | 6744             | 584  | 8.7    |
| 6                    | 1       | 6260             | 503  | 8.0    |
| *7                   | 2       | 4414             | 505  | 11.4   |
| Inter-assay Mean RLU |         |                  | 6429 |        |
| Inter-assay SD       |         |                  | 1254 |        |
| Inter-assay CV (%)   |         |                  | 19.5 |        |

\*For Validation runs 4 and 7, n = 8.

**Review comment:** The results of the inter-assay precision experiments demonstrate an acceptable precision for the cell-based NAb assay for abaloparatide -specific ADA.

**Inter-operator Precision (Ruggedness):** The variability between assay validation experiments testing inter- and intra-assay precision performed by three analysts was evaluated, with inter-operator CV in the range of 3.5-7.6% (CV for negative controls was found to be 9.1%), see Table 14, copied below from the submission:

**Table 14. Inter-operator Precision Summary Table**

| Result |                  | Analyst 1 | Analyst 2 | Analyst 3 | Inter-Operator Mean |
|--------|------------------|-----------|-----------|-----------|---------------------|
| HPC    | Normalized Mean  | 3.794     | 3.555     | 3.115     | 3.488               |
|        | Normalized SD    | 0.220     | 0.088     | 0.456     | 0.255               |
|        | Normalized CV(%) | 5.8       | 2.5       | 14.6      | 7.6                 |
| MPC    | Normalized Mean  | 2.571     | 2.652     | 2.469     | 2.564               |
|        | Normalized SD    | 0.154     | 0.146     | 0.101     | 0.134               |
|        | Normalized CV(%) | 6.0       | 5.5       | 4.1       | 5.2                 |
| LPC1   | Normalized Mean  | 1.7       | 1.887     | 1.774     | 1.803               |
|        | Normalized SD    | 0.0       | 0.056     | 0.090     | 0.062               |
|        | Normalized CV(%) | 2.4       | 3.0       | 5.1       | 3.5                 |
| LPC2   | Normalized Mean  | 1.4       | 1.639     | 1.558     | 1.531               |
|        | Normalized SD    | 0.1       | 0.102     | 0.099     | 0.102               |
|        | Normalized CV(%) | 7.7       | 6.2       | 6.3       | 6.7                 |
| *NC    | RLU Mean         | 6042      | 6579      | 7674      | 6765                |
|        | RLU SD           | 308.3     | 332.2     | 1315      | 651.7               |
|        | RLU CV (%)       | 5.1       | 5.0       | 17.1      | 9.1                 |

\*Normalized values for the negative control are defined as 1.000 and are not calculated for mean and CV, therefore RLU data is presented.

**Review comment:** The ruggedness of the cell-based NAb assay for abaloparatide -specific ADA was found to be acceptable, as CV for assays performed separately by three different operators all showed relatively low variability, with all normalized means being close to one another, and all normalized CV% being well below 30%.

**Short-term stability:** Assessment of short-term stability was performed at bench-top and refrigerated conditions: two sets of PC samples (HPC, LPC1, LPC2, NC) were compared to baseline samples after 2:50 and 22:30 hours at room temperature, and another set was stored at 2-8°C for 22:30 hours. All the controls stored at the various conditions were found to measure within the target acceptance criteria, encompassing a range between 85.4% and 118.3% with respect to the baseline samples.

**Review comment:** The results as described would constitute a favorable demonstration of the short-term assay stability; furthermore, the Sponsor has provided information describing procedures for use and storage of the reagents employed in the performance of the MSD cAMP-based NAb assay. These results and procedures appear acceptable for ensuring the stability of the assay. Experimental data for short-term (“bench top”) stability are copied below, incorporated into Table 15 of the submission, along with the freeze-thaw stability data.

**Freeze-thaw stability:** Samples representing the HPC, LPC1, LPC2, and NC were subjected to freeze-thaw cycles of >12 hours at -80±15°C for 3-5 rounds. The NAb assay was performed using these treated samples, demonstrating freezing/thawing stability for the HPC and LPC1 samples as evidenced by recoveries relative to non-frozen/thawed baselines of 99.4-110.8%. The LPC2 sample was not shown to be within the acceptance range for freeze-thaw stability, as determined by reading below the 1.57 cut-point after 3 and 5 cycles (see Table 15, below).

**Table 15. Short-term and Freeze and Thaw Stability**

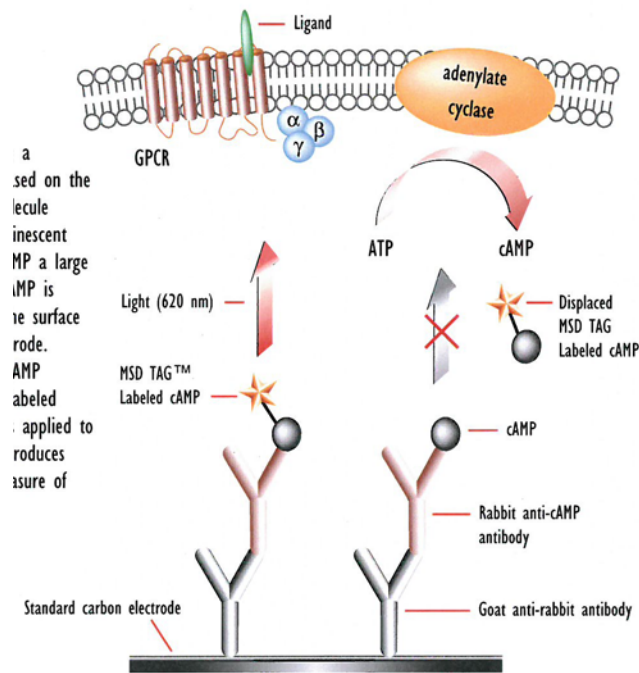
| Control | Stability Test         | Normalized Mean | % CV | *% Recovery |
|---------|------------------------|-----------------|------|-------------|
| HPC     | Baseline               | 4.1970          | 1.5  | 100         |
|         | Refrigerator (>22 hrs) | 4.9540          | 4.1  | 118.0       |
|         | Bench Top (>22 hrs)    | 4.3843          | 9.4  | 104.5       |
|         | Bench Top (2 - 4 hrs)  | 4.3185          | 6.4  | 102.9       |
|         | F/T - 3 Cycles         | 4.6491          | 2.9  | 110.8       |
|         | F/T - 5 Cycles         | 4.4074          | 9.4  | 105.0       |
| LPC1    | Baseline               | 1.8370          | 2.3  | 100         |
|         | Refrigerator (>22 hrs) | 2.0093          | 4.7  | 109.4       |
|         | Bench Top (>22 hrs)    | 1.9435          | 6.1  | 105.8       |
|         | Bench Top (2 - 4 hrs)  | 2.1723          | 8.2  | 118.3       |
|         | F/T - 3 Cycles         | 1.8783          | 3.5  | 102.2       |
|         | F/T - 5 Cycles         | 1.8267          | 9.5  | 99.4        |
| LPC2    | Baseline               | 1.8870          | 5.8  | 100         |
|         | Refrigerator (>22 hrs) | 1.8323          | 12.0 | 97.1        |
|         | Bench Top (>22 hrs)    | 1.6121          | 6.7  | 85.4        |
|         | Bench Top (2 - 4 hrs)  | 1.6516          | 13.4 | 87.5        |
|         | F/T - 3 Cycles         | 1.5451          | 7.6  | 81.9        |
|         | F/T - 5 Cycles         | 1.5473          | 4.2  | 82.0        |

\*For % Recovery, normalized signal from each stability control was divided by the mean normalized signal of the baseline control for the assay plate

**Review comment:** *The stability of the NAb assay to withstand freezing and thawing of the samples is acceptably demonstrated for the High concentration positive control (47 ng/ml) and Low concentration positive control 1 (LPC1 - 0.94 ng/ml), but use of the back-up low positive control (LPC2 - 1.175 ng/ml) was not consistent through 3 and 5 freeze/thaw cycles. This is curious, as the LPC2 has the higher concentration of positive control antibody. It is thought that the failure of the LPC2 samples to read above the cut-point after freezing/thawing of 3 and 5 cycles is most likely not due to failure of the assay, as analysis of the LPC1 samples (which were diluted to a greater extent than the LPC2 samples) was successfully read above the cut-point.*

**ATTACHMENTS:**

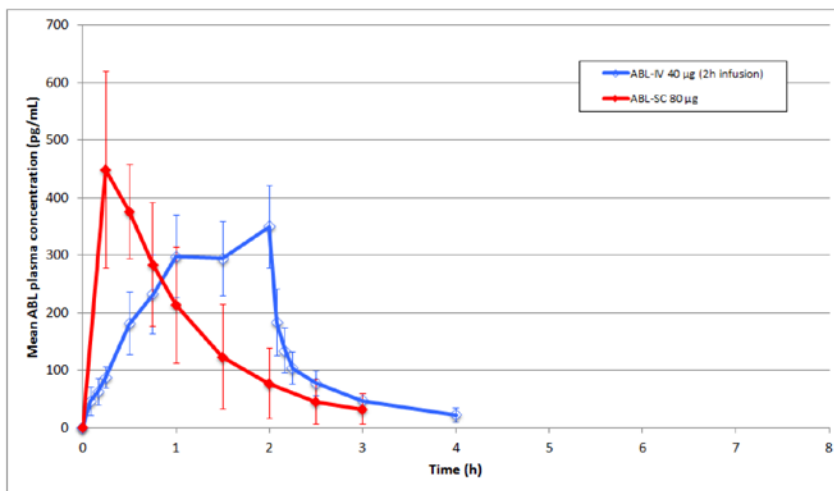
**1. cAMP assay diagram (from MSD product literature)**



**Method:** The detection of cAMP was performed using a competitive electrochemiluminescent assay, where neutralizing antibodies to BA058 result in decreased induction of cAMP by the abaloparatide drug product in the assay, and an increase in assay signal.

**2. Abaloparatide Plasma conc. (08-Feb-2017 IR response submission, page 12 of 13):**

**Figure 6: Study 010 – Mean Abaloparatide Plasma Concentrations After Single SC Injection or IV 2h Infusion (N = 19)**



Source: CSR 010 Table 14.2.1a.

ALB=abaloparatide; IV=intravenous; N=number of patients; SC=subcutaneous.

Notes: Abaloparatide-IV was administered over a 2-hour continuous IV infusion.

Predose values were all below the limit of quantitation; thus, mean was set to 10 pg/mL (one-half LLOQ) in this plot. Data shown as mean ± standard deviation.

## **Review of anti-abaloparatide cross-reactivity with endogenous human PTH and PTHrP:**

The abaloparatide drug shares a significant sequence identity with the human endogenous hormone PTHrP, and homology with the hormone PTH (see figure below):

|                     |                                                                  |           |
|---------------------|------------------------------------------------------------------|-----------|
|                     | <b>1</b>                                                         | <b>34</b> |
| <b>PTH (1-34)</b>   | SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNF– (NH <sub>2</sub> )           |           |
| <b>PTHrP (1-36)</b> | AVSEHQLLHDKGKSIQDLRRR <b>FFLHHUAEIHTAEI</b> – (NH <sub>2</sub> ) |           |
| <b>ABL</b>          | AVSEHQLLHDKGKSIQDLRRR <b>ELLEKLXKLHTA</b> – (NH <sub>2</sub> )   |           |

Therefore, a significant risk exists for cross-reactivity between patient-generated ADA specific for the abaloparatide drug with the endogenous PTH and PTHrP. Consequently, the abaloparatide sponsor developed assays for detection of antibodies against PTH and PTHrP in the serum of patients receiving abaloparatide. These assays were included in the Interim 37-month Anti-abaloparatide Antibody Immunogenicity Testing summary document (submitted 17-Jan-2017).

### **E. Anti-PTH Antibody Detection Assay Validation (b) (4) Method #50289):**

The semi-quantitative anti-PTH antibody detection assay was developed at (b) (4) (Pacific Biomarkers, Inc.), incorporating a 1:6 MRD of patient sera, incubation with <sup>125</sup>I-PTH tracer, then immunoprecipitation with rabbit anti-human IgG/IgA/IgM (RAH) and goat anti-rabbit (GAR) secondary antibody, followed by precipitation. Detection was achieved by centrifugal separation of the anti-PTH antibody-bound <sup>125</sup>I-PTH tracer from unbound tracer, and quantitation of bound tracer by scintillation counter. Surrogate PC rabbit anti-PTH antiserum cat #233-3 is a commercial antibody. The validation parameters for the anti-PTH antibody immunoassay are copied from the submission, Appendix 1, shown below:

**Table 1: Validation Parameters for Anti-PTH Method # 50289**

| <b>Validation parameter</b>                       | <b>Value</b> |
|---------------------------------------------------|--------------|
| Minimum required dilution                         | 1:6          |
| Normal assay cut-point                            | 167.1 cpm    |
| Sensitivity (LLOQ)                                | 278.1 cpm    |
| Normalization Factor                              | 3.6 cpm      |
| Intra-assay Precision (%CV)                       | ≤5.9         |
| Inter-assay Precision (%CV)                       | ≤24.7        |
| Specificity (% binding) CCP for positive controls | >31.1%       |

A summary of clinical anti-PTH antibody data collected using the validated method (Method 50289) in patients enrolled in clinical study BA-058-05-003 is copied from the submission, Appendix 1, shown below:

**Table 2: Summary of Anti-PTH Binding Following abaloparatide-SC therapy (BA058-05-003)**

| Results Summary: Anti-PTH (1-34)                 |                          |              |
|--------------------------------------------------|--------------------------|--------------|
| Category                                         | Criteria                 | # of Samples |
| I. Screened                                      |                          | 593          |
| “Not Detected”                                   | CPM < floating cut point | 533          |
| Putative Positives<br>(Reflexed to Confirmation) | CPM ≥ floating cut point | 60           |
| II. Confirmed (Putative Positives)               |                          | 60           |
| “Not Detected”                                   | Inhibition < 31.1%       | 59           |
| “Detected”<br>(Reflexed to Titer)                | Inhibition ≥ 31.1%       | 0            |
| “Quantity Not Sufficient”                        |                          | 1            |
| III. Titrated                                    |                          | 0            |
| IV. Totals                                       |                          |              |
| “Not Detected”                                   |                          | 592          |
| “Detected”                                       |                          | 0            |
| Titrated                                         |                          | 0            |
| “Quantity Not Sufficient”                        |                          | 1            |

Note 1. Reviewer annotated section (red) revised by sponsor per FDA request to modify CCP (see below):

| Results Summary: Anti-PTH (1-34) |                     |                    |
|----------------------------------|---------------------|--------------------|
| Category                         | Previous CP (31.1%) | Updated CP (22.9%) |
| II. Confirmed                    | 60                  | 60                 |
| “Not Detected”                   | 59                  | 57                 |
| “Detected”                       | 0                   | 2                  |
| “Quantity Not Sufficient”        | 1                   | 1                  |

In order to determine the acceptability of the above data, the method validation is reviewed below. A summary table of the anti-PTH antibody detection assay (Method 50289) validation criteria and results is copied from the submission Validation Report #50289 and shown below:

### Validation Summary Table

| Assay Parameter                          | <i>a priori</i> acceptance criteria                                                                                                                                                     | Results                                                                                                                     |                   |                   |
|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------|
| Minimum Required Dilution                | % difference within $\pm 30\%$ relative to buffer control                                                                                                                               | -16.1% to 10.3%<br>1:6 confirmed                                                                                            |                   |                   |
| Assay Cut Point                          | Duplicate CV replicates $\leq 25\%$<br>4 of 6 positive QCs are within mean signal $\pm 2SD$                                                                                             | All runs passed QC acceptance criteria<br>CP = 167.1 cpm NF = 3.6 cpm                                                       |                   |                   |
| Sensitivity                              | Interpolated value (based on assay cut point) is $\leq 500$ cpm                                                                                                                         | LLOQ = 278.1 cpm                                                                                                            |                   |                   |
| Assay Specificity Confirmatory Cut Point | Positive QCs $\geq 50\%$ inhibition in the presence of 100 ng/mL PTH<br>% Inhibition QCH > QCM > QCL > QCN<br><br>CCP = mean % inhibition + $(2.33 \times SD) \times$ mean % inhibition | > 75% inhibition for all positive assay controls<br>QCH (92.8%) > QCM (85.1%) > QCL (75.0%) > QCN (4.9%)<br><br>CCP = 31.1% |                   |                   |
| Precision                                | Positive controls (QCAPTHL, QCAPTHM, and QCAPTHH) are $\leq 25\%$ CV for intra and inter-assay precision                                                                                | QC Name                                                                                                                     | Intra-assay (%CV) | Inter-assay (%CV) |
|                                          |                                                                                                                                                                                         | QCAPTHL                                                                                                                     | 5.7               | 22.8              |
|                                          |                                                                                                                                                                                         | QCAPTHM                                                                                                                     | 5.9               | 24.7              |
|                                          |                                                                                                                                                                                         | QCAPTHH                                                                                                                     | 5.0               | 24.3              |
| PTH Tolerance                            | $\geq 33$ ng/mL PTH inhibits the anti-PTH (1-34) antibody levels in QCAPTHH                                                                                                             | QCAPTHH > 33 ng/mL PTH Inhibits 86.0% QCAPTHH                                                                               |                   |                   |
| Linearity (Titration)                    | Assay demonstrates the ability to dilute a positive sample to a level which falls below the assay cut point                                                                             | Dilution acceptable to 1:64 – 1:128                                                                                         |                   |                   |

### Addendum Summary Table

| Assay Parameter        | <i>a priori</i> acceptance criteria          | Results     |
|------------------------|----------------------------------------------|-------------|
| Confirmatory Cut Point | CCP = mean % inhibition + $(2.33 \times SD)$ | CCP = 22.9% |

**Reviewer comment:** The listing in the Table above for CCP was corrected in response to an Agency IR (see validation Addendum Summary Table from the 03-02-17 IR response, copied above). The Sponsor recalculated the CCP, changing the false-positive rate from 99.9% to 99.0%, which resulted in the new CCP value of 22.9% (see Assay Specificity (Confirmatory Cut Point) section, below).

**Minimum Required Dilution:** The MRD was determined by serially diluting two normal human serum samples in RIA buffer (ranging from neat to 1:6 dilution), and spiking anti-PTH control antibodies into separate RIA buffers (1:450 to 1:3,000 dilution), then combining serum dilutions and anti-PTH control antibody dilutions 1:1 (thus, the overall dilution of the sera and antibodies ranged from 1:2 to 1:12, and 1:450 to 1:6000). The overall 1:6 MRD of the sera was selected because the positive control antibodies had the highest recovery of the positive and negative

signal in the spiked serum samples relative to the buffer controls. This indicated the minimization of matrix effects with maintenance of adequate assay sensitivity.

Table 1: MRD Data

| MRD Blank                      |       |       |       |       |       |         |
|--------------------------------|-------|-------|-------|-------|-------|---------|
| Sample                         | MRD   |       |       |       |       | Diluent |
|                                | 1:2   | 1:4   | 1:6   | 1:8   | 1:12  |         |
| NHSA                           | 145.7 | 157.5 | 136.0 | 155.6 | 151.7 | 185     |
| NHSB                           | 141.2 | 188.7 | 153.3 | 147.0 | 125.0 | 185     |
| Mean (cpm)                     | 143.5 | 173.1 | 144.7 | 151.3 | 151.7 | 185.0   |
| Difference (%)                 | -29.0 | -6.9  | -27.9 | -22.3 | -22.0 |         |
| Run: # 1 (4/19/2016) Tech: KLR |       |       |       |       |       |         |
| MRD Low Concentration          |       |       |       |       |       |         |
| Sample                         | MRD   |       |       |       |       | Diluent |
|                                | 1:2   | 1:4   | 1:6   | 1:8   | 1:12  |         |
| NHSA                           | 204.1 | 218.9 | 179.5 | 190.6 | 292.0 | 247.3   |
| NHSB                           | 244.7 | 259.4 | 283.6 | 235.3 | 255.0 | 247.3   |
| Mean (cpm)                     | 224.4 | 239.2 | 231.6 | 213.0 | 273.5 | 247.3   |
| Difference (%)                 | -10.2 | -3.4  | -6.8  | -16.1 | 9.6   |         |
| Run: # 1 (4/19/2016) Tech: KLR |       |       |       |       |       |         |
| MRD Mid Concentration          |       |       |       |       |       |         |
| Sample                         | MRD   |       |       |       |       | Diluent |
|                                | 1:2   | 1:4   | 1:6   | 1:8   | 1:12  |         |
| NHSA                           | 453.6 | 425.7 | 491.3 | 401.8 | 382.7 | 396.7   |
| NHSB                           | 370.4 | 399.1 | 393.5 | 433.5 | 407.9 | 396.7   |
| Mean (cpm)                     | 412.0 | 412.4 | 442.4 | 417.7 | 395.3 | 396.7   |
| Difference (%)                 | 3.7   | 3.8   | 10.3  | 5.0   | -0.4  |         |
| Run: # 1 (4/19/2016) Tech: KLR |       |       |       |       |       |         |
| MRD High Concentration         |       |       |       |       |       |         |
| Sample                         | MRD   |       |       |       |       | Diluent |
|                                | 1:2   | 1:4   | 1:6   | 1:8   | 1:12  |         |
| NHSA                           | 791.4 | 836.9 | 853.2 | 773.9 | 864.1 | 833.5   |
| NHSB                           | 806.8 | 854.3 | 784.0 | 882.0 | 793.9 | 833.5   |
| Mean (cpm)                     | 799.1 | 845.6 | 818.6 | 828.0 | 829.0 | 833.5   |
| Difference (%)                 | -4.3  | 1.4   | -1.8  | -0.7  | -0.5  |         |
| Run: # 1 (4/19/2016) Tech: KLR |       |       |       |       |       |         |

**Reviewer comment:** An incorrect Figure 1 (not reproduced here) and Table 1 were included with the original version of this assay validation, therefore an IR was sent to the sponsor on 02-27-17 regarding the MRD determination, due to lack of clarity in the description and regarding the erroneous data table originally included. The Sponsor's response to the IR (03-02-17) included the correct Figure 1 (not reproduced here) and Table 1 (copied from the IR response, shown above), and further details on their assessment of the MRD (which are described above). The data contained in the corrected table and figure demonstrated an acceptable calculation for the MRD.

**Assay Cut Point:** Analysis of fifty single-donor diseased samples was performed for ACP determination; data was considered acceptable if the %CV between replicates was  $\leq 25\%$ , and 66% of reportable results for each concentration of controls fell within the criteria range. The performance of the Assay Controls in the cut point runs is shown below (the variability seen in the negative control readings suggested that a floating cut point was appropriate for the anti-PTH antibody screening assay):

**Table 2: Temporary QC Acceptance Criteria**

| Range     | QCAPTHN | QCAPTHL | QCAPTHM | QCAPTHH |
|-----------|---------|---------|---------|---------|
| QC Mean   | 161.0   | 574.2   | 1012.3  | 2241.4  |
| Min (cpm) | 120.7   | 430.7   | 759.2   | 1681.1  |
| Max (cpm) | 241.4   | 861.4   | 1518.4  | 3362.2  |

The in-house control antibodies were defined in the original submission as shown below:

QCAPTHL: 1:37 spiked positive control antibody into pooled normal human sera

QCAPTHM: 1:248 spiked positive control antibody into pooled normal human sera

QCAPTHH: 1:993 spiked positive control antibody into pooled normal human sera

QCAPTHN: pooled normal human sera

**Reviewer comment:** *It appears that the dilutions of the positive control antibodies are listed incorrectly (in reverse order) due to the QCAPTHH (HiPC) control sample having a listed dilution greater than the QCAPTHL (LowPC) control sample. In the Addendum #1 to Validation #50289 for the Anti-PTH (1-34) Antibody Assay (sent in Feb. 2017), the list of control antibodies was shown corrected (copied below):*

**Controls Selection**

**Positive Controls:**  
 QCAPTHL: in-house control, 1:993 spiked antibody into a pooled normal human sera.  
 QCAPTHM: in-house control, 1:248 spiked antibody into a pooled normal human sera.  
 QCAPTHH: in-house control, 1:37 spiked antibody into a pooled normal human sera.  
**Negative Control:**  
 QCAPTHN: in-house control, pooled normal human sera.

The performance of assay controls in the cut point runs was found to be satisfactory, see Table 4, below, copied from the submission:

**Table 4: Assay Control Performance in Cut point Runs**

| Control | Assay Control Performance |        |        |        |        |        |        |        |        |        |        |        | Overall Performance |       |        |
|---------|---------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------------------|-------|--------|
|         | Run #4                    |        | CV (%) | Run #5 |        | CV (%) | Run #6 |        | CV (%) | Run #7 |        | CV (%) | Mean                | SD    | CV (%) |
|         | 1                         | 2      |        | 1      | 2      |        | 1      | 2      |        | 1      | 2      |        |                     |       |        |
| QCAPTHN | 166.8                     | 126.9  | 19.2   | 148.4  | 200.5  | 21.1   | 144.7  | 235.3  | 33.7   | 103.1  | 110.2  | 4.7    | 143.8               | 27.1  | 18.8   |
|         | 117.4                     | 140.6  | 12.7   | 168.2  | 178.3  | 4.1    | 135.1  | 135.0  | 0.1    | 137.6  | 144.8  | 3.6    |                     |       |        |
| QCAPTHL | 684.2                     | 646.5  | 4.0    | 703.1  | 708.0  | 0.5    | 423.6  | 415.4  | 1.4    | 396.9  | 402.0  | 0.9    | 577.2               | 124.7 | 21.6   |
|         | 650.5                     | 669.3  | 2.0    | 725.9  | 715.1  | 1.1    | 618.6  | 464.8  | 20.1   | 460.3  | 455.8  | 0.7    |                     |       |        |
| QCAPTHM | 1244.1                    | 1233.1 | 0.6    | 1280.3 | 1216.1 | 3.6    | 767.1  | 814.6  | 4.2    | 690.3  | 669.5  | 2.2    | 1028.9              | 256.0 | 24.9   |
|         | 1296.1                    | 1268.2 | 1.5    | 1319.0 | 1177.7 | 8.0    | 713.1  | 847.5  | 12.2   | 759.2  | 790.7  | 2.9    |                     |       |        |
| QCAPTHH | 2963.0                    | 2829.2 | 3.3    | 2635.7 | 2729.4 | 2.5    | 1759.1 | 1761.5 | 0.1    | 1677.1 | 1711.1 | 1.4    | 2335.1              | 561.6 | 24.1   |
|         | 2862.9                    | 2856.0 | 0.2    | 2739.8 | 2914.2 | 4.4    | 1666.1 | 1705.4 | 1.6    | 1730.5 | 1835.8 | 4.2    |                     |       |        |
|         | 2861.5                    | 2793.4 | 1.7    |        |        |        |        |        |        |        |        |        |                     |       |        |

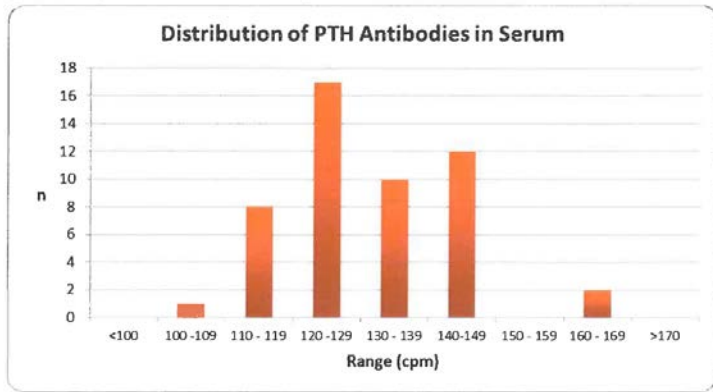
Yellow = duplicate CV% ≥ 25  
 Pink = biological outlier

**Reviewer comment:** *The above data confirms the previous comment regarding the preparation of the QC controls; the QCAPTHH sample produces higher assay readout than the QCAPTHL*

sample, indicating that the QCAPTHH sample is the HiPC and contains a greater concentration of antibodies than the QCAPTHL sample.

The overall distribution of the diseased samples analytical data is shown in the Figure 2, below, copied from the submission, demonstrating parametric distribution:

Figure 2: Cut point Distribution Summary



No biological outliers were observed, with the overall mean across all samples found to be 131.2 cpm (SD 21.8 cpm).

The Table shown below, copied from the submission, shows the anti-PTH immunoassay values from the fifty placebo-administered disease control subjects, demonstrating the Assay Cut Point determination:

| Sample ID | anti-PTH (cpm) | Sorted anti-PTH (cpm) | Range (cpm) | n  |
|-----------|----------------|-----------------------|-------------|----|
| IFZ 1969  | 143.1          | 168.0                 | <100        | 0  |
| IFZ 1973  | 118.7          | 166.0                 | 100 - 109   | 1  |
| IFZ 1975  | 148.1          | 148.1                 | 110 - 119   | 8  |
| IFZ 1978  | 125.3          | 146.5                 | 120 - 129   | 17 |
| IFZ 1983  | 108.0          | 145.6                 | 130 - 139   | 10 |
| IFZ 1985  | 131.4          | 145.3                 | 140 - 149   | 12 |
| IFZ 1995  | 144.7          | 144.7                 | 150 - 159   | 0  |
| IFZ 1996  | 131.4          | 144.7                 | 160 - 169   | 2  |
| IFZ 1998  | 129.5          | 144.0                 | >170        | 0  |
| IFZ 2003  | 137.7          | 144.0                 |             |    |
| IFZ 2004  | 138.6          | 143.1                 |             |    |
| IFZ 2011  | 127.4          | 142.7                 |             |    |
| IFZ 2012  | 144.0          | 141.4                 |             |    |
| IFZ 2014  | 112.8          | 140.9                 |             |    |
| IFZ 2025  | 123.5          | 138.6                 |             |    |
| IFZ 2026  | 126.1          | 137.7                 |             |    |
| IFZ 2027  | 140.9          | 136.4                 |             |    |
| IFZ 2030  | 129.1          | 136.1                 |             |    |
| IFZ 2032  | 123.8          | 132.9                 |             |    |
| IFZ 2041  | 136.1          | 132.4                 |             |    |
| IFZ 2042  | 130.4          | 131.4                 |             |    |
| IFZ 2051  | 142.7          | 131.4                 |             |    |
| IFZ 2054  | 119.7          | 131.1                 |             |    |
| IFZ 2055  | 114.6          | 130.4                 |             |    |
| IFZ 2056  | 125.7          | 129.5                 |             |    |
| IFZ 2058  | 128.8          | 129.1                 |             |    |
| IFZ 2064  | 120.1          | 128.8                 |             |    |
| IFZ 2065  | 123.1          | 127.8                 |             |    |
| IFZ 2072  | 121.4          | 127.4                 |             |    |
| IFZ 2076  | 166.0          | 126.1                 |             |    |
| IFZ 2080  | 144.0          | 125.7                 |             |    |
| IFZ 2082  | 127.8          | 125.3                 |             |    |
| IFZ 2087  | 119.0          | 123.8                 |             |    |
| IFZ 2089  | 115.2          | 123.5                 |             |    |
| IFZ 2091  | 122.5          | 123.4                 |             |    |
| IFZ 2099  | 121.5          | 123.1                 |             |    |
| IFZ 2103  | 132.9          | 122.5                 |             |    |
| IFZ 2104  | 119.7          | 121.5                 |             |    |
| IFZ 2106  | 121.5          | 121.5                 |             |    |
| IFZ 2109  | 145.6          | 121.4                 |             |    |
| IFZ 2112  | 144.7          | 120.1                 |             |    |
| IFZ 2113  | 123.4          | 119.7                 |             |    |
| IFZ 2116  | 131.1          | 119.7                 |             |    |
| IFZ 2125  | 136.4          | 119.2                 |             |    |
| IFZ 2128  | 132.4          | 119.0                 |             |    |
| IFZ 2134  | 168.0          | 118.7                 |             |    |
| IFZ 2138  | 146.5          | 115.2                 |             |    |
| IFZ 2142  | 119.2          | 114.6                 |             |    |
| IFZ 2145  | 145.3          | 112.8                 |             |    |
| IFZ 2146  | 141.4          | 108.0                 |             |    |

|            |       |
|------------|-------|
| Quartile 1 | 121.7 |
| Quartile 3 | 141.3 |
| High Limit | 170.7 |
| Low Limit  | 92.4  |

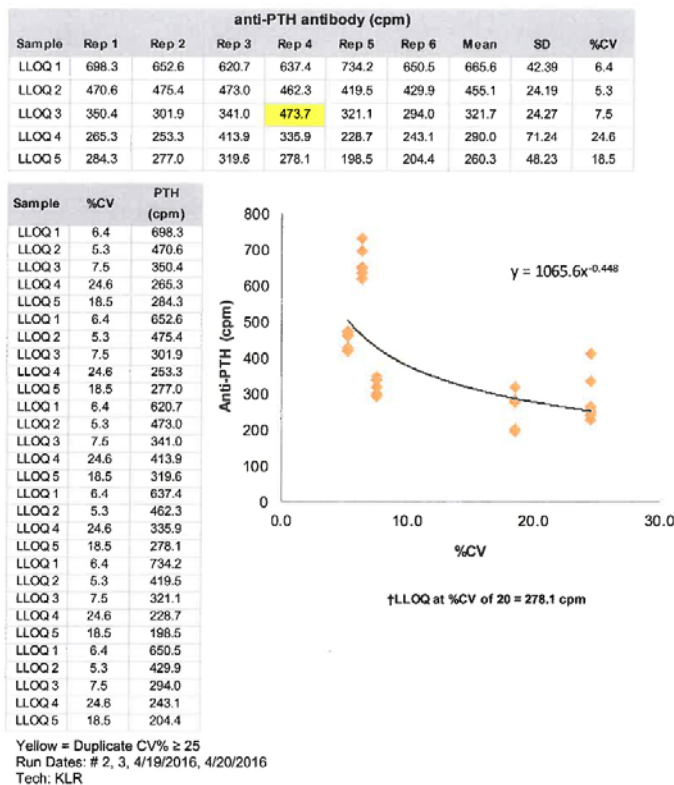
|                       |           |
|-----------------------|-----------|
| Mean                  | 131.4     |
| Median                | 129.3     |
| SD                    | 12.6      |
| Absolute Range:       | 108 - 168 |
| Overall Sample Mean:  | 131.2     |
| Overall SD:           | 21.8      |
| Cutpoint:             | 167.1     |
| Normalization Factor: | 23.3      |
| 95th Percentile       | 147.4     |
| Alternate NF:         | 3.6       |

The reviewer-annotated red box above shows the sorted values of the data obtained from the 50 placebo-treated diseased serum samples; only one sample analysis gave a value above the calculated 167.1 CPM cutpoint. To be consistent with the 5% false-positive recommendation, the 95<sup>th</sup> percentile (5% false positive rate) was calculated to yield an alternate cutpoint of 147.4 cpm. Using the recommended alternate cutpoint, and the mean value calculated for the Negative Control QCAPTHN (see Table 4, above), the Normalization Factor was calculated: 147.4 cpm – 143.8 cpm = 3.6 cpm. Therefore, the recommended floating cut point for clinical sample analysis is: CPV=mean QCAPTHN of the run + 3.6 cpm.

**Reviewer comment:** The assay cut point is calculated appropriately, and is acceptable. From the disease state serum samples tested above, the SD-based cutpoint was not selected, due to low false-positive (FP) incorporation rate of ~2% (1 in 50 diseased subjects). Calculation of an alternative cutpoint, based on the 95% percentile (incorporating a 5% FP) using a normalization factor + the NC QCAPTHN mean response results in a cutpoint of 147.4 cpm, yielding a rate of 3 in 50 subjects (or 6%) for the disease state treatment-naïve subjects tested above. This FP rate is acceptable.

**Assay Sensitivity:** To determine the lowest level of anti-PTH antibody that may be measured (LLOQ) using the (b) (4) anti-PTH antibody detection RIA assay, the low assay control (QCAPTHL) was serially diluted for a range from 2-16 fold, in addition the 1:6 MRD (thus final dilution 12-96 fold). These QCAPTHL dilutions were assayed by ≥6 dilutional series, and analyzed over 3 runs. Sensitivity of ≤500 cpm was considered acceptable (see Figure 3, below, copied from submission):

Figure 3: Sensitivity Data



Shown in Figure 3 (above) the mean results of 6 titrations of the low control QCAPTHL gave mean values from 260.3-665.6, with %CV from 5.3-24.6%. The values obtained from the assay, plotted against the %CV calculations yielded a curve from the power fit of the data relating the cpm values to the %CV with the formula  $y=1065.6x^{-0.448}$  (shown above). Using the formula, the

20% CV value is calculated to occur at a count of 278.1 cpm. Therefore, the anti-PTH antibodies are shown to be quantifiable down to 278.1 cpm with precision of  $\leq 20\%$  CV.

**Reviewer note:** This sensitivity value, similar to the sensitivity value for the (b) (4) anti-PTHrP cross-reactivity binding assay described below in this memo, is reported in CPM. This unit is not amenable to reviewer evaluation of sensitivity per the Agency Immunogenicity method validation guidance, where mass units per mL of undiluted sample are recommended. This reviewer is unsure of the ability of the sponsor to provide data in the requested format, due to the method design. Thus, this “functional” sensitivity limit is acceptable, in this situation.

**Assay Specificity (Confirmatory Cut Point):** The anti-PTH antibody detection assay was performed with RIA buffer (for naïve), or excess unlabeled PTH (100 ng/ml) in the reaction, to determine the potential for inhibition of the readout as a measure of specificity for PTH, and determine the confirmatory cut point (CCP). As confirmation that the assay is specific, the unlabeled PTH should be able to compete for binding with the positive control antibodies in the normal human serum samples, causing a decrease in signal. The same 50 single-donor diseased serum samples as used previously for cut point assessment were assayed (see Table 1, below, copied from the submission), in addition to the high SPC, medium SPC, low SPC, and negative controls. Specificity was considered acceptable in the case of  $\geq 50\%$  inhibition of the positive controls in the presence of the unlabeled PTH (an internal *a priori* acceptance criteria), and if the mean % inhibition was observed in the order of high control > medium control > low control > negative control. The CCP was assigned based on the 99% confidence interval for the mean % inhibition of the 50 donor samples using the formula: mean % inhibition + (2.33\*SD). The calculation using SD method resulted in CCP=22.9% for confirmation of putative positive samples in the anti-PTH antibody detection assay (see Table 1 below, copied from the submission):

| Sample  | Naïve  |       |      | Overall Performance |      |      |              |              |
|---------|--------|-------|------|---------------------|------|------|--------------|--------------|
|         | Mean   | SD    | %CV  | Confirmatory        |      |      | $\Delta$ cpm | % Inhibition |
| Mean    | SD     | %CV   | Mean | SD                  | %CV  |      |              |              |
| QCAPTHN | 162.1  | 17.6  | 10.9 | 154.2               | 14.1 | 9.1  | 8.0          | 4.9%         |
| QCAPTHL | 661.3  | 34.8  | 5.3  | 165.3               | 14.4 | 8.7  | 496.0        | 75.0%        |
| QCAPTHM | 1231.7 | 71.0  | 5.8  | 183.1               | 29.1 | 15.9 | 1048.6       | 85.1%        |
| QCAPTHH | 2893.5 | 129.1 | 4.5  | 207.0               | 27.1 | 13.1 | 2686.5       | 92.8%        |

The table shown above (copied from submission) shows that the acceptance criterion regarding inhibitory relationship of high control > medium control > low control > negative control was observed.

**Table 1. Diseased sample naïve and confirmatory anti-PTH antibody mean values with % inhibition.**

| Sample ID  | Naïve          | *Confirmatory  | PTH inhibition (%)          | Sorted             |
|------------|----------------|----------------|-----------------------------|--------------------|
|            | anti-PTH (cpm) | anti-PTH (cpm) |                             | PTH inhibition (%) |
| IFZ 1969   | 144.4          | 132.0          | 8.6%                        | 22.8%              |
| IFZ 1973   | 128.6          | 135.6          | -5.4%                       | 22.5%              |
| IFZ 1975   | 146.5          | 153.1          | -4.5%                       | 19.6%              |
| IFZ 1978   | 113.6          | 119.7          | -5.4%                       | 13.9%              |
| IFZ 1983   | 145.6          | 133.4          | 8.4%                        | 13.6%              |
| IFZ 1985   | 145.8          | 164.5          | -12.9%                      | 10.6%              |
| IFZ 1995   | 164.7          | 160.2          | 2.7%                        | 8.6%               |
| IFZ 1996   | 137.3          | 161.3          | -17.5%                      | 8.4%               |
| IFZ 1998   | 153.9          | 119.3          | 22.5%                       | 7.2%               |
| IFZ 2003   | 142.5          | 149.4          | -4.8%                       | 7.2%               |
| IFZ 2004   | 154.9          | 159.5          | -2.9%                       | 4.7%               |
| IFZ 2011   | 149.2          | 142.3          | 4.7%                        | 4.4%               |
| IFZ 2012   | 132.0          | 158.0          | -19.7%                      | 3.5%               |
| IFZ 2014   | 135.1          | 157.1          | -16.3%                      | 2.7%               |
| IFZ 2025   | 145.4          | 160.3          | -10.2%                      | 2.7%               |
| IFZ 2026   | 134.1          | 130.6          | 2.7%                        | 2.4%               |
| IFZ 2027   | 162.9          | 163.8          | -0.6%                       | 0.6%               |
| IFZ 2030   | 148.1          | 166.6          | -12.5%                      | 0.5%               |
| IFZ 2032   | 139.4          | 144.5          | -3.7%                       | 0.3%               |
| IFZ 2041   | 142.7          | 170.4          | -19.4%                      | -0.6%              |
| IFZ 2042   | 154.3          | 159.3          | -3.2%                       | -1.0%              |
| IFZ 2051   | 149.6          | 144.3          | 3.5%                        | -2.6%              |
| IFZ 2054   | 143.0          | 132.7          | 7.2%                        | -2.9%              |
| IFZ 2055   | 133.0          | 139.4          | -4.8%                       | -3.1%              |
| IFZ 2056   | 146.1          | 125.8          | 13.9%                       | -3.2%              |
| IFZ 2058   | 156.4          | 120.8          | 22.8%                       | -3.7%              |
| IFZ 2064   | 141.7          | 113.9          | 19.6%                       | -3.7%              |
| IFZ 2065   | 144.4          | 138.1          | 4.4%                        | -4.5%              |
| IFZ 2072   | 132.3          | 142.5          | -7.8%                       | -4.8%              |
| IFZ 2076   | 169.5          | 168.9          | 0.3%                        | -4.8%              |
| IFZ 2080   | 150.1          | 149.3          | 0.5%                        | -5.4%              |
| IFZ 2082   | 139.1          | 143.5          | -3.1%                       | -5.4%              |
| IFZ 2087   | 134.4          | 161.2          | -19.9%                      | -6.1%              |
| IFZ 2089   | 128.5          | 144.1          | -12.1%                      | -7.8%              |
| IFZ 2091   | 132.3          | 122.8          | 7.2%                        | -8.6%              |
| IFZ 2099   | 138.3          | 119.4          | 13.6%                       | -9.3%              |
| IFZ 2103   | 144.0          | 128.6          | 10.6%                       | -9.4%              |
| IFZ 2104   | 145.1          | 144.3          | 0.6%                        | -10.2%             |
| IFZ 2106   | 124.9          | 136.6          | -9.4%                       | -11.8%             |
| IFZ 2109   | 127.2          | 135.0          | -6.1%                       | -12.1%             |
| IFZ 2112   | 149.5          | 162.3          | -8.6%                       | -12.1%             |
| IFZ 2113   | 137.6          | 141.1          | -2.6%                       | -12.5%             |
| IFZ 2116   | 137.4          | 142.5          | -3.7%                       | -12.9%             |
| IFZ 2125   | 126.9          | 149.1          | -17.5%                      | -16.3%             |
| IFZ 2128   | 150.1          | 146.5          | 2.4%                        | -17.5%             |
| IFZ 2134   | 137.9          | 154.6          | -12.1%                      | -17.5%             |
| IFZ 2138   | 134.1          | 149.9          | -11.8%                      | -19.4%             |
| IFZ 2142   | 139.9          | 141.3          | -1.0%                       | -19.7%             |
| IFZ 2145   | 133.6          | 146.0          | -9.3%                       | -19.9%             |
| IFZ 2146   | 125.5          | 156.7          | -24.8%                      | -24.8%             |
|            |                |                | Mean                        | -2.7%              |
|            |                |                | Median                      | -3.4%              |
|            |                |                | SD                          | 11.0%              |
|            |                |                | Absolute Range              | -24.8% to 22.8%    |
| Quartile 1 | -10.0%         |                |                             |                    |
| Quartile 3 | 3.3%           |                |                             |                    |
| High Limit | 23.4%          |                |                             |                    |
| Low Limit  | -30.1%         |                |                             |                    |
|            |                |                | Confirmatory Cutpoint (99%) | 22.9%              |

Table 1, copied from the submission (shown above; the source is the Anti-PTH Antibody Assay Addendum #2, Feb. 2017, detailed in the comment below), shows the assay results of the 50 single-donor diseased serum samples with or without the unlabeled PTH inhibitory reagent.

**Reviewer Comment:** *The 50% Inhibition figure that was chosen to serve as the cut-off for determining Specificity was never justified by the sponsor, it appears to either have been chosen arbitrarily or selected based on assay development data not found in the submission. With respect to the confirmatory assay, the sponsor initially chose a higher-stringency method for CCP determination (for confirmation of ADA cross-reactivity with PTH) than currently*

recommended in Agency Immunogenicity assay validation guidance documents. Guidance recommends incorporation of a 1% FP rate for confirmatory assay CP assignment, rather than the 0.1% FP that was used by the sponsor (see Table 6 in the Anti-PTH Antibody Assay, May 2016, not shown), in order to avoid false-negative assignment of samples. An IR comment was sent to the sponsor on 02-27-2017 requesting re-calculation of the CCP based upon a 1% FP rate, and reassignment of PTH cross-reactivity subject incidence rates and revision of the immunogenicity section of the label as necessary. The figure of CCP=22.9% is the result of the re-calculation of the CCP by the sponsor on the basis of the 1% false positive rate. The adjustment of the CCP led to two additional clinical study patients being confirmed as positive for antibodies cross-reactive for PTH. However, both of these patients were found to be positive before commencement of abaloparatide treatment in the study, indicative of either pre-existing antibodies to PTH, or false-positivity. Furthermore, as the study progressed, both patients were later found to be negative for PTH antibodies following 18 months of treatment. Thus the incidence of treatment-emergent abaloparatide antibody cross-reactivity with PTH remained the same (0%) after adjustment of the false-positive percentage used for calculation of the CCP.

**Assay Precision:** The assay was tested for the ability to produce similar results with acceptably small variability over multiple runs. The assay controls QCPTHN, QCPTHM, QCPTHL and QCPTHN were run 6 times in duplicate, in one assay. The inter- and intra-assay precision was considered acceptable if  $CV \leq 25\%$  for each positive control.

**Table 10: Intra-assay Precision Data**

| Replicate | QCPTHN | QCPTHL | QCPTHM | QCPTHH |
|-----------|--------|--------|--------|--------|
| 1         | 210.3  | 656.8  | 1229.3 | 2441.5 |
| 2         | 325.1  | 681.5  | 1120.2 | 2531.3 |
| 3         | 226.0  | 631.7  | 1067.8 | 2471.7 |
| 4         | 246.0  | 605.9  | 1114.9 | 2666.8 |
| 5         | 199.6  | 617.1  | 1125.7 | 2788.3 |
| 6         | 184.2  | 698.3  | 1235.1 | 2599.9 |
| n         | 6      | 6      | 6      | 6      |
| Mean      | 231.9  | 648.6  | 1148.8 | 2583.3 |
| SD        | 50.4   | 36.7   | 67.8   | 130.0  |
| % CV      | 21.7   | 5.7    | 5.9    | 5.0    |

Yellow = Duplicate CV%  $\geq 25$   
 Run # 2, 3, (4/19/2016, 4/20/2016)  
 Tech: KLR

The intra-assay CV values ranged from 5.0-5.9%, meeting the sponsor's  $CV \leq 25\%$  acceptance criteria, see Table 10, above, copied from submission.

**Table 11: Inter-assay Precision Data**

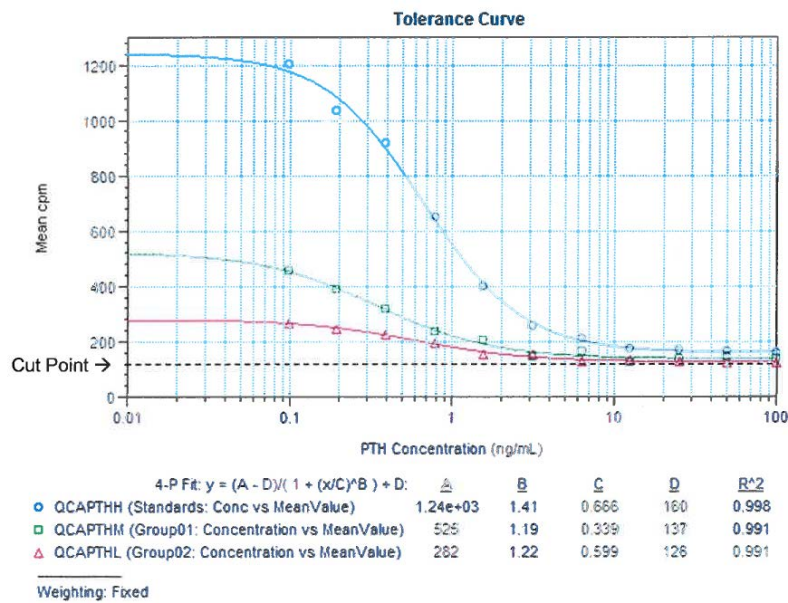
| Run              | QCAPTHN  | QCAPTHL | QCAPTHM | QCAPTHH |        |
|------------------|----------|---------|---------|---------|--------|
| 1                | 177.2    | 682.8   | 1206.1  | 2741.7  |        |
| 1                | 221.0    | 659.1   | 1206.1  | 2707.4  |        |
| 1                | 148.0    | 631.8   | 1111.4  | 2674.0  |        |
| 2                | 190.4    | 622.6   | 1085.0  | 2345.4  |        |
| 2                | 267.9    | 684.3   | 1242.2  | 2397.2  |        |
| 3                | 186.1    | 619.9   | 1101.0  | 2518.4  |        |
| 3                | 233.3    | 707.7   | 1101.8  | 2534.9  |        |
| 3                | 146.9    | 665.4   | 1238.6  | 2896.1  |        |
| 4                | 166.0    | 659.9   | 1282.2  | 2859.5  |        |
| 4                | 129.0    | 624.7   | 1216.5  | 2827.5  |        |
| 4                | 174.5    | 705.6   | 1248.2  | 2682.6  |        |
| 5                | 173.3    | 720.5   | 1248.4  | 2827.0  |        |
| 5                | 190.0    | 419.5   | 790.9   | 1760.3  |        |
| 6                | 135.1    | 541.7   | 780.3   | 1685.8  |        |
| 6                | 106.7    | 399.5   | 679.9   | 1694.1  |        |
| 7                | 141.2    | 458.1   | 775.0   | 1783.2  |        |
| 7                | 121.2    | 363.2   | 652.2   | 1491.9  |        |
| 8                | 148.7    | 379.6   | 621.1   | 1438.4  |        |
| 8                | 146.2    | 364.6   | 646.4   | 1376.5  |        |
| n                | 19       | 19      | 19      | 19      |        |
| Mean             | 168.6    | 574.2   | 1012.3  | 2275.9  |        |
| SD               | 40.5     | 131.0   | 249.7   | 554.1   |        |
| % CV             | 24.0     | 22.8    | 24.7    | 24.3    |        |
| Outliers Removed | Mean     | 161.0   | 574.2   | 1012.3  | 2241.4 |
|                  | SD       | 26.8    | 131.0   | 249.7   | 548.8  |
|                  | % CV     | 16.6    | 22.8    | 24.7    | 24.5   |
|                  | Range    | 214.5   | 836.2   | 1511.7  | 3339.0 |
|                  |          | 107.4   | 312.2   | 512.9   | 1143.8 |
|                  | Q1       | 143.7   | 438.8   | 777.7   | 1727.2 |
|                  | Q3       | 188.1   | 674.1   | 1227.6  | 2724.6 |
|                  | Outliers | 254.6   | 1027.1  | 1902.4  | 4220.6 |
|                  |          | 121.5   | 321.2   | 552.7   | 1228.5 |

Yellow = Duplicate CV% ≥ 25  
Pink = Analytical outliers  
Run #1-8 (4/19/2016, 4/20/2016, 4/21/2016, 4/22/2016, 4/24/2016)  
Techs: KLR, MAP2, MTL

Each assay control was run 19 times; CVs for the QCAPTHN, QCAPTHL, QCAPTHM, QCAPTHH were all within the CV≤25% acceptance criteria (see Table 11, above, copied from submission).

Tolerance to PTH: The anti-PTH antibody assay was tested for ability to tolerate PTH, while still detecting anti-PTH-positive samples. The assay positive controls (QCAPTHL, QCAPTHM, QCAPTHH) were tested with spiked PTH at final concentrations of 0-100 ng/ml, approximating samples from patients. PTH tolerance was determined by interpolation of PTH concentration at each antibody concentration which would inhibit the assay signal to the cut point. Tolerance was considered acceptable if the QCAPTHH could tolerate a minimum of 33 ng/ml PTH and still produce a signal greater than the cut point.

Figure 5: Tolerance Curve



As shown in Figure 6 (above, copied from submission), the PTH tolerance of the assay exceeded the 100 ng/ml concentration for the high and medium anti-PTH antibody levels – the readings never dipped below the 133.9 floating cut point. This met the sponsor’s *a priori* criteria. The % inhibition values for the QCAPTHH, QCAPTHM, and QCAPTHL samples with 100ng/mL PTH competitor were 86.0, 72.9, and 53.5%, respectively. The low anti-PTH antibody level QCAPTHL was shown to be detectable in the presence of up to 12.5 ng/ml of PTH (25 ng/ml of PTH led the QCAPTHL to read below the cut point), the QCAPTHM and QCAPTHH anti-PTH antibody levels were detectable in up to 100 ng/ml of PTH. The sponsor defined acceptable tolerance as the QCAPTHH control antibody being able to read above the cut point even in the presence of up to 33ng/ml PTH.

**Reviewer comment:** *The Sponsor’s experiments demonstrated that the high and medium levels of their control antibodies had PTH tolerances exceeding 100 ng/ml PTH. The tolerance of their assay exceeded the 33 ng/ml PTH acceptance criteria at the high and medium concentration of control antibody, but not at the low concentration. The derivation of >33 ng/ml as the cutoff for successful tolerance was not stated, however it appears adequate in this case, since the normal human range for PTH is in the pg/ml range (see reference ranges obtained from a commercial PTH test kit from Quest Diagnostics, CPT Test Code 83970, which states that individuals >17 years should have serum PTH within the range of 14-64 pg/mL, and the Medscape internet site also states that the PTH reference range is 10-65 pg/mL).*

**Linearity:** The QCAPTHH positive control was serially diluted from Neat to 1:1024 for evaluation by the anti-PTH antibody assay to determine the lower titer reading above the cut point, see data table below, copied from submission:

**Table 13: Linearity Data**

|            | Val Run 1 |        |        | Val Run 2 |         |      | Mean | SD | % |
|------------|-----------|--------|--------|-----------|---------|------|------|----|---|
|            | 1         | 2      | 3      | 1         | 2       | 3    |      |    |   |
| Neat       | 2788.8    | 2422.9 | 2453.5 | 2555.1    | 203.0   | 7.9  |      |    |   |
| 1:2        | 1684.5    | 1488.0 | 1502.8 | 1558.4    | 109.4   | 7.0  |      |    |   |
| 1:4        | 1030.3    | 943.0  | 968.1  | 980.5     | 44.9    | 4.6  |      |    |   |
| 1:8        | 586.0     | 541.2  | 607.0  | 578.1     | 33.6    | 5.8  |      |    |   |
| 1:16       | 349.3     | 395.5  | 416.3  | 387.0     | 34.3    | 8.9  |      |    |   |
| 1:32       | 235.3     | 291.4  | 314.5  | 280.4     | 40.7    | 14.5 |      |    |   |
| 1:64       | 167.7     | 226.2  | 272.0  | 222.0     | 52.3    | 23.6 |      |    |   |
| 1:128      | 159.1     | 266.8  | 254.2  | 226.7     | 58.9    | 26.0 |      |    |   |
| 1:256      | 145.8     | 304.4  | 252.3  | 234.2     | 80.8    | 34.5 |      |    |   |
| 1:512      | 158.4     | 254.9  | 238.1  | 217.1     | 51.6    | 23.7 |      |    |   |
| 1:1024     | 189.2     | 226.5  | 234.6  | 216.8     | 24.2    | 11.2 |      |    |   |
|            | 177.2     |        |        |           |         |      |      |    |   |
| QCAPTHN    | 221.0     | 190.4  | 267.9  | 200.9     | 45.726  | 22.8 |      |    |   |
|            | 148.0     |        |        |           |         |      |      |    |   |
|            | 682.8     |        |        |           |         |      |      |    |   |
| QCAPTHL    | 659.1     | 622.6  | 684.3  | 656.1     | 28.416  | 4.3  |      |    |   |
|            | 631.8     |        |        |           |         |      |      |    |   |
|            | 1206.1    |        |        |           |         |      |      |    |   |
| QCAPTHM    | 1206.1    | 1085.0 | 1242.2 | 1170.2    | 67.967  | 5.8  |      |    |   |
|            | 1111.4    |        |        |           |         |      |      |    |   |
|            | 2741.7    |        |        |           |         |      |      |    |   |
| QCAPTHH    | 2707.4    | 2345.4 | 2397.2 | 2573.1    | 186.703 | 7.3  |      |    |   |
|            | 2674.0    |        |        |           |         |      |      |    |   |
| Cutpoint = | 185.7     | 232.8  | 204.5  |           |         |      |      |    |   |

Run # 1, 2 (4/19/2016)  
Tech: KLR

The Run 1 of Val Run 1, and Run 2 of Val Run 2 both reached their normalized cut points by the 1:64 dilution; however Run 3 of Val Run 2 was not able to reach its normalized cut point. The mean values of all three runs were also not able to be reduced below the cut point. It is suggested by the sponsor that the failure of the mean values to reach the cut point may still be adequate, as the values seem to plateau at the 1:128 dilution through 1:1024 dilution. The sponsor further advises that in use, those titrations that do not reach the normalized cut point, but yield anti-PTH values higher than those observed in the previous dilution, be reported as the titer with the first non-descending value.

**Reviewer comment:** *The proposal of the Sponsor for titration series that fail to reach their cut point is an acceptable solution, as the assay seeks to find the dilution just before the cut point is passed. As the results level off, even if they do so without passing the cut point, it could be inferred that the lowest level of readings has been reached. After all, with a certain degree of false-positivity built into the assay, it is conceivable that such borderline readings represent a kind of “false-positive” noise at the edge of sensitivity. In any case, such questionably “putative positive” reading would be ultimately confirmed as truly positive or negative by the Tier 2 confirmatory assay.*

**F. Anti-PTH Neutralizing Antibody Detection Assay Validation PROTOCOL (BioAgilytix study #BAL-15-227-013):**

**Reviewer Note:** *The submission did not contain the finalized PTH Cross-reactivity Neutralizing Antibody Validation Report, only the validation protocol. It is possible this Validation Report*

*was omitted due to the fact that the assay was not used, since none of the subject samples were originally confirmed positive, so none were reflexed to PTH NAb assay. However, if the requested additional sample testing per the proposed PMC is performed, detection of at least a few subject samples as confirmed PTH-cross-reactive is possible; this will necessitate use of the Tier 2 PTH NAb assay. At that point the sponsor will need to submit PTH NAb assay validation report as part of their clinical analysis plan, prior to sample analysis. The following is a review of the submitted Validation Protocol and discussion of the methods to be used for validation.*

The anti-PTH neutralizing antibody detection assay method developed by BioAgilytix relies on the UMR-106 cell line, which expresses the receptor PTHR1 on its cell surface. Binding of PTH to these receptors activates PKC, which results in elevation of cAMP. The change of cAMP levels in UMR-106 cells is detected by a competitive ECL immunoassay kit (MSD Cyclic AMP Assay, MSD). Therefore, neutralization of PTH by binding of antibody present in the culture medium would result in abrogation of the cAMP elevation, and consequent loss of the immunoassay signal detection. For assay validation, the positive control (PC) consisted of a surrogate anti-PTH positive control antibody. Four dilutions of the PC were made, with final dilutions shown below (included in the final dilutions shown below is the MRD of 1:4, which was established during qualification):

HPC - 1:1920  
MPC – 1:3840  
LPC1 – 1:4800  
LPC2 – 1:6000

Validation parameters for the anti-PTH neutralizing antibody detection assay are shown in Table 6 (below, copied from the submission):

**Table 6: Validation parameters for PTH NAb method BAL-15-227-013**

| Validation parameter                            | Value     |
|-------------------------------------------------|-----------|
| Minimum required dilution                       | 1:4       |
| Assay cut-point (% inhibition)                  | 22.91     |
| PTH concentration                               | 500 pg/mL |
| Inter -assay precision of the positive controls | ≤30%      |
| Inter -assay precision of the negative controls | ≥22.91%   |
| Sensitivity                                     | 1:153     |

Assay cut point determination: Sixty-four disease-state placebo-treated serum samples will be collected for testing in groups of thirty-two, at least thrice, for six runs total, performed by two analysts over >3 days. At least eight replicates of the NC will be included in each plate. Statistical outliers will be removed from the data by Tukey-Kramer connecting letters test in the JMP analysis software package. Raw luminescence unit (RLU) values will be normalized to the NC of each plate:

Normalized RLU = RLU of samples or controls/mean RLU of NCs

The normalized data will then be evaluated by Shapiro Wilk's test for distribution normality, equal means by ANOVA, and unequal variances by Levene's test. In the case of the data being found to be normally distributed, with the means and variances between runs not being statistically significant, the floating cut point calculation, with a 1% false positive rate, will be conducted by the following formula:

$$CP = \text{MeanPlaceboSamplesNormRLU} + 2.33 * SD$$

In the case of non-normal distribution of data, but with means and variances not being statistically different, the data points will be log-transformed, and cut point determination will be carried out using 99% quantile of the data, resulting in ~1% false positivity. Furthermore, the cut point could also be determined by an equation using the log-transformed data for parametric analysis based on population median and median absolute deviation (MAD), assuming appropriate 1% rate of false positivity is found:

$$CP = \text{Median} + 2.33 * (1.483 * MAD)$$

The controls and samples obtained from patients will be analyzed against validation cut points to determine appropriateness of the cut point; if samples are not appropriately identified, the cut point calculation will be re-assessed.

Assay sensitivity: The anti-PTH control antibody will be diluted over the range of 1:480-1:61400; sensitivity will be determined by titration experiments performed in at least 3 runs by at least two analysts. The data collected will be subjected to a four-parameter logistic curve fit interpolation for the point at which the anti-PTH titration crosses the cut point. The acceptance criteria for each individual assay will be dictated by whether the antibody titration curve stays above the assay cut point; at least two of three assays must pass. The sensitivity reading will be calculated by interpolating the dilution of the anti-PTH control antibody.

Specificity by non-specific Ig: Specificity testing of the anti-PTH neutralizing antibody detection assay will be performed by spiking commercial IgG into the assay medium at final concentration of 0.1, 1.0, and 10.0 µg/ml with 6 ng/ml PTH. The acceptance criteria for the assay specifies RLU for the IgG-spiked controls to be within 70-130% of results obtained from drug-spiked pooled normal human serum.

Specificity by tolerance: The anti-PTH neutralizing antibody detection assay will be performed with spikes of at least 3 concentrations of the PTH peptide above the baseline of 500 pg/ml into samples of HPC, LPC1, and LPC2. Increased concentrations of the PTH peptide should decrease the signal inhibition obtained from each of the control antibodies in the assay. The tolerance will be reported as the amount of free PTH that can be present in the assay while still allowing an assay signal above the cut point.

Antibody selectivity: Ten individual serum samples from placebo-treated patients will be spiked with LPC1, or HPC concentrations of control antibodies, along with unspiked samples for analysis by the anti-PTH neutralizing antibody detection assay. The acceptance criteria is that LPC1-spiked samples must yield greater RLU signals than the unspiked samples, and the HPC-spiked samples must be greater than the LPC1-spiked sample in all samples tested. Additionally, at least 80% of the LPC1-spiked selectivity test samples must test above the cut point.

Inter-assay precision: A minimum of four independent preparations of the HPC, MPC, LPC1, LP2, and NC will be prepared in duplicate, and the normalized RLU readings will be analyzed. Acceptance criteria for inter-assay precision requires that the %CV of the normalized RLU readings must be  $\leq 30\%$  for the MPC and the LPC that tests consistently above the CP, while the HPC readings must consistently exceed the MPC and LPC readings.

Intra-assay precision: A minimum of four independent preparations of the HPC, MPC, LPC1, LP2, and NC will be prepared for running in a single assay over two runs by two analysts in a minimum of one day. The assay will be conducted at least twice with at least one assay performed by each of two operators. Acceptance of the assay will require the CV for each antibody control  $\leq 30\%$ .

Inter-operator precision: Evaluation of the variability between inter- and intra-assay validation runs will be analyzed over 1 or more runs per operator. The CV for normalized RLU values for each control must be  $\leq 30\%$  for each operator.

Short-term stability: Antibody reference controls will be tested with antibody stability samples on the same plate. The stability samples will be subjected to room temperature storage for 2-6 hours and 16-24 hours, while refrigerated test samples will be stored at 2-8°C for  $\geq 22$  hours. Samples will be analyzed in quadruplicate. For acceptance, each stability sample must read within 30% of the corresponding reference control for the assay.

Freeze / thaw stability: The HPC, LPC, and NC will be frozen at -80°C for  $\geq 12$  hours, then thawed for at least 1 hour before the next freezing cycle (up to 5 cycles). Samples will be analyzed in replicates of at least 4, with each stability sample required to read within  $\pm 30\%$  of the corresponding reference control.

Robustness: Parameters for normal assay operation associated with conditions of UMR-106 cell culture, starvation, flask density prior to plating, and PTH peptide concentration were confirmed during assay qualification. Optimization of the methods was conducted during assay qualification; all assays are to be performed within the optimized ranges.

***Reviewer Note:*** *The steps outlined in the Anti-PTH Neutralizing Antibody Detection Assay Validation protocol (above) appear reasonable, however judgment of appropriateness of the*

validation will require the submission of a report with detailed analysis of the data that was collected.

**G. Anti-PTHrP Antibody Detection Assay Validation (b) (4) Method #50322):**

The semi-quantitative anti-PTHrP antibody detection assay was developed at (b) (4) incorporating a 1:6 MRD of patient sera, incubation with <sup>125</sup>I-PTHrP tracer, then immunoprecipitation with rabbit anti-human IgG/IgA/IgM (RAH) and goat anti-rabbit (GAR) secondary antibody, followed by precipitation. Detection was achieved by centrifugal separation of the anti-PTHrP antibody-bound <sup>125</sup>I-PTH tracer from unbound tracer, and quantitation of bound tracer by scintillation counter. Surrogate PC rabbit anti-PTHrP antiserum cat# 56-04 is a commercial antibody. The validation parameters for the anti-PTHrP antibody immunoassay are copied from the submission, Appendix 2, shown below:

**Table 3: Validation parameters for anti- PTHrP Method # 50322**

| Validation parameter                              | Value     |
|---------------------------------------------------|-----------|
| Minimum required dilution                         | 1:6       |
| Normal assay cut-point                            | 235.5 cpm |
| Sensitivity (LLOQ)                                | 332.3 cpm |
| Normalization Factor                              | 71.7 cpm  |
| Intra-assay Precision (%CV)                       | ≤14.4     |
| Inter-assay Precision (%CV)                       | ≤14.1     |
| Specificity (% binding) CCP for positive controls | >23.2%    |

A summary of data pertaining to anti-PTHrP antibody detection (Method 50322) in patients enrolled in clinical study BA-058-05-003 is copied from the submission, Appendix 2, shown below:

**Table 4: Summary of Anti-PTHrP Binding Following abaloparatide-SC therapy (BA058-05-003)**

| Results Summary: Anti-PTHrP (1-34)            |                          |              |
|-----------------------------------------------|--------------------------|--------------|
| Category                                      | Criteria                 | # of Samples |
| I. Screened                                   |                          | 593          |
| “Not Detected”                                | CPM < floating cut point | 561          |
| Putative Positives (Reflexed to Confirmation) | CPM ≥ floating cut point | 31           |
| “Cancel”                                      |                          | 1            |
| II. Confirmed “putative positives”            |                          | 31           |
| “Not Detected”                                | Inhibition < 23.2%       | 26           |
| “Detected” (Reflexed to Titer)                | Inhibition ≥ 23.2%       | 5            |
| “Quantity Not Sufficient”                     |                          | 0            |

|                |  |     |
|----------------|--|-----|
| III. Titrated  |  | 5   |
| IV. Totals     |  |     |
| “Not Detected” |  | 587 |
| “Detected”     |  | 5   |
| Titrated       |  | 5   |
| “Cancel”       |  | 1   |

Note 2. Reviewer annotated section (red) was revised by sponsor per FDA request (see below):

| Results Summary: Anti-PTHrP (1-34) |                     |                    |
|------------------------------------|---------------------|--------------------|
| Category                           | Previous CP (23.2%) | Updated CP (16.8%) |
| II. Confirmed                      | 31                  | 31                 |
| “Not Detected”                     | 26                  | 24                 |
| “Detected”                         | 5                   | 7                  |
| “Quantity Not Sufficient”          | 0                   | 0                  |

The sponsor amended their summary validation table per Agency request.

**Reviewer comment:** Copy of amended Confirmatory assay results is included above, from see validation Addendum Summary Table from the 03-02-17 IR response). Note the increase in “Detected” samples from 5 to 7 and the new CCP = 16.8% inhibition.

Five samples originally confirmed as “Detected” for anti-PTHrP antibodies, based upon the stringent CCP definition, were subsequently assayed for “Titration”:

**Table 5: Anti-PTHrP Titration Results for Confirmed Positives (Report # 5489)**

| PBI Accession Number | Sample ID    | Subject ID | Scheduled Time Point | Floating Cut Point (FCP) | CPM ×6 dilution | CPM ×12 dilution | Titer Result |
|----------------------|--------------|------------|----------------------|--------------------------|-----------------|------------------|--------------|
| 1634038              | 22A403719-88 | 1210495    | Visit 9              | 202.2                    | 258.7           | 243.0            | 1:12         |
| 1634122              | 22A401012-88 | 1260012    | Visit 9              | 202.2                    | 220.5           | 177.0            | MRD          |
| 1634207              | 22A406452-88 | 1320106    | Visit 9              | 202.2                    | 187.4           | 171.7            | MRD          |
| 1634335              | 22A403395-88 | 1810183    | Visit 9              | 202.2                    | 280.5           | 198.3            | MRD          |
| 1634343              | 22A403419-88 | 1810221    | Visit 9              | 202.2                    | 181.2           | 171.7            | MRD          |

Four of the five samples only tested above the cut point when they were diluted no further than the 1:6 MRD (any further dilution resulted in a reading below the cut point), whereas one sample (subject 1210495) was able to be diluted by a further 1:2 in addition to the 1:6 MRD, and still read above the cut point. Therefore, any further dilution of this sample resulted in a reading below the cut point.

**Reviewer comment:** In an IR filed by the Agency in February 2017, it was pointed out to the Sponsor that their confirmatory cut point calculation for their anti-PTHrP assay had depended on an assumption of 99.9% FP rate, which is not consistent with the FDA recommendations.

Therefore, the Sponsor recalculated the confirmatory cut point based on the recommended 99% FP rate (see details in subsequent sections of this review), as a result, two further abaloparatide patients, 1260037 and 1310419, were found to be confirmed positive for anti-PTHrP antibodies, raising the total number of positive patients from 5 to 7. Neither of these newly-confirmed patients was found to be cross-reactive with PTH, nor did they display any clinically significant impact on safety or efficacy endpoints. Additionally, the two newly-determined anti-PTHrP antibody-positive patients did not have any clinical evidence of low endogenous PTHrP-related adverse events (such as abnormal blood calcium), and both patients experienced increases in their lumbar spine, total hip, and femoral neck bone mineral density, consistent with the intended bone anabolic effects of abaloparatide (see “Response to 27 February 2017 FDA Additional Request for Information” for summaries of the clinical histories of these two additional patients with regard to their immunogenicity findings, and the efficacy of their treatment with abaloparatide). Sponsor may need to adjust PI to reflect these new values.

A table summarizing anti-PTHrP antibody detection assay (Method 50322) validation results is copied from the submission Validation #50322, shown below:

Validation Summary Table

| Assay Parameter                             | a priori acceptance criteria                                                                                                                       | Results                                                                                                                    |                   |                   |
|---------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------|
| MRD                                         | % difference within $\pm 30\%$ relative to buffer control                                                                                          | Low: -31.1 to -15.7%<br>Medium: -62.2 to -39.8%<br>High: -44.6 to -34.3%                                                   |                   |                   |
| Assay Cut Point                             | Duplicate CV replicates $\leq 25\%$<br>4 of 6 positive QCs are within mean signal $\pm 2SD$                                                        | All runs passed QC acceptance criteria<br>CP = 235.5 cpm NF = 71.7 cpm                                                     |                   |                   |
| Sensitivity                                 | Interpolated value (based on assay cut point) is $\leq 500$ cpm                                                                                    | LLOQ = 332.3 cpm                                                                                                           |                   |                   |
| Assay Specificity<br>Confirmatory Cut Point | Positive QCs $\geq 50\%$ inhibition in the presence of PTHrP<br>% Inhibition QCH > QCM > QCL > QCN<br>CCP = mean % inhibition + (3.09 $\times$ SD) | > 69.0% inhibition for all positive assay controls<br>QCH (89.1%) > QCM (74.1%) > QCL (69.0%) > QCN (-2.8%)<br>CCP = 23.2% |                   |                   |
| Precision                                   | Positive controls (QCPHRL, QCPHRLM and QCPHRRH) are $\leq 25\%$ CV for intra and inter-assay precision                                             | QC                                                                                                                         | Intra-assay (%CV) | Inter-assay (%CV) |
|                                             |                                                                                                                                                    | QCPHRL                                                                                                                     | 9.4               | 12.8              |
|                                             |                                                                                                                                                    | QCPHRLM                                                                                                                    | 14.4              | 14.1              |
| QCPHRRH                                     | 2.7                                                                                                                                                | 9.4                                                                                                                        |                   |                   |
| PTHrP Tolerance                             | $\geq 33$ ng/mL PTHrP inhibits the anti-PTHrP (1-34) antibody levels in QCPHRRH                                                                    | QCPHRRH > 33 ng/mL PTHrP inhibits 89.4% QCPHRRH                                                                            |                   |                   |
| Linearity (Titration)                       | Assay demonstrates the ability to dilute a positive sample to a level which falls below the assay cut point                                        | Dilution acceptable to 1:16 – 1:32                                                                                         |                   |                   |

**Reviewers comment:** The CCP shown in the table above assumes a 0.1% false positive rate, which is more stringent than recommended by the Agency. FDA Guidance recommends incorporation of a 1% FP rate for confirmatory CP assignment, which results in the CCP of

*16.8%. The CCP was corrected by the sponsor upon request of the Agency, see “Assay specificity, Confirmatory Cut Point” section, below.*

**Minimum Required Dilution:** The MRD of 1:6 was identified during assay development as being sufficient to precipitate the human anti-PTHrP antibodies with the rabbit anti-human antibodies in the serum samples, yet still have acceptable sensitivity and low background. Two normal human serum samples were diluted in RIA buffer to 1:2, 1:3, 1:4, and 1:6. The control antibodies were spiked into RIA buffer at 0, 1:225, 1:675, and 1:3000 concentrations. The diluted serum samples were then combined with the control antibody dilutions, to achieve final MRDs of 1:2, 1:4, 1:6, 1:8, and 1:12, with control antibody dilutions of 1:450, 1:1350, and 1:6000. The % difference for control antibody-spiked NHS samples relative to spiked diluent ranged from -62.1% to -20.2% (see Table 1, copied from the submission, below). The acceptance of the MRD experiments was conditional upon the MRD dilutions resulting in assay readings within  $\pm 30\%$  of the buffer control. The 1:6 MRD of the NHS samples was found to yield the best results; the % differences observed for the anti-PTHrP antibody spiked NHS sampled relative to spiked diluent was only within the  $\pm 30\%$  acceptance criteria at the low anti-PTHrP antibody concentration, yielding the best agreement with the diluent.

**Table 1: MRD Data**

**MRD Blank**

| Sample         | MRD   |       |       |       |       | Diluent |
|----------------|-------|-------|-------|-------|-------|---------|
|                | 1:2   | 1:4   | 1:6   | 1:8   | 1:12  |         |
| NHSA           | 339.4 | 305.6 | 314.1 | 299.5 | 300.6 | 343.0   |
| NHSB           | 362.5 | 385.6 | 296.8 | 405.1 | 351.7 | 343.0   |
| Mean (cpm)     | 339.4 | 345.6 | 305.5 | 299.5 | 326.2 | 343.0   |
| Difference (%) | -1.1  | 0.8   | -12.3 | -14.5 | -5.2  | NA      |

Run: #1 (4/19/16) Tech: MAP2

**MRD Low Concentration**

| Sample         | MRD   |       |       |       |       | Diluent |
|----------------|-------|-------|-------|-------|-------|---------|
|                | 1:2   | 1:4   | 1:6   | 1:8   | 1:12  |         |
| NHSA           | 389.8 | 362.3 | 489.0 | 400.8 | 373.2 | 448.5   |
| NHSB           | 385.7 | 321.7 | 363.1 | 343.1 | 819.3 | 448.5   |
| Mean (cpm)     | 387.8 | 342.0 | 363.1 | 372.0 | 373.2 | 448.5   |
| Difference (%) | -15.7 | -31.1 | -23.5 | -20.6 | -20.2 | NA      |

Run: #1 (4/19/16) Tech: MAP2

**MRD Mid Concentration**

| Sample         | MRD   |       |       |       |       | Diluent |
|----------------|-------|-------|-------|-------|-------|---------|
|                | 1:2   | 1:4   | 1:6   | 1:8   | 1:12  |         |
| NHSA           | 446.1 | 411.9 | 472.9 | 479.5 | 521.0 | 677.3   |
| NHSB           | 389.7 | 428.5 | 495.9 | 426.1 | 405.1 | 677.3   |
| Mean (cpm)     | 417.9 | 420.2 | 484.4 | 452.8 | 463.1 | 677.3   |
| Difference (%) | -62.1 | -61.2 | -39.8 | -49.6 | -46.3 | NA      |

Run: #1 (4/19/16) Tech: MAP2

**MRD High Concentration**

| Sample         | MRD   |       |       |       |       | Diluent |
|----------------|-------|-------|-------|-------|-------|---------|
|                | 1:2   | 1:4   | 1:6   | 1:8   | 1:12  |         |
| NHSA           | 747.9 | 776.8 | 799.1 | 782.7 | 808.9 | 1078.9  |
| NHSB           | 743.9 | 781.5 | 807.2 | 718.9 | 757.2 | 1078.9  |
| Mean (cpm)     | 745.9 | 779.2 | 803.2 | 750.8 | 783.1 | 1078.9  |
| Difference (%) | -44.6 | -38.5 | -34.3 | -43.7 | -37.8 | NA      |

Run: #1 (4/19/16) Tech: MAP2

Yellow = Duplicate CV% > 25

**Reviewer comment:** The Sponsor came to the conclusion that the 1:6 MRD yielded the best agreement between the results obtained from assaying the anti-PTHrP positive control antibody spiked into human serum samples relative to the spiked diluent samples, indicating the best minimization of matrix effects was achieved at the 1:6 dilution. This represents an acceptable result for the MRD, which was used for the further anti-PTHrP immunogenicity assay validations.

**Assay cut point:** Analysis of fifty single-donor diseased samples was performed for ACP determination; data was considered acceptable if the %CV between replicates was  $\leq 25\%$ , and 66% of reportable results for each concentration of controls fell within the criteria range. The performance of the Assay Controls in the cut point runs is shown below (the variability seen in the negative control readings suggested that a floating cut point was appropriate for the anti-PTHrP antibody screening assay):

| Control  | Assay Control Performance |        |        |        |        |      |        |        |      |        |        |      | Overall Performance |       |        |
|----------|---------------------------|--------|--------|--------|--------|------|--------|--------|------|--------|--------|------|---------------------|-------|--------|
|          | Run #4                    |        | CV (%) | Run #5 |        |      | Run #6 |        |      | Run #7 |        |      | Mean                | SD    | CV (%) |
|          | 1                         | 2      |        | 1      | 2      | (%)  | 1      | 2      | (%)  | 1      | 2      | (%)  |                     |       |        |
| QCPTHRN  | 180.6                     | 155.0  | 10.8   | 251.8  | 188.9  | 20.2 | 130.6  | 128.6  | 1.1  | 117.0  | 130.4  | 7.7  | 163.8               | 35.2  | 21.5   |
|          | 190.3                     | 179.6  | 4.1    | 175.8  | 271.7  | 30.3 | 136.3  | 168.2  | 14.8 | 140.0  | 261.2  | 42.7 |                     |       |        |
| QCPTHRHL | 169.4                     | 165.9  | 1.5    |        |        |      |        |        |      |        |        |      | 550.9               | 59.1  | 10.7   |
|          | 581.9                     | 618.3  | 4.3    | 562.1  | 574.2  | 1.5  | 498.3  | 494.7  | 0.5  | 515.5  | 496.9  | 2.6  |                     |       |        |
| QCPTHRIM | 623.5                     | 602.5  | 2.4    | 615.1  | 655.2  | 4.5  | 487.9  | 463.8  | 3.6  | 499.0  | 490.5  | 1.2  | 740.1               | 92.5  | 12.5   |
|          | 598.1                     | 539.2  | 7.3    |        |        |      |        |        |      |        |        |      |                     |       |        |
| QCPTHRHM | 769.8                     | 770.1  | 0.0    | 830.6  | 818.4  | 1.0  | 642.8  | 651.4  | 0.9  | 646.1  | 605.8  | 4.6  | 2527.9              | 235.9 | 9.3    |
|          | 784.1                     | 783.3  | 0.1    | 929.3  | 759.5  | 14.2 | 623.1  | 671.5  | 5.3  | 1204.4 | 869.6  | 22.8 |                     |       |        |
| QCPTHRHH | 2701.1                    | 2753.7 | 1.4    | 2845.6 | 2927.3 | 2.0  | 2354.2 | 2283.8 | 2.1  | 2311.1 | 2301.9 | 0.3  |                     |       |        |
|          | 2605.8                    | 2619.4 | 0.4    | 2723.2 | 2784.3 | 1.6  | 2178.2 | 2259.9 | 2.6  | 2367.8 | 2278.2 | 2.7  |                     |       |        |
|          | 2552.5                    | 2654.2 | 2.8    |        |        |      |        |        |      |        |        |      |                     |       |        |

Yellow = Duplicate CV% > 25  
Pink = Analytical outlier(s)

Run # 4, 5, 6, 7, (4/21/2016)  
Techs: KLR, MTL

The anti-PTHrP immunoassay values obtained from analysis of fifty single-donor diseased samples were used to calculate the assay cut point (see Table, below, copied from the submission):

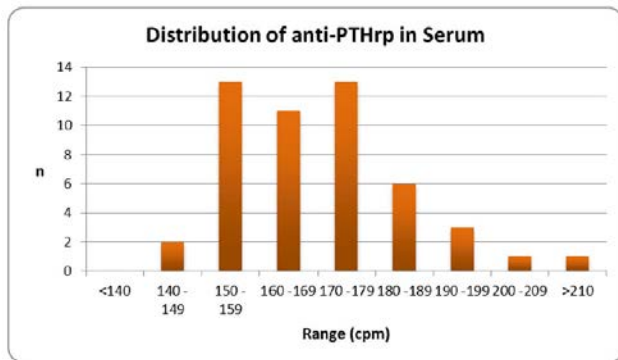
| Sorted    |                  |                  |             |    |
|-----------|------------------|------------------|-------------|----|
| Sample ID | Anti-PTHrp (cpm) | Anti-PTHrp (cpm) | Range (cpm) | n  |
| IFZ 1969  | 161.3            | 210.3            | <140        | 0  |
| IFZ 1973  | 157.4            | 205.0            | 140 - 149   | 2  |
| IFZ 1975  | 163.0            | 197.0            | 150 - 159   | 13 |
| IFZ 1978  | 157.8            | 195.8            | 160 - 169   | 11 |
| IFZ 1983  | 154.0            | 190.0            | 170 - 179   | 13 |
| IFZ 1985  | 175.3            | 189.3            | 180 - 189   | 6  |
| IFZ 1995  | 179.4            | 189.1            | 190 - 199   | 3  |
| IFZ 1996  | 171.5            | 188.0            | 200 - 209   | 1  |
| IFZ 1998  | 158.6            | 183.2            | >210        | 1  |
| IFZ 2003  | 176.7            | 182.0            |             |    |
| IFZ 2004  | 188.0            | 180.5            |             |    |
| IFZ 2011  | 180.5            | 179.4            |             |    |
| IFZ 2012  | 156.7            | 178.9            |             |    |
| IFZ 2014  | 153.2            | 178.3            |             |    |
| IFZ 2025  | 178.9            | 177.9            |             |    |
| IFZ 2026  | 158.1            | 177.2            |             |    |
| IFZ 2027  | 159.1            | 176.7            |             |    |
| IFZ 2030  | 155.7            | 176.3            |             |    |
| IFZ 2032  | 148.9            | 175.9            |             |    |
| IFZ 2041  | 173.2            | 175.3            |             |    |
| IFZ 2042  | 197.0            | 173.2            |             |    |
| IFZ 2051  | 190.0            | 172.8            |             |    |
| IFZ 2054  | 210.3            | 171.5            |             |    |
| IFZ 2055  | 172.8            | 170.3            |             |    |
| IFZ 2056  | 189.3            | 169.8            |             |    |
| IFZ 2058  | 165.6            | 169.0            |             |    |
| IFZ 2064  | 170.3            | 166.6            |             |    |
| IFZ 2065  | 160.8            | 165.6            |             |    |
| IFZ 2072  | 169.0            | 164.7            |             |    |
| IFZ 2076  | 178.3            | 163.6            |             |    |
| IFZ 2080  | 166.6            | 163.0            |             |    |
| IFZ 2082  | 175.9            | 161.7            |             |    |
| IFZ 2087  | 147.2            | 161.3            |             |    |
| IFZ 2089  | 157.0            | 160.8            |             |    |
| IFZ 2091  | 160.3            | 160.3            |             |    |
| IFZ 2099  | 155.4            | 159.1            |             |    |
| IFZ 2103  | 151.5            | 158.6            |             |    |
| IFZ 2104  | 169.8            | 158.1            |             |    |
| IFZ 2106  | 164.7            | 157.8            |             |    |
| IFZ 2109  | 177.2            | 157.4            |             |    |
| IFZ 2112  | 205.0            | 157.0            |             |    |
| IFZ 2113  | 156.0            | 156.7            |             |    |
| IFZ 2116  | 183.2            | 156.0            |             |    |
| IFZ 2125  | 163.6            | 155.7            |             |    |
| IFZ 2128  | 176.3            | 155.4            |             |    |
| IFZ 2134  | 177.9            | 154.0            |             |    |
| IFZ 2138  | 161.7            | 153.2            |             |    |
| IFZ 2142  | 195.8            | 151.5            |             |    |
| IFZ 2145  | 189.1            | 148.9            |             |    |
| IFZ 2146  | 182.0            | 147.2            |             |    |

|            |       |
|------------|-------|
| Quartile 1 | 158.2 |
| Quartile 3 | 178.8 |
| High Limit | 209.6 |
| Low Limit  | 127.4 |

Biological Outlier

|                       |               |
|-----------------------|---------------|
| Mean                  | 169.7         |
| Median                | 169.0         |
| SD                    | 13.7          |
| Absolute Range:       | 147.2 - 210.3 |
| Overall Sample Mean:  | 169.9         |
| Overall SD:           | 39.9          |
| Cutpoint:             | 235.5         |
| Normalization Factor: | 71.7          |
| 95th Percentile:      | 193.5         |
| Alternate NF:         | 29.7          |

One biological outlier was observed, and the sample distribution was considered parametric (see Figure below, copied from the submission):



The overall sample mean of the fifty single-donor diseased samples was determined to be 169.9 cpm (SD 39.9 cpm), with the cut point determined to be 235.5, based on parametric distribution

of the assay values ranging from 147.2-210.3 cpm. The mean value for the negative control was 163.8 (see Assay Controls data chart, above), thus the normalization factor was calculated as:

$$\text{CPV} - \text{mean negative control value, or } 235.5 \text{ cpm} - 163.8 \text{ cpm} = 71.7 \text{ cpm NF.}$$

However, in order to ensure a 5% false positive rate when screening clinical samples, the 95<sup>th</sup> percentile of the diseased patient range was calculated as an alternate cut point; the value was determined to be 193.5 cpm. This calculation allowed 4 of the 50 samples to exceed the cut point value. The normalization factor calculation was therefore  $193.5 \text{ cpm} - 163.8 \text{ cpm} = 29.7 \text{ cpm}$ , thus the cut point for analysis of clinical samples was determined to be:

$$\text{ACP} = \text{mean Neg Control of the run} + 29.7 \text{ cpm.}$$

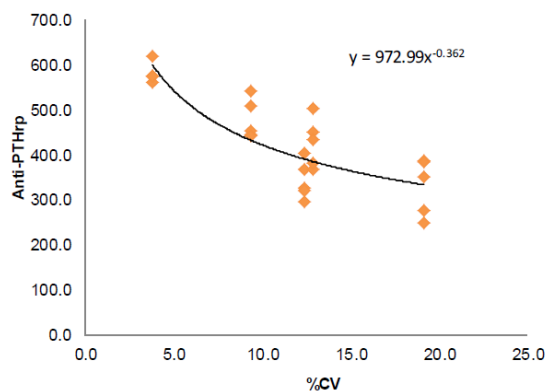
**Reviewer Comment:** *The use of a floating cut point was chosen for the anti-PTHrP antibody screening assay because of the variability that was observed among the negative control values, and is an appropriate choice. Furthermore, an adequate number of samples were tested for the validation, and the 5% false positive rate is consistent with the recommended practice of Agency guidelines. Use of the 95<sup>th</sup> percentile to generate an alternative cutpoint for the clinical samples provides a 5% FP rate – thus ensuring capture of borderline positive samples.*

**Sensitivity:** To determine the lowest level of anti-PTHrP antibody that may be measured by the assay (LLOQ), the positive control antibody was diluted by the MRD, then an additional 2-, 4-, 8-, and 16-fold in assay buffer, for analysis in three runs.

**Figure 3: Sensitivity Data**

| Sample | anti-PTH-rp antibody (cpm) |       |       |       |       |       | Mean  | SD    | %CV  |
|--------|----------------------------|-------|-------|-------|-------|-------|-------|-------|------|
|        | Rep 1                      | Rep 2 | Rep 3 | Rep 4 | Rep 5 | Rep 6 |       |       |      |
| LLOQ 1 |                            | 621.1 | 562.7 | 576.9 | 577.2 | 577.7 | 583.1 | 22.15 | 3.8  |
| LLOQ 2 |                            | 510.8 | 542.9 | 446.0 | 455.4 | 442.4 | 479.5 | 44.94 | 9.4  |
| LLOQ 3 |                            | 452.7 | 504.8 | 369.0 | 381.6 | 436.6 | 428.9 | 55.25 | 12.9 |
| LLOQ 4 |                            | 328.0 | 369.2 | 404.0 | 297.2 | 321.2 | 343.9 | 42.43 | 12.3 |
| LLOQ 5 |                            | 386.9 | 352.0 | 385.2 | 278.3 | 249.2 | 330.3 | 63.19 | 19.1 |

| Sample | %CV  | PTH-rP (cpm) |
|--------|------|--------------|
| LLOQ 1 | 3.8  | 621.1        |
| LLOQ 2 | 9.4  | 510.8        |
| LLOQ 3 | 12.9 | 452.7        |
| LLOQ 4 | 12.3 | 328.0        |
| LLOQ 5 | 19.1 | 386.9        |
| LLOQ 1 | 3.8  | 562.7        |
| LLOQ 2 | 9.4  | 542.9        |
| LLOQ 3 | 12.9 | 504.8        |
| LLOQ 4 | 12.3 | 369.2        |
| LLOQ 5 | 19.1 | 352.0        |
| LLOQ 1 | 3.8  | 576.9        |
| LLOQ 2 | 9.4  | 446.0        |
| LLOQ 3 | 12.9 | 369.0        |
| LLOQ 4 | 12.3 | 404.0        |
| LLOQ 5 | 19.1 | 385.2        |
| LLOQ 1 | 3.8  | 577.2        |
| LLOQ 2 | 9.4  | 455.4        |
| LLOQ 3 | 12.9 | 381.6        |
| LLOQ 4 | 12.3 | 297.2        |
| LLOQ 5 | 19.1 | 278.3        |
| LLOQ 1 | 3.8  | 577.7        |
| LLOQ 2 | 9.4  | 442.4        |
| LLOQ 3 | 12.9 | 436.6        |
| LLOQ 4 | 12.3 | 321.2        |
| LLOQ 5 | 19.1 | 249.2        |



Run Dates: # 2, 3, 4 (4/19/2016, 4/20/2016, 4/21/2016)

Tech: MAP2

\* LLOQ was calculated from 25 values using the equation derived from a power fit of the data:  $972.99x^{-0.362}$

Run Dates: # 2, 3 4/19/2016, 4/20/2016

Tech: KLR

From the 5 separate titrations that were considered (see figure above, copied from the submission), mean anti-PTHrP antibody values were found to be within the range of 330.3-583.1, with %CV from 3.8-19.1%. Thus, the LLOQ was calculated from the power fit of the data, where a 20% CV was calculated to occur at a count of 332.3 cpm. As the sensitivity was found to be less than the 500cpm acceptance criteria, it was considered acceptable by the study author.

**Reviewer note:** This sensitivity value, similar to the sensitivity value for the <sup>(b) (4)</sup> anti-PTH cross-reactivity binding assay reviewed above, is reported in CPM. This unit is not amenable to reviewer evaluation of sensitivity per the Agency Immunogenicity method validation guidance, where mass units per mL of undiluted sample are recommended. Again, this reviewer is unsure of the ability of the sponsor to provide data in the requested format, due to the method design. Thus, this “functional” sensitivity limit is acceptable, in this situation.

Assay specificity, Confirmatory Cut Point: The specificity of the assay to detect binding anti-PTHrP antibodies was qualified by assessment of the ability of competition with excess unlabeled PTHrP to inhibit detection by the positive control anti-PTH antibody controls. Subsequently, fifty individual disease-state samples, with the assay controls, were used for cut-point assessment after incubation with buffer (naïve), or 100 ng/ml PTHrP solution, prior to addition of the tracer. Specificity was considered acceptable by the study author if the controls showed  $\geq 50\%$  inhibition in the presence of the unlabeled PTHrP (an internal *a priori* acceptance criteria), and the mean % inhibition was observed in the order of high control > medium control > low control > negative control. Originally, the CCP was assigned using a stringent 99.9% confidence interval – which is not congruent with current Agency guidelines, resulting in a CCP = 23.2%. Per Agency request, the sponsor revised the CCP assignment based on the 99%

confidence interval for the mean % inhibition of the 50 donor samples using the formula: mean % inhibition+(2.33\*SD). The calculation using SD method resulted in **CCP=16.8%** for confirmation of putative positive samples in the anti-PTHrP antibody detection assay (see Table 1 below, copied from the submission):

| Sample  | Naïve  |        |        |        |        |        |        |        |        |        | *Confirmatory |       |       |       |       |        |       |       |       |       |
|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------------|-------|-------|-------|-------|--------|-------|-------|-------|-------|
|         | Tech 1 |        |        |        |        | Tech 2 |        |        |        |        | Tech 1        |       |       |       |       | Tech 2 |       |       |       |       |
|         | Rep 1  | Rep 2  | Rep 3  | Rep 4  | Mean   | Rep 5  | Rep 6  | Rep 7  | Rep 8  | Mean   | Rep 1         | Rep 2 | Rep 3 | Rep 4 | Mean  | Rep 5  | Rep 6 | Rep 7 | Rep 8 | Mean  |
| QCPTHRN | 170.2  | 147.5  | 145.1  | 152.8  | 153.9  | 146.8  | 145.9  | 159.8  | 216.5  | 167.3  | 176.8         | 195.6 | 178.5 | 168.8 | 179.9 | 186.6  | 183.0 | 270.1 | 247.6 | 221.8 |
|         | 210.6  | 207.2  | 159.0  | 174.9  | 187.9  | 170.1  | 185.5  | 199.5  | 198.7  | 188.5  | 157.2         | 157.4 | 160.6 | 148.1 | 155.8 | 193.6  | 160.7 | 139.4 | 144.2 | 159.5 |
| QCPTHRL | 619.6  | 618.4  | 614.9  | 641.8  | 623.7  | 604.9  | 615.4  | 642.3  | 613.4  | 619.0  | 225.2         | 177.5 | 175.8 | 161.1 | 184.9 | 224.9  | 210.3 | 212.8 | 226.6 | 218.7 |
|         | 637.3  | 673.7  | 653.2  | 623.1  | 646.8  | 669.7  | 569.3  | 758.6  | 633.3  | 657.7  | 182.5         | 202.8 | 206.3 | 187.8 | 194.9 | 160.7  | 184.3 | 211.7 | 205.9 | 190.7 |
| QCPTHRM | 812.1  | 780.6  | 800.1  | 835.6  | 807.1  | 778.2  | 815.5  | 815.4  | 783.4  | 798.1  | 256.6         | 181.1 | 164.9 | 179.3 | 195.5 | 195.7  | 242   | 234.3 | 245.8 | 229.5 |
|         | 764.4  | 830.1  | 848.4  | 786.7  | 807.4  | 813.4  | 761.2  | 816.4  | 774.6  | 791.4  | 230.0         | 175.9 | 199.8 | 244.0 | 212.4 | 148.2  | 148.1 | 248.2 | 225.1 | 192.4 |
| QCPTHRH | 2764.2 | 2722.7 | 2877.7 | 2761.2 | 2781.5 | 2730.2 | 2853.5 | 2732.8 | 2888.5 | 2801.3 | 312.4         | 326.6 | 309.3 | 294.0 | 310.6 | 175.8  | 184.7 | 429.3 | 308.7 | 274.6 |
|         | 2525.2 | 2796.7 | 2924.3 | 2751.3 | 2749.4 | 2803.1 | 2752.5 | 2993.3 | 2777.3 | 2831.6 | 324.2         | 290.0 | 290.9 | 273.2 | 294.6 | 331.3  | 332.7 | 323.2 | 340.2 | 331.9 |

| Sample  | Naïve  |       |      | *Confirmatory |        |       | Δ cpm  | % Inhibition |
|---------|--------|-------|------|---------------|--------|-------|--------|--------------|
|         | Mean   | SD    | %CV  | Mean          | SD     | %CV   |        |              |
| QCPTHRN | 174.4  | 25.3  | 14.5 | 179.3         | 17.2   | 6.4   | -4.9   | -2.8%        |
| QCPTHRL | 636.8  | 41.2  | 6.5  | 197.3         | 226.5  | 106.5 | 439.5  | 69.0%        |
| QCPTHRM | 801.0  | 26.2  | 3.3  | 207.4         | 300.6  | 128.3 | 593.6  | 74.1%        |
| QCPTHRH | 2790.9 | 105.5 | 3.8  | 302.9         | 1248.5 | 290.8 | 2488.0 | 89.1%        |

The controls in the specificity assay met the acceptance criteria for  $\geq 50\%$  inhibition in the presence of 100 ng/ml PTHrP, and the order of high control > medium control > low control > negative control was met as well, thus specificity of the assay was considered met. Statistical evaluation of the confirmatory assay determined that the CCP was fixed, at 16.8%, based on the mean % inhibition+(2.33\*SD), see Table 1, below (copied from the submission):

**Table 1. Diseased sample naïve and confirmatory anti-PTHrp antibody mean values with % inhibition.**

| Sample ID         | Naïve               | *Confirmatory         | anti-PTHrp<br>inhibitor<br>(%) | Sorted<br>anti-PTHrp<br>inhibitor<br>(%) |
|-------------------|---------------------|-----------------------|--------------------------------|------------------------------------------|
|                   | anti-PTHrp<br>(cpm) | anti-PTHrp<br>(cpm)   |                                |                                          |
| IFZ 1969          | 157.3               | 200.5                 | -27.4%                         | 25.6%                                    |
| IFZ 1973          | 155.2               | 160.1                 | -3.2%                          | 21.7%                                    |
| IFZ 1975          | 169.2               | 161.8                 | 4.4%                           | 14.1%                                    |
| IFZ 1978          | 150.0               | 171.1                 | -14.1%                         | 13.6%                                    |
| IFZ 1983          | 189.1               | 169.5                 | 10.3%                          | 12.8%                                    |
| IFZ 1985          | 206.4               | 202.5                 | 1.9%                           | 10.3%                                    |
| IFZ 1995          | 178.8               | 172.8                 | 3.4%                           | 9.2%                                     |
| IFZ 1996          | 177.8               | 175.8                 | 1.1%                           | 4.7%                                     |
| IFZ 1998          | 163.7               | 171.3                 | -4.7%                          | 4.4%                                     |
| IFZ 2003          | 175.9               | 174.9                 | 0.5%                           | 4.0%                                     |
| IFZ 2004          | 216.3               | 161.0                 | 25.6%                          | 3.4%                                     |
| IFZ 2011          | 167.3               | 163.7                 | 2.2%                           | 3.0%                                     |
| IFZ 2012          | 181.2               | 176.6                 | 2.6%                           | 2.6%                                     |
| IFZ 2014          | 189.5               | 196.9                 | -3.9%                          | 2.2%                                     |
| IFZ 2025          | 162.2               | 186.7                 | -15.1%                         | 2.0%                                     |
| IFZ 2026          | 173.0               | 189.1                 | -9.3%                          | 1.9%                                     |
| IFZ 2027          | 178.3               | 184.6                 | -3.5%                          | 1.9%                                     |
| IFZ 2030          | 211.8               | 182.9                 | 13.6%                          | 1.5%                                     |
| IFZ 2032          | 174.5               | 177.3                 | -1.6%                          | 1.2%                                     |
| IFZ 2041          | 172.5               | 150.5                 | 12.8%                          | 1.1%                                     |
| IFZ 2042          | 195.0               | 152.6                 | 21.7%                          | 0.5%                                     |
| IFZ 2051          | 208.7               | 189.4                 | 9.2%                           | -0.4%                                    |
| IFZ 2054          | 250.9               | 247.2                 | 1.5%                           | -1.2%                                    |
| IFZ 2055          | 186.4               | 208.3                 | -11.8%                         | -1.5%                                    |
| IFZ 2056          | 143.4               | 170.3                 | -18.8%                         | -1.6%                                    |
| IFZ 2058          | 174.6               | 186.6                 | -6.9%                          | -1.8%                                    |
| IFZ 2064          | 190.1               | 197.4                 | -3.8%                          | -2.0%                                    |
| IFZ 2065          | 173.3               | 183.8                 | -6.1%                          | -3.2%                                    |
| IFZ 2072          | 176.9               | 179.6                 | -1.5%                          | -3.5%                                    |
| IFZ 2076          | 196.3               | 236.5                 | -20.5%                         | -3.8%                                    |
| IFZ 2080          | 173.1               | 190.7                 | -10.2%                         | -3.9%                                    |
| IFZ 2082          | 189.5               | 185.8                 | 1.9%                           | -4.7%                                    |
| IFZ 2087          | 163.0               | 188.2                 | -15.5%                         | -5.7%                                    |
| IFZ 2089          | 157.5               | 166.4                 | -5.7%                          | -6.1%                                    |
| IFZ 2091          | 180.8               | 178.6                 | 1.2%                           | -6.2%                                    |
| IFZ 2099          | 172.3               | 165.5                 | 4.0%                           | -6.5%                                    |
| IFZ 2103          | 187.6               | 182.0                 | 3.0%                           | -6.9%                                    |
| IFZ 2104          | 181.8               | 156.3                 | 14.1%                          | -6.9%                                    |
| IFZ 2106          | 164.7               | 179.0                 | -8.7%                          | -8.7%                                    |
| IFZ 2109          | 154.5               | 182.8                 | -18.3%                         | -9.3%                                    |
| IFZ 2112          | 187.3               | 216.6                 | -15.6%                         | -10.2%                                   |
| IFZ 2113          | 176.1               | 179.3                 | -1.8%                          | -11.8%                                   |
| IFZ 2116          | 190.1               | 193.9                 | -2.0%                          | -14.1%                                   |
| IFZ 2125          | 183.1               | 185.4                 | -1.2%                          | -15.1%                                   |
| IFZ 2128          | 187.8               | 188.6                 | -0.4%                          | -15.5%                                   |
| IFZ 2134          | 200.3               | 190.9                 | 4.7%                           | -15.6%                                   |
| IFZ 2138          | 175.2               | 186.5                 | -6.5%                          | -18.3%                                   |
| IFZ 2142          | 168.5               | 180.1                 | -6.9%                          | -18.8%                                   |
| IFZ 2145          | 170.6               | 181.2                 | -6.2%                          | -20.5%                                   |
| IFZ 2146          | 165.0               | 161.6                 | 2.0%                           | -27.4%                                   |
|                   |                     | <b>Mean</b>           |                                | -2.8%                                    |
|                   |                     | <b>Median</b>         |                                | -1.8%                                    |
|                   |                     | <b>SD</b>             |                                | 8.4%                                     |
|                   |                     | <b>Absolute Range</b> |                                | -27.4% to 25.6%                          |
| <b>Quartile 1</b> | -6.9                |                       |                                |                                          |
| <b>Quartile 3</b> | 2.5                 |                       |                                |                                          |
| <b>High Limit</b> | 16.5                |                       |                                |                                          |
| <b>Low Limit</b>  | -20.9               |                       |                                |                                          |

Pink = Analytical outlier(s)

Confirmatory Cutpoint (99%) 16.8%

**Reviewer Comment:** The sponsor initially chose a higher-stringency CCP (resulting in a CCP of 23.2%) for confirmation of ADA cross-reactivity with PTHrP than currently recommended in Agency Immunogenicity assay validation guidance documents. Guidance recommends incorporation of a 1% FP rate for confirmatory assay CP assignment, rather than the 0.1% FP used by the sponsor, in order to avoid false-negative assignment of samples. An IR comment was sent to the sponsor on 02-27-2017 requesting re-calculation of the CCP based upon a 1% FP rate, and reassignment of PTHrP cross-reactivity subject incidence rates and revision of the immunogenicity section of the label as necessary. The revised CCP =16.8% (shown in Table 1, above) is the result of the re-calculation of the CCP by the sponsor on the basis of the 1% false

positive rate. The adjustment of the CCP during assessment of the ADA-positive study samples collected at Visit 9 led to the discovery of two additional abaloparatide-treated ADA<sup>+</sup> patients confirmed for PTHrP cross reactive ADA (study summary data table not included in this review), raising the number from 5 (0.8%) to 7 (1.1%) of 610 evaluable patients. Neither of these newly-confirmed anti-PTHrP antibody-positive patients had any adverse events that were indicative of immune reactions against abaloparatide, PTH, or PTHrP, such as anaphylaxis. Additionally, no clinical evidence was found in these patients that would have suggested low endogenous PTHrP (such as abnormal serum calcium). It was actually found that these anti-PTHrP antibody-positive patients had increased BMD above baseline at the lumbar spine, hip, and femoral neck, at all timepoints in the clinical studies, which was the anticipated effect consistent with abaloparatide bone anabolic effects.

**Assay Precision:** The intra-assay precision of the assay was established by the results of the assay controls run 6 times in one assay (see Table 10, below, copied from the submission):

**Table 10: Intra-assay Precision Data**

| Replicate | QCPTHNRN | QCPTHRL | QCPTHRM | QCPTHRH |
|-----------|----------|---------|---------|---------|
| 1         | 227.8    | 596.8   | 757.6   | 2415.0  |
| 2         | 214.7    | 631.4   | 802.9   | 2445.2  |
| 3         | 223.8    | 619.8   | 1068.5  | 2432.8  |
| 4         | 217.0    | 716.8   | 766.5   | 2569.1  |
| 5         | 232.7    | 574.4   | 777.4   | 2431.7  |
| 6         | 288.4    | 551.9   | 797.1   | 2551.4  |
| n         | 6        | 6       | 6       | 6       |
| Mean      | 234.1    | 615.2   | 828.3   | 2474.2  |
| SD        | 27.4     | 57.6    | 118.9   | 67.6    |
| % CV      | 11.7     | 9.4     | 14.4    | 2.7     |

Run(s): 2, 3 (4/19/2016, 4/20/2016)  
Tech: MAP2

The intra-assay precision was successfully demonstrated by meeting the acceptance criteria of  $\%CV \leq 25\%$  (see Table 10, above).

The inter-assay precision was demonstrated by analysis of assay controls over eight analytical runs (19 times total).

**Table 11: Inter-assay Precision Data**

| Run  | QCPTHR <sub>N</sub> | QCPTHR <sub>L</sub> | QCPTHR <sub>M</sub> | QCPTHR <sub>H</sub> |
|------|---------------------|---------------------|---------------------|---------------------|
| 1    | 217.5               | 712.2               | 893.8               | 2863.2              |
|      | 341.2               | 690.7               | 819.2               | 2758.6              |
|      | 272.2               | 692.8               | 830.0               | 2795.1              |
| 2    | 299.7               | 536.3               | 722.0               | 2412.5              |
|      | 224.3               | 596.4               | 743.6               | 2394.1              |
| 3    | 183.6               | 532.4               | 738.9               | 2429.2              |
|      | 235.9               | 601.7               | 760.6               | 2693.0              |
| 4    | 167.8               | 600.1               | 770.0               | 2727.4              |
|      | 185.0               | 613.0               | 783.7               | 2612.6              |
|      | 167.7               | 568.7               | 712.8               | 2603.4              |
| 5    | 220.4               | 568.2               | 824.5               | 2886.5              |
|      | 223.8               | 635.2               | 844.4               | 2753.8              |
| 6    | 129.6               | 496.5               | 647.1               | 2319.0              |
|      | 152.3               | 475.9               | 647.3               | 2219.1              |
| 7    | 123.7               | 506.2               | 626.0               | 2306.5              |
|      | 200.6               | 494.8               | 1037.0              | 2323.0              |
| 8    | 170.2               | 494.8               | 653.8               | 2348.9              |
|      | 159.4               | 559.3               | 626.6               | 2159.7              |
|      | 154.2               | 491.5               | 645.0               | 2251.9              |
| n    | 19                  | 19                  | 19                  | 19                  |
| Mean | 201.5               | 571.9               | 754.0               | 2518.8              |
| SD   | 57.0                | 73.4                | 106.6               | 236.9               |
| % CV | 28.3                | 12.8                | 14.1                | 9.4                 |

| Outliers Removed | Mean   | SD    | % CV | Range  | Q1     | Q3     | Outliers |
|------------------|--------|-------|------|--------|--------|--------|----------|
|                  | 205.7  | 44.1  | 21.4 | 293.8  | 163.6  | 224.1  | 314.8    |
|                  | 571.9  | 73.4  | 12.8 | 117.6  | 501.4  | 607.4  | 766.4    |
|                  | 738.3  | 84.0  | 11.4 | 425.1  | 510.4  | 821.9  | 1078.8   |
|                  | 2518.8 | 236.9 | 9.4  | 906.2  | 650.6  | 2740.6 | 3370.0   |
|                  |        |       |      | 2992.5 | 2321.0 | 2740.6 | 3370.0   |
|                  |        |       |      | 2045.1 | 2321.0 | 2740.6 | 3370.0   |
|                  |        |       |      | 2321.0 | 2321.0 | 2740.6 | 3370.0   |
|                  |        |       |      | 2740.6 | 2321.0 | 2740.6 | 3370.0   |
|                  |        |       |      | 3370.0 | 2321.0 | 2740.6 | 3370.0   |
|                  |        |       |      | 2111.2 | 2321.0 | 2740.6 | 3370.0   |

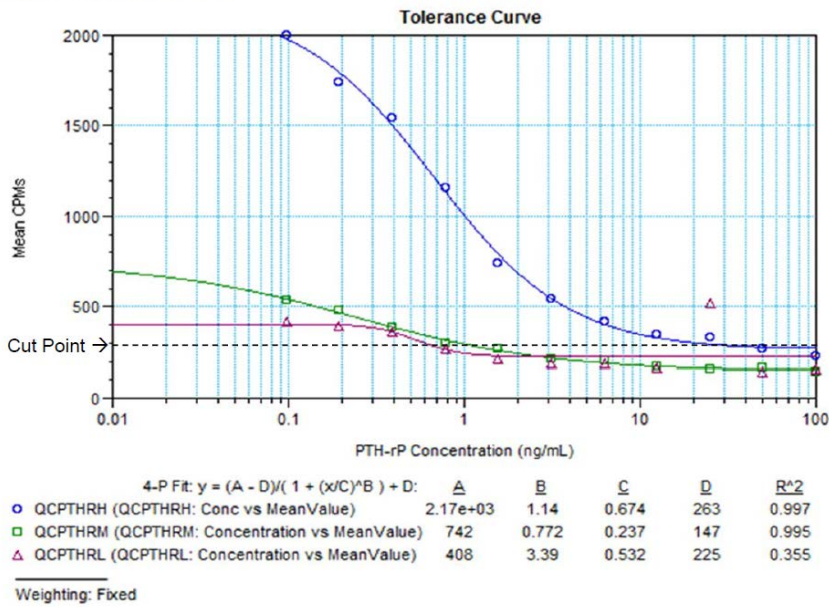
Run(s): 1, 2, 3, 4, 5, 6, 7, 8 (4/19/2016, 4/20/2016, 4/21/2016, 4/22/2016, 4/24/2016)  
 Techs: KLR, MAP2, MTL  
 Yellow cells = Duplicate %CV > 25  
 Pink cells = Analytical outlier(s)

Removal of duplicate CVs and outliers in the negative control assays yielded %CV values for all control runs that were within the  $\leq 25\%$  specification criteria.

**Reviewer Comment:** *The experiments performed to investigate precision were appropriately designed, and the data shown above demonstrate acceptable intra-assay and inter-assay precision, both meeting the specification of  $\%CV \leq 25\%$ . In the inter-assay precision data, the NC data initially did not meet the specification, but after removal of outliers, the specification was met.*

**Assay tolerance:** The highest concentration of PTHrP in the assay that could still allow the assay to read above the cut point was determined by spiking various concentrations of PTHrP peptide into the serum samples, and assaying with the positive control antibody preparations. The assay positive controls (QCPTHR<sub>L</sub>, QCPTHR<sub>M</sub>, QCPTHR<sub>H</sub>) were tested with spiked PTHrP at final concentrations of 0-100 ng/ml, approximating samples from patients. A dose-response curve was generated for each control antibody and % inhibition was calculated. PTHrP tolerance was determined by interpolation of the PTHrP concentration that inhibits the signal to the cut point for each level of the control antibody. Tolerance was considered acceptable if the QCPTHR<sub>H</sub> could tolerate a minimum of 33 ng/ml PTHrP and still produce a signal greater than the cut point.

Figure 5: Tolerance Curve



\*Dashed line added to graph to indicate approximate assay cut point of 157.1 cpm.

From the dose response curve (see above, copied from the submission), the ability of the anti-PTHrP antibody detection assay to tolerate the presence of PTHrP was greater than 100 ng/ml in the high positive control antibody level assay. The 100 ng/ml PTHrP was only able to inhibit the detection by 89.4%, and the cut point was never reached. In the case of the medium positive control antibody level, the assay was able to tolerate up to 12.5 ng/ml PTHrP, while the low positive control antibody level was able to tolerate only 3.125 ng/ml. Comparison of the % Inhibition to the confirmatory cut point of 23.2% suggests that all three concentrations of the positive control antibody could tolerate up to 0.391 ng/ml PTHrP, while still giving positive results in confirmatory assays (see Table 12: PTHrP Tolerance Data, not copied here, for brevity).

**Reviewer Comment:** It appears that the cut point is drawn incorrectly in the Tolerance graph above, though the curve lines seem to be plotted appropriately, in relation to the data given in Table 12. The derivation of >33 ng/ml as the cutoff for successful tolerance was not stated, however it is adequate in this case, as the normal human range for PTHrP is in the 14-27 pg/mL pg/ml range (see reference ranges for Quest Diagnostics, CPT Test Code 83519). By the stated acceptance criteria for the tolerance of their assay as exceeding 33 ng/ml PTHrP, the high antibody concentration achieved this aim – although the QCPTHRH antibody was never completely inhibited in binding to the level of the cut point, even with the 100 ng/ml highest concentration of added PTHrP. On the other hand, the QCPTHRM and QCPTHRL assays were not found to be as tolerant of added PTHrP. This result is generally acceptable due to their lower antibody concentrations as a result of higher dilution.

Assay linearity: The anti-PTHrP detection assay was evaluated for the ability to titrate positive samples below the assay cut point. Three high level positive controls were serially diluted 1:2 for ten times in normal serum, for evaluation in the assay. All three titrations successfully diluted below the cut point value (see Table 13, below, copied from the submission):

Table 13: Linearity Data (in cpm)

| Sample  | Val Run 2 |        |        | Mean (CPMs) | SD (CPMs) | % CV |
|---------|-----------|--------|--------|-------------|-----------|------|
|         | Val Run 1 | 1      | 2      |             |           |      |
| Neat    | 2887.6    | 2428.6 | 2514.3 | 2610.2      | 244.1     | 9.4  |
| 1:2     | 1854.6    | 1467.2 | 1450.3 | 1590.7      | 228.7     | 14.4 |
| 1:4     | 1165.8    | 852.4  | 913.5  | 977.2       | 166.1     | 17.0 |
| 1:8     | 694.5     | 493.0  | 571.2  | 586.2       | 101.6     | 17.3 |
| 1:16    | 454.5     | 370.4  | 354.0  | 393.0       | 53.9      | 13.7 |
| 1:32    | 344.6     | 288.4  | 369.3  | 334.1       | 41.5      | 12.4 |
| 1:64    | 336.4     | 287.4  | 331.4  | 318.4       | 27.0      | 8.5  |
| 1:128   | 240.8     | 223.9  | 349.2  | 271.3       | 68.0      | 25.1 |
| 1:256   | 244.4     | 223.3  | 264.7  | 244.1       | 20.7      | 8.5  |
| 1:512   | 260.8     | 235.3  | 235.0  | 243.7       | 14.8      | 6.1  |
| 1:1024  | 256.7     | 241.9  | 248.3  | 249.0       | 7.4       | 3.0  |
| QCPTHrN | 217.5     | 299.7  | 224.3  | 271.0       | 51.953    | 19.2 |
|         | 341.2     |        |        |             |           |      |
|         | 272.2     |        |        |             |           |      |
| QCPTHrL | 712.2     | 536.3  | 596.4  | 645.7       | 75.935    | 11.8 |
|         | 690.7     |        |        |             |           |      |
|         | 692.8     |        |        |             |           |      |
| QCPTHrM | 893.8     | 722.0  | 743.6  | 801.7       | 69.493    | 8.7  |
|         | 819.2     |        |        |             |           |      |
|         | 830.0     |        |        |             |           |      |
| QCPTHrH | 2863.2    | 2412.5 | 2394.1 | 2644.7      | 223.636   | 8.5  |
|         | 2758.6    |        |        |             |           |      |
|         | 2795.1    |        |        |             |           |      |

Cutpoint: 306.7 291.7 300.7

Run(s): 1, 2 (4/19/2016)

Tech: MAP2

Samples that are confirmed as true positives during confirmatory testing will be serially diluted to below the cut-point; the last dilution that yields a reading above the cut point will be regarded as the cross-reactive PTHrP ADA titer.

## **H. Anti-PTHrP NAb Detection Assay Validation (BioAgilytix study #BAL-15-227-027):**

The anti-PTHrP neutralizing antibody detection assay developed by BioAgilytix relies on the UMR-106 cell line, which express the receptor PTHR1 on their cell surfaces. Binding of PTHrP to these receptors activates PKC, which results in elevation of cAMP. The change of cAMP levels in UMR-106 cells is detected by a competitive ECL immunoassay kit. Therefore, neutralization of PTHrP by binding of antibody present in the culture medium would result in abrogation of the cAMP elevation, and consequent increase of the immunoassay signal detection. For assay validation, the surrogate positive control (SPC) consisted of a commercial rabbit anti-human/rat/mouse PTHrP (1-34) positive control antibody (cat#H-056-04, Phoenix Pharmaceuticals). Four dilutions of the SPC were made, with final dilutions shown below (the MRD of 1:4, which was established during qualification, is included in the final dilutions shown below):

HPC – 1:120

MPC – 1:240

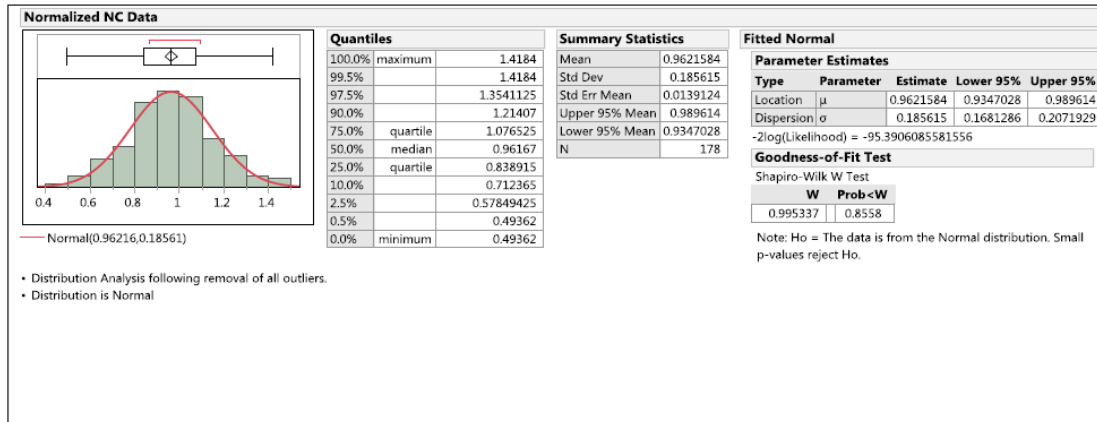
LPC1 – 1:500

**Reviewer Comment:** Assay development data supporting the selected concentration of the PTHrP dose (dose-response curve analysis) used for stimulation of the UMR-106 cell line in the PTHrP cross-reactive ADA NAb assay was not provided. The PTHrP cell stimulation level should be demonstrated as expected to be sensitive to neutralization by low levels/titers of spiked anti-PTHrP SPC antibodies. This dose-response information was also missing from the report initially supplied by the sponsor for the BioAgilytix abaloparatide ADA NAb assay reviewed above, but was supplied upon request. Due to review time constraints, PTHrP dose-response curve will not be requested.

**Assay cut point determination:** The ACP was established by assaying 64 individual disease-state serum samples obtained from placebo-treated patients. Assays were run in groups of 32, three times, for 6 runs total, by 3 analysts. The NC was run at a minimum of 8 replicates on each plate. All data points were normalized by the formula:

$$\text{Normalized value} = \text{Sample RLU} / \text{Mean Negative Control RLU}$$

Distribution analysis of the runs by JMP 12.0 software identified 15 outliers. Six outliers accounted for two biological outliers. Following outlier exclusion, the data showed normal distribution (see figure below, copied from the submission):



One-way ANOVA analysis found that the normalized data across the 6 runs were statistically different in variances (see figure below, copied from the submission):

| Analysis of Variance |     |                |             |         |          |
|----------------------|-----|----------------|-------------|---------|----------|
| Source               | DF  | Sum of Squares | Mean Square | F Ratio | Prob > F |
| Run No.              | 5   | 1.1854686      | 0.237094    | 8.3010  | <.0001 * |
| Error                | 172 | 4.9126991      | 0.028562    |         |          |
| C. Total             | 177 | 6.0981677      |             |         |          |

| Means for Oneway Anova |        |         |           |           |           |
|------------------------|--------|---------|-----------|-----------|-----------|
| Level                  | Number | Mean    | Std Error | Lower 95% | Upper 95% |
| 1                      | 30     | 0.89471 | 0.03086   | 0.8338    | 0.9556    |
| 2                      | 28     | 1.06332 | 0.03194   | 1.0003    | 1.1264    |
| 3                      | 31     | 1.05950 | 0.03035   | 0.9996    | 1.1194    |
| 4                      | 31     | 0.95536 | 0.03035   | 0.8954    | 1.0153    |
| 5                      | 29     | 0.83524 | 0.03138   | 0.7733    | 0.8972    |
| 6                      | 29     | 0.96439 | 0.03138   | 0.9024    | 1.0263    |

The sponsor analysis of the normalized data indicated that a floating cut point delta (the difference between the 99<sup>th</sup> quantile of samples and the NC mean) was required for the evaluation of each assay plate. The 99<sup>th</sup> quantile value was determined by analysis of non-normalized RLU values, which found that after removal of outliers, the data met the assumption of normal distribution (see Figure 3, below, copied from the submission) with the 99<sup>th</sup> percentile represented by 6047.7 RLU:

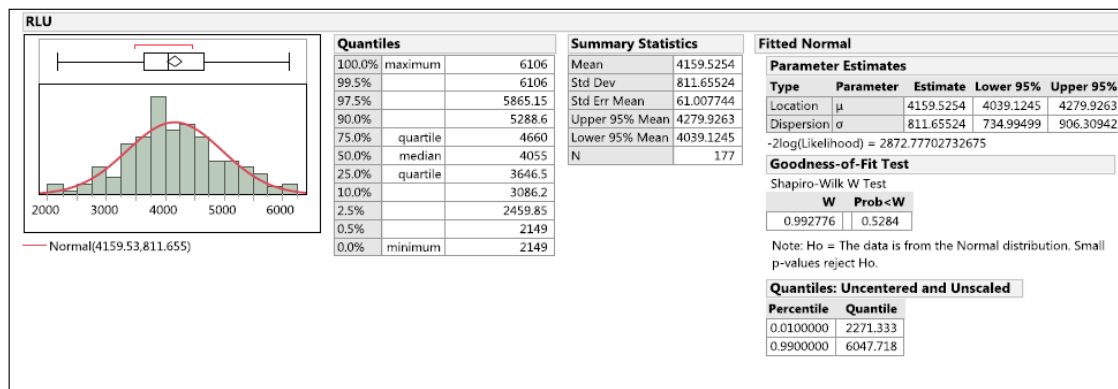


**Figure 3. Final Distribution of Cut Point Samples**

Following removal of Outliers, the Relative Light Units (RLU) data of the cut-point samples met the assumption of normality (Shapiro-Wilk Prob > F < 0.001). The Quantiles table shows the 99 percentile of 6047.7 RLU

The NC mean was calculated from non-normalized RLU values of the NC assays, showing a mean RLU value of 4405.98 (see Figure 4: Negative Control Distribution Analysis, not reproduced here for brevity), for the determination of NC RLU mean.

The cut point delta was therefore calculated as:  $6047.7 - 4406 = 1641.7$

Cut points for each plate are thus calculated by adding the mean NC RLU of each plate to the cut point delta value of 1641.7 (see Table 5 for validation plate cut point determinations using the cut point delta (not reproduced here for brevity)). The false positive rate of the placebo samples was 2 out of 177 samples after outlier exclusion, thus the false positive rate was 1.13% (see Table 6, below, copied from the submission):

**Table 6. Cut Point Sample Results**

| Summary (expected False Positive 1%) |      |
|--------------------------------------|------|
| Total Samples                        | 192  |
| Total Outliers                       | 15   |
| Remaining                            | 177  |
| > Cutpoint (non-outliers)            | 2    |
| % False Positive                     | 1.13 |

**Reviewer Comment:** *The method for calculation of the cut point for each analytical plate is appropriate because it allows for approximately a 1% false positive rate, which is suitably stringent, per recommendations in current Agency Immunogenicity Validation guidance. As the NAb assay is the highest tier assay, and thus is less likely to encounter false-positive samples, as compared to the screening, and confirmatory assays the 1% FP rate is appropriate.*

**Assay sensitivity:** To investigate assay sensitivity, the surrogate Positive Control (SPC) antibody was spiked into assay matrix at 1:16 dilution (4X) then serially diluted 2-fold. Dilution samples were evaluated by the anti-PTHrP neutralizing antibody detection assay in the absence and presence of 600 pg/ml PTHrP. The Sensitivity was defined as the lowest concentration of antibody that consistently produced signal above the cut point (see Table 7, below, copied from the submission):

**Table 7. Antibody Sensitivity**

| 4X MRD SPC Dilution | Adjusted SPC Dilution | Analyst 1 |                |          | Analyst 2 |                |          | Analyst 3 |                |          |
|---------------------|-----------------------|-----------|----------------|----------|-----------|----------------|----------|-----------|----------------|----------|
|                     |                       | Mean RLU  | Plate Cutpoint | Results  | Mean RLU  | Plate Cutpoint | Results  | Mean RLU  | Plate Cutpoint | Results  |
| 16                  | 64                    | 12455     | 5841.6         | Positive | 13842.5   | 5790.2         | Positive | 9738      | 5787.1         | Positive |
| 32                  | 128                   | 9010      |                | Positive | 8489.5    |                | Positive | 5764.5    |                | Negative |
| 64                  | 256                   | 6133      |                | Positive | 5955      |                | Positive | 5031.5    |                | Negative |
| 128                 | 512                   | 4819      |                | Negative | 4304      |                | Negative | 3833      |                | Negative |
| 256                 | 1024                  | 4394      |                | Negative | 4290      |                | Negative | 3371.5    |                | Negative |
| 512                 | 2048                  | 3920.5    |                | Negative | 3506      |                | Negative | 3043      |                | Negative |
| 2,048               | 8192                  | 4206      |                | Negative | 3695      |                | Negative | 3072.5    |                | Negative |
| 8,192               | 32768                 | 3985.5    |                | Negative | 3782      |                | Negative | 3142      |                | Negative |

*Adjusted SPC is the dilution of SPC in the assay plate. Final Sensitivity was calculated based on the assay MRD of 4-fold.*

The sensitivity of the assay was determined to be the SPC antibody dilution of 1:64 – BioAgilytix notes that the lower dilutions of the positive control will likely lead to readings below detection.

**Reviewer Comment:**

*As noted for the BioAgilytix abaloparatide NAb assay reviewed above, the current report also defines sensitivity as a titer of the SPC antibody. Although previously the Immunogenicity Team had asked the sponsor to provide a calculation of the assay sensitivity as mass units per mL of undiluted serum to bring that value into alignment with the Agency Immunogenicity validation guidance, the necessity of that calculation here is unclear, based upon the reported detection of*

low-titer ADA only and the unknown relationship between the SPC and the disease-state human ADA antibody preparations.

**Assay specificity:** The reactivity of human IgG in the assay was evaluated to determine specificity. Three IgG concentrations were used: 10, 1.0, 0.1 µg/ml were spiked into the human serum pool (NC) for evaluation in the presence of 600 pg/ml PTHrP. The baseline was NC without IgG. Assay results are shown in Table 8, copied from the submission, below:

**Table 8. Specificity Results**

| Condition                                                | RLU   | Mean RLU | StDev  | CV(%) | Results<br>RLU Mean > CP =<br>Positive | Cutpoint |
|----------------------------------------------------------|-------|----------|--------|-------|----------------------------------------|----------|
| IgG 10ug/mL                                              | 4253  | 3990.5   | 371.2  | 9.3   | Negative                               | 5378.7   |
|                                                          | 3728  |          |        |       |                                        |          |
| *IgG 1.0 ug/mL                                           | 17200 | 16273.5  | 1310.3 | 8.1   | Positive                               |          |
|                                                          | 15347 |          |        |       |                                        |          |
| IgG 0.1 ug/mL                                            | 3726  | 3743.5   | 24.7   | 0.7   | Negative                               |          |
|                                                          | 3761  |          |        |       |                                        |          |
| *High signal is atypical. the average HPC RLU was 7697.8 |       |          |        |       |                                        |          |

The specificity samples with 10 and 0.1 µg/ml IgG were recorded below the cut point, and considered negative. The mid IgG condition yielded atypically high signals, according to the data.

**Reviewer comment:** *The addition of non-specific IgG at a concentration as high as 10 µg/ml into the assay did not cause the assay to read positive (above the cut point), supporting the specificity of the assay for PTHrP-specific antibodies. This is an acceptable result.*

**Assay drug tolerance:** The presence of PTHrP in the assay from patient serum may theoretically hamper the accuracy of the readout; therefore to evaluate the potential for this effect, the positive controls were treated with various concentrations of PTHrP, and compared to samples treated with the nominal PTHrP concentration of 600 pg/ml (see Table 9, below, copied from the submission):

**Table 9 Drug Tolerance Results**

| Name            | PTHrP [pg/mL] | Mean    | Std Dev | CV (%) | Result   |
|-----------------|---------------|---------|---------|--------|----------|
| HPC             | 600           | 7697.8  | 398.0   | 5.2    | Positive |
| HPC-1.5xPTHrP   | 900           | 5632.0  | 605.3   | 10.7   | Positive |
| HPC 2x PTHrP    | 1200          | 14708.0 | 3708.1  | 25.2   | Positive |
| HPC 4X PTHrP    | 2400          | 8040.0  | 6320.1  | 78.6*  | ND       |
| LPC1            | 600           | 4632.5  | 212.1   | 4.6    | Negative |
| LPC 1.5X PTHrP  | 900           | 3417.0  | 151.3   | 4.4    | Negative |
| LPC 2X PTHrP    | 1200          | 3825.0  | 101.8   | 2.7    | Negative |
| LPC1 4X PTHrP   | 2400          | 2299.5  | 303.3   | 13.2   | Negative |
| LPC2            | 600           | 4304.5  | 368.4   | 8.6    | Negative |
| LPC2 1.5X PTHrP | 900           | 2838.0  | 137.2   | 4.8    | Negative |
| LPC2 2X PTHrP   | 1200          | 3123.5  | 417.9   | 13.4   | Negative |
| LPC2 4X PTHrP   | 2400          | 7868.0  | 8107.7  | 103.0* | ND       |

Table 9. \* ND = not determined, samples had High CVs and results were inconclusive.

**Reviewer Comment:** The results of the tolerance assay showed that PTHrP concentrations of more than 600 pg/ml, if present in the serum samples, may have negative impact on the ability of the assay to detect neutralizing antibodies.

**Assay Selectivity:** Ten placebo-treated human serum samples were tested unspiked, and spiked with the HPC (1:30) and LPC1 (1:125) dilution of surrogate positive control antibodies, and evaluated at the 1:4 MRD. All samples spiked with the HPC tested positive, while only two of the ten samples spiked with the LPC tested positive. Interestingly, three of the ten samples tested positive without any spike of positive control antibody (see Table 10, below, copied from the submission).

**Table 10. Selectivity Results**

| Validation Run 5 |              |        |        |            | Run CP   | Validation Run 6 |              |         |        |            | Run CP   |
|------------------|--------------|--------|--------|------------|----------|------------------|--------------|---------|--------|------------|----------|
| Sample ID        | 4X SPC Spike | Mean   | CV (%) | % Recovery | 6795.5   | Sample ID        | 4X SPC Spike | Mean    | CV (%) | % Recovery | 6620.4   |
| NC               | 0            | 5153.8 | 12.8   | 100.0      | Negative | NC               | 0            | 4978.7  | 13.2   | 100.0      | Negative |
| HPC              | 1:30         | 9723.0 | 6.2    | 100.0      | Positive | HPC              | 1:30         | 9601.0  | 10.8   | 100.0      | Positive |
| LPC1             | 1:125        | 7246.8 | 19.7   | 100.0      | Positive | LPC1             | 1:125        | 6081.0  | 19.7   | 100.0      | Negative |
| 22A206564        | 0            | 4617.0 | 4.2    | 89.6       | Negative | 22A208498-99     | 0            | 7979.5  | 2.1    | 160.3      | Positive |
|                  | 1:30         | 9723.5 | 14.9   | 100.0      | Positive |                  | 1:30         | 10121.5 | 1.0    | 105.4      | Positive |
|                  | 1:125        | 4417.0 | 24.2   | 61.0       | Negative |                  | 1:125        | 8152.0  | 5.5    | 134.1      | Positive |
| 22A203618        | 0            | 4347.5 | 18.8   | 84.4       | Negative | 22A211189        | 0            | 5690.0  | 6.7    | 114.3      | Negative |
|                  | 1:30         | 8462.5 | 18.7   | 87.0       | Positive |                  | 1:30         | 8644.0  | 19.1   | 90.0       | Positive |
|                  | 1:125        | 5415.5 | 6.5    | 74.7       | Negative |                  | 1:125        | 5627.5  | 4.9    | 92.5       | Negative |
| 22A207171        | 0            | 4549.5 | 20.4   | 88.3       | Negative | 22A211276-99     | 0            | 5933.0  | 12.0   | 119.2      | Negative |
|                  | 1:30         | 7001.5 | 4.1    | 72.0       | Positive |                  | 1:30         | 8025.5  | 11.0   | 83.6       | Positive |
|                  | 1:125        | 4392.0 | 4.1    | 60.6       | Negative |                  | 1:125        | 6473.0  | 0.3    | 106.4      | Negative |
| 22A204696        | 0            | 5011.0 | 11.7   | 97.2       | Negative | 22A205759        | 0            | 6458.5  | 6.3    | 129.7      | Negative |
|                  | 1:30         | 8921.0 | 14.4   | 91.8       | Positive |                  | 1:30         | 9540.0  | 10.9   | 99.4       | Positive |
|                  | 1:125        | 5466.5 | 8.8    | 75.4       | Negative |                  | 1:125        | 7583.5  | 0.8    | 124.7      | Positive |
| 22A203830        | 0            | 7722.0 | 3.5    | 149.8      | Positive | 22A206870        | 0            | 7073.5  | 15.8   | 142.1      | Positive |
|                  | 1:30         | 8505.0 | 3.7    | 87.5       | Positive |                  | 1:30         | 9977.0  | 4.6    | 103.9      | Positive |
|                  | 1:125        | 5814.5 | 5.7    | 80.2       | Negative |                  | 1:125        | 6574.5  | 15.3   | 108.1      | Negative |

The final dilution of positive control antibody in the assay plate is 1:120 for HPC and 1:500 for LPC1.

%Recovery = (mean signal for spiked sample/mean signal for respective positive control) x 100. Bolded samples were positive without spike.

**Reviewer comment:** The results of the assay showed that NAb against PTHrP could be detected in the matrix of human serum samples. Furthermore, the magnitude of the signal did not seem to be unduly reduced by the presence of the human serum matrix, as all samples spiked with the HPC returned readings reflective of recovery rates within 30% of the values obtained by the respective positive control. Furthermore, there were no instances of negativity in the HPC-spiked samples that were accompanied by positivity in the LPC1-spiked reading, and all HPC-spiked readings returned readings of greater magnitude to their accompanying LPC1-spiked reading. These are acceptable results, supporting assay validation.

**Intra-assay precision:** The intra-assay precision was tested by reading concentrations of the positive and negative control. The intra-assay evaluations were found to be within the target

acceptance criteria, with results largely consistent with the required ranking relationship: HPC>MPC>LPC1/2>NC (see Tables 11 and 12, reproduced from the submission, below).

**Table 11. Intra-Assay Evaluation of Antibody Controls**

| Validation Run # | Plate Cutpoint | Control ID | Intra-Assay Mean | Intra-Assay St.Dev | Intra-Assay %CV | Cutpoint Result |
|------------------|----------------|------------|------------------|--------------------|-----------------|-----------------|
| 1                | 5841.6         | HPC        | 7730.6           | 655.4              | 8.5             | Positive        |
|                  |                | MPC        | 6339.9           | 405.8              | 6.4             | Positive        |
|                  |                | LPC1       | 5764.3           | 512.0              | 8.9             | Negative        |
|                  |                | LPC2       | 5681.3           | 375.3              | 6.6             | Negative        |
| 2                | 5790.2         | HPC        | 8875.1           | 541.6              | 6.1             | Positive        |
|                  |                | MPC        | 7023.3           | 552.1              | 7.9             | Positive        |
|                  |                | LPC1       | 6137.8           | 418.4              | 6.8             | Positive        |
|                  |                | LPC2       | 5834.6           | 309.6              | 5.3             | Positive        |
| 3                | 5787.1         | HPC        | 8124.6           | 446.0              | 5.5             | Positive        |
|                  |                | MPC        | 5734.8           | 461.6              | 8.0             | Negative        |
|                  |                | LPC1       | 5985.5           | 549.0              | 9.2             | Positive        |
|                  |                | LPC2       | 5072.8           | 282.1              | 5.6             | Negative        |
| 4                | 5378.7         | HPC        | 7697.8           | 398.0              | 5.2             | Positive        |
|                  |                | MPC        | 5035.0           | 173.3              | 3.4             | Negative        |
|                  |                | LPC1       | 4632.5           | 183.8              | 4.0             | Negative        |
|                  |                | LPC2       | 4304.5           | 515.5              | 12.0            | Negative        |
| 5                | 6795.5         | HPC        | 9723.0           | 604.6              | 6.2             | Positive        |
|                  |                | MPC        | 8381.0           | 1634.0             | 19.5            | Positive        |
|                  |                | LPC1       | 7246.8           | 1426.8             | 19.7            | Positive        |
|                  |                | LPC2       | 5812.0           | 608.0              | 10.5            | Negative        |
| 6                | 6620.4         | HPC        | 9601.0           | 1034.4             | 10.8            | Positive        |
|                  |                | MPC        | 7879.3           | 659.1              | 8.4             | Positive        |
|                  |                | LPC1       | 6081.0           | 1197.9             | 19.7            | Negative        |
|                  |                | LPC2       | 5179.8           | 396.0              | 7.6             | Negative        |
| 7                | 9863.0         | HPC        | 14132.0          | 1534.4             | 10.9            | Positive        |
|                  |                | MPC        | 10881.0          | 336.6              | 3.1             | Positive        |
|                  |                | LPC1       | 10087.0          | 582.7              | 5.8             | Positive        |
|                  |                | LPC2       | 8980.0           | 53.7               | 0.6             | Negative        |

**Table 12. Intra-Assay Evaluation of Negative Controls**

| Validation Run # | Plate Cutpoint | Intra-Assay Mean | Intra-Assay St.Dev | Intra-Assay %CV |
|------------------|----------------|------------------|--------------------|-----------------|
| 1                | 5841.6         | 4199.9           | 732.3              | 17.4            |
| 2                | 5790.2         | 4148.5           | 293.0              | 7.1             |
| 3                | 5787.1         | 4145.4           | 301.3              | 7.3             |
| 4                | 5378.7         | 3737.0           | 287.1              | 7.7             |
| 5                | 6795.5         | 5153.8           | 657.7              | 12.8            |
| 6                | 6620.4         | 4978.7           | 655.1              | 13.2            |
| 7*               | 9863.0         | 8221.3           | 695.8              | 8.5             |

\*For Validation run 7, n = 8. For all other runs n = 10.

**Inter-assay precision:** Each run included one or more of the HPC, MPC, LPC, and NC in at least duplicate, as assayed over 7 runs by 3 analysts in 2 days. The inter-assay evaluations for normalized data were within the criteria for each control, and %CV ranged from 9.8-13.5%. The results also followed the expected ranking of HPC>MPC>LPC1/2>NC (see Table 13 and 14, copied from the submission, below):

**Table 13. Inter-Assay Precision of Antibody Positive Controls**

| Validation Run #    | Analyst | HPC Normalized to Mean | MPC Normalized to Mean | LPC1 Normalized to Mean | LPC2 Normalized to Mean |
|---------------------|---------|------------------------|------------------------|-------------------------|-------------------------|
| 1                   | JNN     | 1.7160                 | 1.4505                 | 1.4853                  | 1.2431                  |
| 1                   | JNN     | 2.1203                 | 1.6717                 | 1.2807                  | 1.2510                  |
| 2                   | DLM     | 2.3192                 | 1.7920                 | 1.4991                  | 1.2332                  |
| 2                   | DLM     | 2.3211                 | 1.5516                 | 1.5328                  | 1.3976                  |
| 3                   | DLM     | 1.9682                 | 1.4674                 | 1.4672                  | 1.1982                  |
| 3                   | DLM     | 2.0244                 | 1.4949                 | 1.2187                  | 1.1022                  |
| 4                   | DLM     | 1.9529                 | 1.2879                 | 1.1707                  | 0.98716                 |
| 4                   | DLM     | 2.0752                 | 1.3548                 | 1.2510                  | 1.1266                  |
| 5                   | BLS     | 1.8190                 | 1.3972                 | 1.1904                  | 1.2833                  |
| 5                   | BLS     | 1.8109                 | 1.3811                 | 1.2385                  | 1.0538                  |
| 6                   | DLM     | 1.7157                 | 1.4492                 | 0.88798                 | 0.97375                 |
| 6                   | DLM     | 2.1309                 | 1.5848                 | 1.2025                  | 1.1451                  |
| 7                   | DLM     | 1.5870                 | 1.2946                 | 1.1768                  | 1.0969                  |
| 7                   | DLM     | 1.8509                 | 1.3525                 | 1.2771                  | 1.0877                  |
| Inter-Assay Mean    |         | 1.9580                 | 1.4664                 | 1.2771                  | 1.1557                  |
| Inter-Assay St. Dev |         | 0.223                  | 0.144                  | 0.172                   | 0.119                   |
| Inter Assay %CV     |         | 11.4                   | 9.8                    | 13.5                    | 10.3                    |

**Table 14. Inter-Assay Precision of Negative Controls**

|                     |        |
|---------------------|--------|
| NC Inter-Assay Mean | 0.9960 |
| NC Inter-Assay SD.  | 0.111  |
| NC Inter-Assay %CV  | 11.1   |

**Reviewer Comment:** *The assay appears to possess an appropriate inter-assay precision, as the %CV values calculated were all less than 15%. This is an acceptable level of precision.*

**Inter-operator precision (ruggedness):** Three operators were selected to run the assay, inter-operator %CV ranged from 4.6% to 13.2% (see Table 15, copied from the submission, below):

**Table 15. Inter-Operator Precision Summary Table**

| Result |                 | JNN     | BLS     | DLM     | Inter-Operator Mean |
|--------|-----------------|---------|---------|---------|---------------------|
| HPC    | Normalized Mean | 1.9181  | 1.8150  | 2.3201  | 2.0177              |
|        | SD              | 0.286   | 0.006   | 0.001   | 0.267               |
|        | CV(%)           | 14.9    | 0.3     | 0.1     | 13.2                |
| MPC    | Normalized Mean | 1.5611  | 1.3892  | 1.6718  | 1.5407              |
|        | SD              | 0.156   | 0.011   | 0.170   | 0.142               |
|        | CV(%)           | 10.0    | 0.8     | 10.2    | 9.2                 |
| LPC1   | Normalized Mean | 1.3830  | 1.2144  | 1.5160  | 1.3711              |
|        | SD              | 0.145   | 0.034   | 0.024   | 0.151               |
|        | CV(%)           | 10.5    | 2.8     | 1.6     | 11.0                |
| LPC2   | Normalized Mean | 1.2471  | 1.1686  | 1.3154  | 1.2437              |
|        | SD              | 0.006   | 0.162   | 0.116   | 0.073               |
|        | CV(%)           | 0.4     | 13.9    | 8.8     | 5.9                 |
| NC     | Normalized Mean | 0.98027 | 0.95949 | 1.04751 | 0.99575             |
|        | SD              | 0.030   | 0.012   | 0.092   | 0.046               |
|        | CV(%)           | 3.1     | 1.2     | 8.8     | 4.6                 |

**Reviewer Comment:** The assay appears to demonstrate an acceptable ruggedness. The inter-operator %CV values range from 13.2% to 4.6% throughout the evaluation of the positive control levels and the negative control.

**Freeze and thaw stability:** F/T stability assessment was performed using HPC, LPC1/2, and NC samples. Conditions included processing through F/T (-80±15°C for >12 hours, with 1 hour thaw at RT). F/T assessment results are shown in Tables 16 and 17, below, copied from the submission).

**Short-term stability:** Two sets of stability controls samples were assessed for bench-top (RT for 2.83 or 22.5 hours) and one set for refrigerator (22.5 hours) stability. The bench-stored HPC and LPC1 samples were generally within the acceptance criteria with recoveries between 103.5 and 116.0%, with a single unusually high reading of 137.8% recovery.

**Table 16. Short-Term and Freeze and Thaw Stability of Negative Control**

| Negative Control               | Mean | CV (%) | Results  |
|--------------------------------|------|--------|----------|
| Baseline                       | 8221 | 8.5    | Negative |
| F/T – 3 Cycles                 | 8906 | 7.7    | Negative |
| F/T – 5 Cycles                 | 8570 | 7.9    | Negative |
| Refrigerator (22 hrs. 30 min.) | 9911 | 7.2    | Positive |
| Bench Top A (22 hrs. 30 min.)  | 7400 | 5.1    | Negative |
| Bench Top B (2 hrs. 50 min.)   | 7936 | 7.0    | Negative |

**Table 17 Short-Term and Freeze and Thaw Stability of Positive Controls**

| Control | Stability Test              | Mean  | % CV | *% Recovery | Results<br>RLU Mean ><br>CP = Positive |
|---------|-----------------------------|-------|------|-------------|----------------------------------------|
| HPC     | Baseline                    | 14132 | 10.9 | N/A         | Positive                               |
|         | F/T - 3 Cycles              | 13543 | 7.4  | 95.8        | Positive                               |
|         | F/T - 5 Cycles              | 13904 | 4.4  | 98.4        | Positive                               |
|         | Refrigerator <sup>(1)</sup> | 16420 | 8.1  | 116.2       | Positive                               |
|         | Bench Top A <sup>(1)</sup>  | 14633 | 9.1  | 103.5       | Positive                               |
|         | Bench Top B <sup>(2)</sup>  | 14685 | 6.7  | 103.9       | Positive                               |
| LPC1    | Baseline                    | 10087 | 5.8  | N/A         | Positive                               |
|         | F/T - 3 Cycles              | 11448 | 7.8  | 113.5       | Positive                               |
|         | F/T - 5 Cycles              | 11252 | 10.5 | 111.5       | Positive                               |
|         | Refrigerator <sup>(1)</sup> | 13904 | 6.9  | 137.8       | Positive                               |
|         | Bench Top A <sup>(1)</sup>  | 11222 | 2.8  | 111.2       | Positive                               |
|         | Bench Top B <sup>(2)</sup>  | 11701 | 9.6  | 116.0       | Positive                               |
| LPC2    | Baseline                    | 8980  | 0.6  | N/A         | Negative                               |
|         | F/T - 3 Cycles              | 9348  | 2.5  | 104.1       | Negative                               |
|         | F/T - 5 Cycles              | 9429  | 8.4  | 105.0       | Negative                               |
|         | Refrigerator <sup>(1)</sup> | 13592 | 7.5  | 151.4       | Positive                               |
|         | Bench Top A <sup>(1)</sup>  | 8325  | 7.3  | 92.7        | Negative                               |
|         | Bench Top B <sup>(2)</sup>  | 7936  | 4.7  | 88.4        | Negative                               |

**Reviewer comment:** The NC samples interestingly had a positive reading after storage for 22.5 hours at refrigerator temperature, though all other F/T cycles and RT storage conditions tested

*for the NC did not result in positivity. This is acceptable, as the lone positive reading is explained by the false-positive rate built into the assay. The almost consistently negative readings of all conditions by the LPC2 sample (with only one exception, refrigerator storage) are explained by the supposition that the LPC2 sample was simply below the detection of the assay (even the baseline read negative).*

Long-term stability and Robustness: were previously established for antibodies stored at -60°C to -80°C, as indicated in Method Validation Report references 1-3. Additional data not supplied in submission.

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

/s/  
-----

WILLIAM H HALLETT  
04/06/2017

HAROLD L DICKENSHEETS  
04/06/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service Food and Drug  
Administration Center for Devices and  
Radiological Health  
Office of Compliance, Division of Manufacturing & Quality  
Respiratory, ENT, General Hospital, Ophthalmic Device Branch (REGO)

---

**Date:** February 27, 2016

**To:** Krishna Ghosh, CDER/OPQ/OLDF  
Krishnakali.Ghosh@fda.hhs.gov

Juandria Williams,  
CDER/OPQ/OLDF  
[Juandria.Williams@fda.hhs.gov](mailto:Juandria.Williams@fda.hhs.gov)  
[v](#)

Office of combination products at [combination@fda.gov](mailto:combination@fda.gov)

**RPM:** Krishnakali Ghosh

**Through:** Ronald Swann, Branch Chief, ASDB, DMQ, OC, CDRH. WO-66, Room 3456

Ronald L. Swann -S  
2017.03.01 17:33:55 -05'00'

---

**From:** Latoya Oliver-Powell, ASDB, DMQ, OC, CDRH. WO-66, Room 3464

**Applicant:** Radius Health, Inc.  
950 Winter St.  
Waltham, MA 02451  
FEI# 3012498539

**Application #** NDA208743

**Consult #** ICC#1600236

**Product Name:** Abaloparatide-SC

**Documentation Review:** No Additional Information Required

**Final Recommendation:** **Approval**

---

The Office of Compliance at CDRH received a consult request from CDER to identify and evaluate the relevant device constituent manufacturing facilities and determine acceptability to support the current application.

## **REGULATORY HISTORY**

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

### **Inspection Recommendation**

1. Vetter Pharma-Fertigung GmbH & Co. KG Ravensburg,  
Baden-Wuerttemberg, 88214 Germany FEI# 3005987757

Responsibility – This firm is involved in the manufacturing of the Abaloparatide-SC combination product.

Inspectional History – The most recent inspection was conducted July 18-July 26, 2016. This was a comprehensive Preapproval and GMP inspection which was conducted in accordance with Compliance Program Guidance Manual 7356.002 Drug Manufacturing Inspections; 7356.002A Sterile Drug Process Inspections; and 7382.845, Inspection of Medical Device Manufactures. No deficiencies were noted.

2. Ypsomed, AG  
Weissensteinstrasse 26  
Solothurn, CH-4503 Switzerland  
FEI# 3005170966

Responsibility – This firm is involved in the manufacturing of the Abaloparatide-SC combination product.

Inspectional History – The most recent inspection was conducted August 22-August 25, 2016. This was a comprehensive inspection conducted in accordance with 7382.845, Inspection of Medical Device Manufactures. No deficiencies were noted.

### **Inspection Recommendation**

3. Vetter Pharma-Fertigung GmbH & Co. KG  
Eisenbahnstrasse 2-4  
Langenargen, Germany  
FEI# 3002808846

Responsibility – This firm is involved in the manufacturing of the Abaloparatide-SC combination product.

Inspectional History – The most recent inspection was conducted February 13-February 20, 2016. This was a comprehensive inspection which was conducted in accordance with Compliance Program Guidance Manual 7356.002 Drug Manufacturing Inspections. No deficiencies were noted during this inspection; however the most recent device inspection is unknown. Therefore, CDRH cannot attest to the compliance of the firm as it relates to 21 CFR 820.

### **Inspection Recommendation**

4. Vetter Pharma Holbeinstrasse (HOL), 40 88212

Ravensburg, Germany

3003882331

Responsibility – This firm is involved in the manufacturing of the Abaloparatide-SC combination product.

Inspectional History – No EIR was provided for review; therefore CDRH cannot attest to the compliance of the firm as it relates to 21 CFR 820. CDRH Office of Compliance defers to CDER as it relates to the approvability of the application given the lack of information for this firm.

**DOCUMENTATION REVIEW**

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

**Management Control, 21 CFR 820.20**

The firm provided an organizational chart which appears to describe the organizational structure. It also appears to explain how it controls all levels of the structure.

The information provided by the firm appears to have adequately addressed the requirements of 21 CFR 820.20.

(b) (4)



(b) (4)



The summary provided by the firm appears to have adequately addressed the requirements of 21 CFR 820.30.

(b) (4)





The summary provided by the firm appears to have adequately addressed the requirements of 21 CFR 820.100.

**Installation, 21 CFR 820.170**

Installation is not required for this combination product.

**Servicing, 21 CFR 820.200**

Servicing is not required for this combination product.

MANUFACTURING



4 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

**Documentation Review Recommendation**

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality system Requirements showed no deficiencies. No additional information is required for the documentation review.

**OVERALL RECOMMENDATION**

As documented above, the consult request noted the need for an evaluation for four firms. Three EIR’s were provided out of the four sites listed. Two EIR’s documented device inspections and the other documented a drug inspection, only. There was no EIR provided for the last site.

Based on the information provided to the Office of Compliance for review, it appears that the application is approvable from the perspective of the compliance of Baden-Wurttemberg, Germany, VetterPharm, and Ypsomed site. CDRH defers to CDER as it relates to the approvability of the application based on the lack of information available for the Langenargen, Germany, and Ravensburg, Germany sites.

Additionally, CDRH Office of Compliance has reviewed summaries provided by the firm for the requirements under 21 CFR 820. Based on the summaries provided, it appears that the application is approvable in regards to the 820 regulation requirements. However, CDRH recommends a post approval inspection to be conducted.

Latoya Oliver-  
powell -S



Digitally signed by Latoya Oliver-powell S  
DN: c US o U.S. Government ou HHS  
ou FDA ou People  
0.9.2342.19200300.100.1.1.2000354592  
cn Latoya Oliver-powell S  
Date: 2017.02.28 13:02:56 -05'00'

Latoya Oliver-Powell

Prepared: LOliver-Powell: 11/3/16  
Reviewed: FMLast name: 03/01/2017

NDA 208743

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

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

/s/  
-----

THAO M VU  
03/03/2017  
upload on behalf of CDRH-OC

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: February 22, 2017

To: Hylton V. Joffe, MD  
Director  
**Division of Bone, Reproductive and Urologic Products (DBRUP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Marcia Williams, PhD  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Twanda Scales, RN, BSN, MSN/Ed.  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Jina Kwak, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG) and  
Instructions for Use (IFU)

Drug Name (established name): TYMLOS (abaloparatide)

Dosage Form and Route: Injection, for subcutaneous use

Application Type/Number: NDA 208743

Applicant: Radius Health, Inc.

## 1 INTRODUCTION

On March 30, 2016, Radius Health, Inc. submitted for the Agency's review a New Drug Application (NDA 208743) for abaloparatide Injection, for subcutaneous use indicated for the treatment of postmenopausal women with osteoporosis. The proposed dose is 80 mg, once daily, administered by subcutaneous self-injection, to the periumbilical region.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on June 8, 2016, and May 23, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for TYMLOS (abaloparatide) Injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed December 9, 2016.

## 2 MATERIAL REVIEWED

- Draft TYMLOS (abaloparatide) MG and IFU received on March 30, 2016, and received by DMPP and OPDP on February 10, 2017.
- Draft TYMLOS (abaloparatide) Prescribing Information (PI) received on March 30, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 10, 2017.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG and IFU the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The MG and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

28 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/  
-----

TWANDA D SCALES  
02/22/2017

JINA KWAK  
02/23/2017

MARCIA B WILLIAMS  
02/23/2017

LASHAWN M GRIFFITHS  
02/23/2017

---

## 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:** February 15, 2017

**Requesting Office or Division:** Division of Bone, Reproductive, and Urologic Products (DBRUP)

**Application Type and Number:** NDA 208743

**Product Name and Strength:** Tymlos (abaloparatide) Injection 3120 mcg/1.56 mL (2000 mcg/mL)

**Submission Date:** December 19, 2016

**Applicant/Sponsor Name:** Radius Health, Inc.

**OSE RCM #:** 2016-790-1

**DMEPA Primary Reviewer:** Walter Fava, RPh., MEd.

**DMEPA Team Leader:** Lolita White, PharmD.

---

#### 1 PURPOSE OF MEMO

The Division of Bone, Reproductive, and Urologic Products (DBRUP), requested that we review the revised container label and carton labeling for Tymlos (abaloparatide) (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>a</sup>

#### 2 CONCLUSION

The revised container label and carton labeling for Tymlos is acceptable from a medication error perspective. We have no further recommendations at this time.

---

<sup>a</sup> Smith J. Label and Labeling Review for PRODUCT NAME (NDA XXXXXX). 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); YYYY MON DD. 32 p. OSE RCM No.: XXXX-XX.

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

/s/  
-----

WALTER L FAVA  
02/15/2017

LOLITA G WHITE  
02/17/2017

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

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

**Memorandum**

**Date:** February 16, 2017

**To:** Samantha Bell  
Regulatory Project Manager  
Division of Bone, Reproductive and Urologic Products (DBRUP)

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

**Subject:** **NDA 208743**  
OPDP labeling comments for TYMLOS™ (abaloparatide) injection

---

As requested in DBRUP's consult dated May 23, 2016, OPDP has reviewed the draft PI and proposed carton and container labeling for TYMLOS™ (abaloparatide) injection.

OPDP has reviewed the proposed substantially complete version of the PI emailed by Samantha Bell on February 10, 2017. OPDP's comments are provided below.

OPDP has also reviewed the proposed carton and container labeling emailed by Samantha Bell on February 14, 2017 and we have no comments.

Our review of the Medication Guide and Instruction for Use will be conducted jointly with the Division of Medical Policy Programs and filed under separate cover.

Thank you for the opportunity to review and provide comments on these materials. If you have any questions, please contact Jina Kwak at (301) 796-4809 or via email [Jina.Kwak@fda.hhs.gov](mailto:Jina.Kwak@fda.hhs.gov)

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

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

/s/  
-----

JINA KWAK  
02/16/2017

## Clinical Inspection Summary

|                                   |                                                                                                                                                                      |
|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Date</b>                       | February 7, 2016                                                                                                                                                     |
| <b>From</b>                       | Roy Blay, Ph.D., Reviewer, GCPAB\OSI<br>Janice K. Pohlman, M.D., M.P.H., Team Leader, GCPAB\OSI<br>Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB\OSI               |
| <b>To</b>                         | DBRUP\Project Manager\Samantha Bell<br>DBRUP\Medical Officer\Stephen Voss<br>DBRUP\Team Leader\Theresa Kehoe<br>Division of Bone Reproductive, and Urologic Products |
| <b>NDA/BLA #</b>                  | NDA 208743                                                                                                                                                           |
| <b>Applicant</b>                  | Radius Health, Inc.                                                                                                                                                  |
| <b>Drug</b>                       | Abaloparatide                                                                                                                                                        |
| <b>NME (Yes/No)</b>               | Yes                                                                                                                                                                  |
| <b>Therapeutic Classification</b> | Standard Review                                                                                                                                                      |
| <b>Proposed Indication(s)</b>     | Treatment of postmenopausal women with osteoporosis                                                                                                                  |
| <b>Consultation Request Date</b>  | June 7, 2016                                                                                                                                                         |
| <b>Summary Goal Date</b>          | February 10, 2017                                                                                                                                                    |
| <b>Action Goal Date</b>           | March 30, 2017                                                                                                                                                       |
| <b>PDUFA Date</b>                 | March 30, 2017                                                                                                                                                       |

### 1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Alexandersen, Hala, Lau, and Russo were inspected in support of this NDA. The final classification of these clinical site inspections was No Action Indicated (NAI). In addition, the sponsor, Radius Health, was also inspected. The final classification of this sponsor inspection was Voluntary Action Indicated (VAI).

The clinical studies of Drs. Alexandersen, Hala, Lau, and Russo appear to have been conducted adequately. The isolated deviations noted during the sponsor inspection of Radius Health would not appear to have a significant effect on safety or efficacy considerations; therefore, the data generated by these clinical sites and submitted by the sponsor sites appear acceptable in support of the respective indication.

(b) (4)

. OSI recommends that the review division perform a sensitivity analysis for the data from Dr. Hala's site. (b) (4)

.

## 2. BACKGROUND

The Applicant submitted this NDA to support the use of abaloparatide for the treatment of postmenopausal women with osteoporosis. Protocol BA058-05-003 is entitled “A Randomized, Double-blind, Placebo-controlled, Comparative Phase 3 Multicenter Study to Evaluate the Safety and Efficacy of BA058 for Injection for Prevention of Fracture in Ambulatory Postmenopausal Women with Severe Osteoporosis and at Risk of Fracture”, and

Protocol BA058-05-005 is entitled “An Extension Study to Evaluate Six Months of Standard-of-Care Osteoporosis Management Following Completion of 18 Months of BA058 or Placebo Treatment in Protocol BA058-05-003”. Both protocols were inspected in support of this application.

### **Protocol BA058-05-003**

The primary objective of this study was to determine the safety and efficacy of abaloparatide-SC when compared to a matching placebo for prevention of vertebral fracture in otherwise healthy ambulatory postmenopausal women at risk of fracture from severe osteoporosis.

This was a randomized, double-blind, placebo-controlled, comparative Phase 3, multicenter, international study. Subjects were randomized to abaloparatide-SC 80 µg, a matching placebo, or teriparatide 20 µg for 18 months (Visit 9, End-of-Treatment).

The primary efficacy endpoint was the number of Abaloparatide-SC-treated patients showing new vertebral fractures at End-of-Treatment when compared to Placebo.

The study was conducted at 28 sites internationally and enrolled 2463 subjects.

According to the sponsor, this study demonstrated that abaloparatide treatment as compared to placebo, resulted in consistent and significant reductions in fracture rates, increased BMD, and a significant reduction in hypercalcemia as compared to teriparatide treatment.

### **Protocol BA058-05-005**

The primary objective was to confirm the efficacy of abaloparatide-SC for prevention of vertebral fracture up to Month 25 in patients who had completed Study BA058-05-003 and received 18 months of blinded treatment with abaloparatide-SC or placebo and then transitioned to 6 months of treatment with alendronate.

Subjects were dispensed 10 mg of alendronate daily in addition to standard-of-care treatment for osteoporosis for a six-month extension period. Safety parameters monitored included incidence and severity of adverse events, pathological changes in laboratory values, and fracture incidence.

Protocol BA058-05 enrolled subjects across 25 centers in the U.S worldwide. According to the sponsor's interim six-month report dated October 30, 2015, which analyzed 1139 subjects these studies demonstrated that subjects who received 18 months of abaloparatide-SC followed by 6 months of alendronate achieved clinically meaningful BMD and fracture benefit without altering the safety profile of alendronate as compared to patients who previously received 18 months of placebo. The final clinical study report would present analyses of outcomes of 12, 18, and 24 months of alendronate treatment.

Dr. Alexandersen of Vejle, Denmark (Site 103) enrolled a high % of screened patients (76%). He also has high enrollments in the two studies (155 in Study 003, 81 in Study 005) with a low reporting rate of non-serious adverse events (NSAEs), no history of inspections, and has demographics similar to the US.

Dr. Russo of Rio de Janeiro, Brazil (Site 121) enrolled large numbers of subjects in both studies (380 in Study 003, 171 in Study 005). He has minimal experience as a Principal Investigator (PI) with no history of inspections. These studies were conducted at a non-ICH site and have a low rate of NSAE reporting and a high discontinuation rate (29%). This site has an unusually large number of records (compared to other sites) that are missing values for all timing variables related to disposition events and records for end time points related to adverse event, concomitant medication, and medical history, such that it is unclear when disposition occurred or when this information was collected.

Dr. Lau of Hong Kong (Site 181) enrolled the largest number of subjects across the two studies (387 in Study 003, 204 in Study 005). She has minimal experience as a PI with no history of inspections. The research site is non-ICH. OSI has two records regarding Dr. Lau in its database.

(b) (4)

(b) (4)

OSI

subsequently included Dr. Lau's site for inspection as one of the clinical sites inspected in support of the review of this application.

Dr. Tomas Hala of Pardubice, Czech Republic (Site 131) was part of the same complaints encompassing Dr. Lau

(b) (4)

(b) (4)

**3. RESULTS (by site):**

| <b>Site #/<br/>Name of CI/<br/>Address</b>                                                                                                                             | <b>Protocol #/<br/># of Subjects<br/>(enrolled)</b> | <b>Inspection<br/>Dates</b> | <b>Classification</b> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------|
| 103/<br>Peter Alexandersen, M.D.<br>CCBR A/S<br>Orla Lehmannsgade 1, 3,<br>7100 Vejle, Denmark                                                                         | BA058-05-003/<br>155<br>BA058-05-005/<br>81         | 12-22 Sep 17                | NAI                   |
| 121/<br>Luis Russo, M.D., M.Sc., Ph.D.<br>CCBR Brasil – Centro de<br>Pesquisas e Analises Clinicas Ltda<br>Rua Mena Barreto,<br>33 Botafogo,<br>Rio de Janeiro, Brazil | BA058-05-003/<br>380<br>BA058-05-005/<br>171        | 10-18 Oct 17                | NAI                   |
| 181/<br>Edith Lau, M.D.<br>Center for Health and Medical<br>Research 6/F,<br>New World Tower II, Central Hong Kong,<br>Hong Kong                                       | BA058-05-003/<br>387<br>BA058-05-005/<br>204        | 12-24 Sep 2016              | NAI                   |
| 131/<br>Tomas Hala, M.D.<br>Center for Clinical and Basic<br>Research (CCBR) a.s.<br>Trida Miru 2800<br>53002 Pardubice, Czech Republic                                | BA058-05-003/<br>290<br>BA058-05-005/<br>136        | 7-18 Nov 17                 | NAI                   |
| Radius Health, Inc.<br>950 Winter Street<br>Waltham, MA<br>02451                                                                                                       | BA058-05-003<br>BA058-05-005                        | 2-14 Nov 17                 | VAI                   |

**Key to Compliance 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 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

**1. Peter Alexandersen, M.D.**

At this site for Protocol BA058-05-003, 203 subjects were screened, 155 subjects were randomized, and 131 subjects completed the study. From this study, 81 subjects were randomized into Protocol BA058-05-005, an extension of the previous study that is currently ongoing.

For Protocols BA058-05-003 and BA058-05-005, the consent forms for all 155 and 81 randomized subjects, respectively, were reviewed. All subjects signed the consent forms prior to any study-related procedures.

For Protocols BA058-05-003 and BA058-05-005, the records of 60 and 46 study subjects were reviewed, respectively. These records were compared with protocol requirements and the data listings. Record review included, but was not limited to inclusion/exclusion criteria, randomization, physical exams, medical histories, ECGs, collection of blood samples, 24 hour urine samples, DXA scans, X-rays, primary and secondary endpoint data, monitoring correspondence, adverse events, concomitant medications, and test article administration and accountability.

A Form FDA 483 was not issued at the conclusion of the inspection. These studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

## **2. Luis Russo, M.D., M.Sc., Ph.D.**

At this site for Protocol BA058-05-003, 631 subjects were screened, and 380 subjects were enrolled. From this study, 171 subjects were enrolled into Protocol BA058-05-005, an extension of the previous study.

For Studies 003 and 005, 96 and 55 subject records were reviewed, respectively. Review of the informed consent forms for these subjects indicated that informed consent was obtained appropriately prior to study participation.

Source documents were compared to data line listings for verification. Specific records and data verified, included, but were not limited to, financial disclosure statements, sponsor and monitor correspondence, delegation of responsibilities log, monitoring logs, protocol deviations, visit dates, randomization assignment, adverse events, primary and secondary endpoints, laboratory results, concomitant medications, test article accountability and storage, ECGs, DEXA scans, and radiology reports.

A Form FDA 483 was not issued at the conclusion of the inspection. These studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

## **3. Edith Lau, M.D.**

At this site for Protocol BA058-05-003, 659 subjects were screened, 387 subjects were randomized, 329 subjects completed the study, and 58 subjects discontinued the study. For Protocol BA058-05-005, an extension of the previous study, 213 subjects were screened, and 204 subjects were enrolled.

Review of the informed consent forms for 51 subjects in Protocol BA-058-05-003, and for 29 subjects in Protocol BA-058-05-005 indicated that informed consent was obtained appropriately prior to any study-related testing. All source documentation was captured on paper. This documentation was then transcribed to an electronic database. The records of 51 subjects were reviewed for Protocol BA-058-05-003, and the records of 23 subjects were reviewed for Protocol BA-058-05-005.

Review of these records included, but was not limited to, financial disclosure, site training logs, ethic review committee approvals, site signature and responsibility logs, medical histories, inclusion/exclusion criteria, laboratory results, concomitant medications, adverse events, incidence of clinical and radiological fractures, monitoring reports, and, drug accountability including receipt, inventory, dispensation, storage, and final accountability records.

A Form FDA 483 was not issued at the conclusion of the inspection. These studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

#### **4. Tomas Hala, M.D.**

At this site for Protocol BA058-05-003, 492 subjects were screened, and 290 subjects were randomized into the study. From this study, 136 subjects were enrolled into Protocol BA058-05-005, an extension of the previous study.

For Protocol BA058-05-003, the study records and informed consent forms for 33 subjects were reviewed along with the study records of 15 subjects continuing from Protocol BA058-05-003 into Protocol BA058-05-005. These subjects signed the consent forms prior to any study-related procedures. The records of six subjects who failed screening were also reviewed.

For Protocols BA058-05-003 and BA058-05-005, source documents were compared with the data listings. Records reviewed for Protocol BA058-05-003 included but were not limited to screening and enrollment criteria, informed consent forms, medical histories (obtained verbally by the investigator), laboratory values, previous use of bisphosphonate products, DXA examinations, x-ray results confirming previous fracture, BMD scores, ECG results, physical exams, vital signs, test article exposure, hypotensive incidences, and heights and weights for BMI calculations. Records reviewed for Protocol BA058-05-005 included but were not limited to ECG results, concomitant medications adverse event reporting, protocol deviations and violations, vital signs, randomization and treatment assignment, and subject diaries. Review of records of study training, monitoring activities, financial disclosure, and test article accountability and storage were conducted for both protocols.

A Form FDA 483 was not issued at the conclusion of the inspection. These studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

## 5. Radius Health, Inc.

The inspection audited Protocols BA058-05-003 and BA058-05-005 and focused on the following clinical investigators: Drs. Alexandersen, Russo, Lau, and Hala.

The inspection reviewed the following which included, but were not limited to, organizational charts, standard operating procedures, monitor selection and training, monitoring plans and reports, quality assurance, adverse event reporting, transfer of obligations, correspondence, FDA 1572s, financial disclosure forms, electronic case report forms (eCRFs), safety plans, and test article accountability. A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection which noted that the transfer of obligations to a contract research organization was not described in writing for Protocol BA058-05-003. Specifically, Work Statement plans for pharmacovigilance, clinical monitoring, and clinical study management were not approved until after the study was started. A second observation noted that the study was not properly monitored. Of five clinical sites reviewed, three began screening subjects prior to approval of the monitoring guidelines with one site randomizing their first subject prior to the first interim monitoring visit.

Radius responded in writing to these observations on the Form 483 in a letter dated December 2, 2016. Radius acknowledged the observations and did not dispute the facts presented. Radius stated that the observations did not affect either subject safety or data integrity; however, Radius stated it would implement corrective actions via SOPs and appropriate training to prevent such observations from occurring in future studies.

The sponsor appears to have satisfactorily addressed the observations on the Form FDA 483. Notwithstanding these deficiencies, the studies appear to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

(b) (4)



*{See appended electronic signature page}*

Roy Blay, Ph.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

CC:

Central Doc. Rm.\NDA 208743

DBRUP\Division Director\Hylton Joffe

DBRUP\Team Leader\Theresa Kehoe

DBRUP\Medical Officer\Stephen Voss

DBRUP\Project Manager\Samantha Bell

OSI\DCCE\Division Director\Ni Khin

OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew

OSI\DCCE\GCPAB\Team Leader\Janice Pohlman

OSI\DCCE\GCPAB\Reviewer\Roy Blay

OSI\DCCE\Program Analysts\Joseph Peacock\Yolanda Patague

OSI\Database Project Manager\Dana Walters

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

/s/  
-----

ROY A BLAY  
02/08/2017

JANICE K POHLMAN  
02/09/2017

KASSA AYALEW  
02/09/2017

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Pharmacovigilance Memo**

**Date:** February 8, 2017

**Reviewers:** Samantha Cotter, PharmD, BCPS, FISMP  
Peter Waldron, MD (Medical Officer)  
Division of Pharmacovigilance (DPV) II

**Team Leader:** Neha Gada, PharmD, BCPS  
DPV II

**Product Name:** Proposed Trade Name Tymlos (Abaloparatide)

**Subject:** Enhanced Pharmacovigilance Protocol and Targeted  
Questionnaire

**Application Type/Number:** NDA 208743

**Applicant/Sponsor:** Radius Health Inc.

**OSE RCM #:** 2016-2680

## 1 INTRODUCTION

This memo is the Division of Pharmacovigilance (DPV) appraisal of the draft enhanced pharmacovigilance protocol proposed by Radius Pharmaceuticals, Inc. for the Division of Bone, Reproductive, and Urologic Products (DBRUP) to consider in their negotiations with the sponsor. (b) (4)

The full draft protocol is appended in Section 5 of this memo.

## 2 BACKGROUND

Abaloparatide is a recombinant 34-amino acid peptide, including 41% homology to human parathyroid hormone (PTH) 1-34 and 76% homology to human parathyroid hormone-related peptide 1-34. Abaloparatide binds to the PTH1 receptor (PTHR1) to activate the cAMP signaling pathway to increase bone formation, bone mass and bone strength. Abaloparatide is now undergoing FDA review (PDUFA date March 30, 2017), for the indication of treatment of postmenopausal women with osteoporosis to reduce vertebral and nonvertebral fractures. The recommended dose is 80 mcg administered subcutaneously once daily. Abaloparatide has not been approved outside the US. The sponsor of abaloparatide is seeking approval for use in the treatment of postmenopausal women with osteoporosis at high risk for fracture. Currently, there is one PTH analog available, teriparatide (Forteo), for the treatment of osteoporosis.

Preclinical studies show a dose- and treatment duration-dependent, increased risk for osteosarcoma in rats (but not in monkeys) at 3-58 times higher systemic exposure than in humans. The bone tumors in rats occurred in association with a large increase in bone mass and focal osteoblast hyperplasia which is the hypothetical, biological mechanism for the risk for osteosarcoma. It is also hypothesized that the rat skeleton is more sensitive than monkey or human skeletons to the pharmacological effects of parathyroid hormone (PTH) in the formation of new bone and osteosarcomas. Since bone metabolism in rats differs from that in humans, the relevance of the animal finding to humans is uncertain. However, FDA has previously approved two other parathyroid hormone agents: 1) teriparatide (Forteo) a recombinant human parathyroid hormone analog (1-34) for the treatment of osteoporosis, and 2) parathyroid hormone (Natpara) for the treatment of hypoparathyroidism (see Appendix A for relevant Natpara label information). Both of these agents also showed a higher risk of osteosarcoma in rodents. Both products have a boxed warning to mitigate the potential risk of osteosarcoma in humans.

As part of a prospective roadmap for pharmacovigilance activities during a product's life cycle safety management, the Division of Pharmacovigilance-II (DPV-II) is recommending performance of enhanced pharmacovigilance (EPV) for Tymlos, trade name for abaloparatide.

## 3 MATERIALS REVIEWED

(b) (4)

26 Pages 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/  
-----

SAMANTHA A COTTER  
02/08/2017

PETER E WALDRON  
02/08/2017

NEHA GADA  
02/08/2017

**M E M O R A N D U M**

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

---

DATE: December 12, 2016

TO: Hylton V. Joffe, MD., M.M.Sc.  
Director  
Office of New Drug (OND), Office of Drug Evaluation  
III/Division of Bone, Reproductive, and Urologic  
Products (DBRUP)

And

Dennis Bashaw, PharmD., M.P.H.  
Director  
Office of Translational Sciences/Office of Clinical  
Pharmacology/Division of Clinical Pharmacology-III.

FROM: Hasan Irier, Ph.D.  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance  
Office of Translational Sciences

THROUGH: Elise Murphy  
Deputy Director (Acting)  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance  
Office of Translational Sciences

SUBJECT: Review of Establishment Inspection Report (EIR)  
covering NDA 208743, Abaloparatide SC, sponsored by Radius  
Health, Inc., 950 Winter Waltham, MA 02451 USA

---

**Inspection Summary:**

At the request of the Office of Study Integrity and Surveillance (OSIS), Office of Translational Sciences (OTS) assigned a clinical inspection to the Office of Regulatory Affairs for PRA Health Sciences Corp. Marlton, NJ 08053-2047 for NDA 208743(Abaloparatide SC). This reviewer recommends accepting Study BA058-05-016 for further Agency (FDA) review.

**Inspected Study:**

| Application | Study        | Study Site                                                                             | Sponsor                                               | Recommendation |
|-------------|--------------|----------------------------------------------------------------------------------------|-------------------------------------------------------|----------------|
| NDA 208743  | BA058-05-016 | <b>Site#1:</b><br>PRA Health Sciences Corp.<br>Lenexa, KS 66219<br>Phone: 913-410-2000 | Radius Health, Inc., 950 Winter Waltham, MA 02451 USA | Acceptable     |
|             |              | <b>Site #2:</b><br>PRA Health Sciences Corp.<br>Marlton, NJ 08053-2047                 |                                                       | Acceptable     |

**Study Title:** "A randomized, open label, single-dose, 2-way crossover study to determine the bioequivalence of abaloparatide administered subcutaneously from two similar pen injectors to healthy postmenopausal women sponsored by Radius health, Inc. under Investigational New Drug (IND) 073176"

**Study Dates:** 01/12/2016 to 02/10/2016

**Study Site #1:** During August 8-12, 2016, ORA investigator Vickie J Kanion audited the clinical study BA058-05-016 at the PRA Health Sciences Corp. Marlton, Lenexa, KS 66219. The audit included a thorough review of issues related to training, IRB approval, the relevant protocol, subject consent forms, subject records, and drug accountability. Following the inspection, no objectionable condition was found, and the ORA investigator did not issue a Form FDA 483.

**Study Site #2:** During October 12-20, 2016, ORA investigator Loretta Nemchik audited the clinical study BA058-05-016 at the PRA Health Sciences Corp. Marlton, NJ 08053. The audit included a thorough review of issues related to training, IRB approval, the relevant protocol, subject consent forms, subject records, and drug accountability. Following the inspection, no significant objectionable condition or findings were observed. No Form FDA 483, Inspectional Observations was issued to any of the sites.

**Recommendation:**

As a result of no inspectional findings, this reviewer

concludes that the data from the audited study BA058-05-016 are reliable, and recommends accepting the data from study BA058-05-016 for further Agency (FDA) review.

Hasan A. Irier, Ph.D.  
Division of Generic Drug Bioequivalence Evaluation (DGDBE)  
Office of Study Integrity and Surveillance (OSIS)  
Office of Translational Sciences (OTS)

Young Mbon Choi, Ph.D.  
Team Lead  
OSIS, DGDBE

Elise Murphy  
Deputy Director (Acting)  
OSIS, DGDBE

**Final Site Classification:**

**NAI - PRA Health Sciences Corp. Lenexa, KS ( Site #1)**  
**FEI: 3007467677**

**NAI - PRA Health Sciences Corp. Marlton, NJ ( Site #2)**  
**FEI: 3012575890**

CC:  
OSIS/Kassim/Taylor/Haidar/Miller/Nkah/Fenty-Stewart/Kadavil  
OSIS/DGDBE/Cho/Murphy/Choi/Skelly/Au/Irier  
OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

Draft: HI 11/25/2016 and 12/6/2016  
Edit: YMC 12/6/2016

ECMS (Site #1): Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/CLINICAL SITES/PRA International, Lenexa, KS/NDA208743\_Abaloparatide SC

ECMS (Site #2): Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/CLINICAL SITES/PRA Healthsciences, Marlton, NJ/NDA208743\_abaloparatide SC/REVIEW (EIR COVER)

OSIS File#:7226

FACTS #: 11654772

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

/s/  
-----

HASAN A IRIER  
12/27/2016

ELISE A MURPHY  
12/27/2016

**M E M O R A N D U M**

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

---

DATE: December 12, 2016

TO: Hylton V. Joffe, MD., M.M.Sc.  
Director  
Office of New Drug (OND), Office of Drug Evaluation  
III/Division of Bone, Reproductive, and Urologic  
Products (DBRUP)

And

Dennis Bashaw, PharmD., M.P.H.  
Director  
Office of Translational Sciences/Office of Clinical  
Pharmacology/Division of Clinical Pharmacology-III.

FROM: Hasan Irier, Ph.D.  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance  
Office of Translational Sciences

THROUGH: Elise Murphy  
Deputy Director (Acting)  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance  
Office of Translational Sciences

SUBJECT: Review of Establishment Inspection Report (EIR)  
covering NDA 208743, Abaloparatide SC, sponsored by Radius  
Health, Inc., 950 Winter Waltham, MA 02451 USA

---

**Inspection Summary:**

At the request of the Office of Study Integrity and Surveillance (OSIS), Office of Translational Sciences (OTS) assigned a clinical inspection to the Office of Regulatory Affairs for PRA Health Sciences Corp. Marlton, NJ 08053-2047 for NDA 208743(Abaloparatide SC). This reviewer recommends accepting Study BA058-05-016 for further Agency (FDA) review.

**Inspected Study:**

| Application | Study        | Study Site                                                                             | Sponsor                                               | Recommendation |
|-------------|--------------|----------------------------------------------------------------------------------------|-------------------------------------------------------|----------------|
| NDA 208743  | BA058-05-016 | <b>Site#1:</b><br>PRA Health Sciences Corp.<br>Lenexa, KS 66219<br>Phone: 913-410-2000 | Radius Health, Inc., 950 Winter Waltham, MA 02451 USA | Acceptable     |
|             |              | <b>Site #2:</b><br>PRA Health Sciences Corp.<br>Marlton, NJ 08053-2047                 |                                                       | Acceptable     |

**Study Title:** "A randomized, open label, single-dose, 2-way crossover study to determine the bioequivalence of abaloparatide administered subcutaneously from two similar pen injectors to healthy postmenopausal women sponsored by Radius health, Inc. under Investigational New Drug (IND) 073176"

**Study Dates:** 01/12/2016 to 02/10/2016

**Study Site #1:** During August 8-12, 2016, ORA investigator Vickie J Kanion audited the clinical study BA058-05-016 at the PRA Health Sciences Corp. Marlton, Lenexa, KS 66219. The audit included a thorough review of issues related to training, IRB approval, the relevant protocol, subject consent forms, subject records, and drug accountability. Following the inspection, no objectionable condition was found, and the ORA investigator did not issue a Form FDA 483.

**Study Site #2:** During October 12-20, 2016, ORA investigator Loretta Nemchik audited the clinical study BA058-05-016 at the PRA Health Sciences Corp. Marlton, NJ 08053. The audit included a thorough review of issues related to training, IRB approval, the relevant protocol, subject consent forms, subject records, and drug accountability. Following the inspection, no significant objectionable condition or findings were observed. No Form FDA 483, Inspectional Observations was issued to any of the sites.

**Recommendation:**

As a result of no inspectional findings, this reviewer

concludes that the data from the audited study BA058-05-016 are reliable, and recommends accepting the data from study BA058-05-016 for further Agency (FDA) review.

Hasan A. Irier, Ph.D.  
Division of Generic Drug Bioequivalence Evaluation (DGDBE)  
Office of Study Integrity and Surveillance (OSIS)  
Office of Translational Sciences (OTS)

Young Mbon Choi, Ph.D.  
Team Lead  
OSIS, DGDBE

Elise Murphy  
Deputy Director (Acting)  
OSIS, DGDBE

**Final Site Classification:**

**NAI - PRA Health Sciences Corp. Lenexa, KS ( Site #1)**  
**FEI: 3007467677**

**NAI - PRA Health Sciences Corp. Marlton, NJ ( Site #2)**  
**FEI: 3012575890**

CC:  
OSIS/Kassim/Taylor/Haidar/Miller/Nkah/Fenty-Stewart/Kadavil  
OSIS/DGDBE/Cho/Murphy/Choi/Skelly/Au/Irier  
OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

Draft: HI 11/25/2016 and 12/6/2016  
Edit: YMC 12/6/2016

ECMS (Site #1): Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/CLINICAL SITES/PRA International, Lenexa, KS/NDA208743\_Abaloparatide SC

ECMS (Site #2): Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/CLINICAL SITES/PRA Healthsciences, Marlton, NJ/NDA208743\_abaloparatide SC/REVIEW (EIR COVER)

OSIS File#:7226

FACTS #: 11654772

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

/s/  
-----

HASAN A IRIER  
12/15/2016

ELISE A MURPHY  
12/22/2016



**GENERAL HOSPITAL DEVICES BRANCH  
INTERCENTER CONSULT MEMORANDUM**

**Date:** December 13, 2016

**To:** Mark Seggel, Chemist  
Center for Drug Evaluation and Research (CDER)

**From:** Robert Meyer, Mechanical Engineering Reviewer  
General Hospital Devices Branch (GHDB),  
Division of Anesthesiology, General Hospital, Respiratory,  
Infection Control, & Dental Devices (DAGRID),  
Office of Device Evaluation (ODE),  
Center for Devices and Radiological Health (CDRH)

**Through:** CDR Alan Stevens, Branch Chief  
General Hospital Devices Branch

**Subject:** Consult for NDA 208743 / ICC 1600245

|                             |                                                                                                                                                                                                                |
|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Applicant                   | Radius Health, Inc.                                                                                                                                                                                            |
| Indication for Use          | Abaloparatide-SC is indicated for the treatment of postmenopausal women with osteoporosis. The proposed dose is 80 µg once daily administered by subcutaneous (SC) self-injection to the periumbilical region. |
| Drug / Biologic Constituent | Abaloparatide-SC is indicated for the treatment of postmenopausal women with osteoporosis.                                                                                                                     |
| Device Constituent          | Pen Injector                                                                                                                                                                                                   |

**Recommendation:** CDRH recommends approval. The device constituents are adequately demonstrated to function as specified after adequate pre-conditions are applied to device. Note: **CDER Clinical team should be aware the dose accuracy is  $\pm \frac{(b)(4)}{(4)}\%$  .040mL  $\pm \frac{(b)(4)}{(4)}$  mL.**

| Digital Signature Concurrence Table |                                                   |
|-------------------------------------|---------------------------------------------------|
| Reviewer                            | Robert Meyer -S<br>2016.12.13 10:12:43 -05'00'    |
| Branch Chief                        | Alan M. Stevens -S<br>2016.12.13 10:25:10 -05'00' |

## I. Purpose / Background

### INSTRUCTIONS

Radius Health, Inc. (Radius) is submitting a 505(b)(1) New Drug Application (NDA) for abaloparatide-SC (IND 073176) for the treatment of postmenopausal women with osteoporosis, thus the Lead Reviewer has requested review of the associated device constituents. This memo outlines the information provided by the Sponsor as it relates to the subject device and our judgment of its acceptability as it relates to safety and effectiveness.

The subject device in this submission is a pen injector, and the name is noted as (b) (4) in draft labeling.

Abaloparatide-SC is indicated for the treatment of postmenopausal women with osteoporosis. The proposed dose is 80 µg once daily administered by subcutaneous (SC) self-injection to the periumbilical region.

| Product                 | Indications for Use                                                                                                                                                                                         |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Disposable Pen Injector | TRADENAME is indicated for the treatment of postmenopausal women with osteoporosis. In postmenopausal women with osteoporosis, TRADENAME reduces the risk of vertebral fractures and nonvertebral fractures |

## II. Administrative

### Documents Reviewed:

| Ref. # | Document Title                                           | Document File | Location |
|--------|----------------------------------------------------------|---------------|----------|
| 1      | Draft Instructions for Use                               |               | (b) (4)  |
| 2      | Abaloparatide 1.2 Reviewer's Guide                       |               |          |
| 3      | container-closure-medical-device-engineering-report.pdf  |               |          |
| 4      | Container Closure System (Device Uno pen CE Ypsomed).pdf |               |          |

|    |                                                                 |         |
|----|-----------------------------------------------------------------|---------|
| 5  | container-closure-system.pdf                                    | (b) (4) |
| 6  | Abaloparatide<br>1.14.1.2 Annotated Draft<br>Labeling Text      |         |
| 7  | Draft Medication Guide                                          |         |
| 8  | container-closure-system-abaloparatide.pdf<br>(summative study) |         |
| 9  | container-closure-systemdevice.pdf                              |         |
| 10 | Design specifications                                           |         |
| 11 | Lot Release                                                     |         |
| 12 | Dose accuracy test descriptions                                 |         |
| 13 | ISO 11608 Report                                                |         |
| 14 | Human Factors Summative Report                                  |         |
| 15 | Risk Analysis                                                   |         |

**CDRH Review Team:**

| Team Member                    | Role                       | Deficiencies |
|--------------------------------|----------------------------|--------------|
| Robert Meyer {(CDRH/ODE/GHDB)} | Lead Reviewer – Mechanical | N/A          |

|  |          |  |
|--|----------|--|
|  | Engineer |  |
|--|----------|--|

### III. Device Description and Performance Requirements

Device Image:



Instructions for use:



(b) (4)

**Description:**

The subject pen is a pen injector for the subcutaneous injection of multiple doses of abaloparatide. The pen is an “adaptation” of the UnoPen platform manufactured by Ypsomed. The Sponsor states the drug is intended for injection up to (b) (4), and the pen device is designed to be used for 30 days. It contains a (b) (4) glass cartridge which is prefilled with the noted drug. It is noted the pen is to be used in with mylife® Clickfin® 31 gauge x 8mm length needles which are marketed and sold separately.

The drug product is administered in fixed doses of 40 µL. The pen allows the delivery of 30 doses, (b) (4). The abaloparatide dose is indicated in the display window, where “80” corresponds to 40 µL of a 2 mg/mL solution.

The Sponsor states “*The pen does not come into contact with the drug during administration. The pen is to be used with compatible pen needles, which are not supplied with the pen*” (Ref.4).

The Sponsor has provided the device specifications in reference 10 attached above. Noted specifications are included in the table below.

| Device Characteristic                                                                                                                                                                                                         | Description / Specification                                                                                                                                                                                                                                        | Ref. #   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| Injector Name                                                                                                                                                                                                                 | "Trade name"                                                                                                                                                                                                                                                       | 1        |
| Injector Platform Name                                                                                                                                                                                                        | Ypsomed – UnoPen™                                                                                                                                                                                                                                                  | 4 pg. 4  |
| Priming Dose / Volume                                                                                                                                                                                                         | 40 µL – one time when you initially get the pen, not before every use.                                                                                                                                                                                             | 4 pg. 4  |
| Dose accuracy                                                                                                                                                                                                                 | Dose limits (b) (4) mL to (b) (4) mL                                                                                                                                                                                                                               |          |
| Injection Time                                                                                                                                                                                                                | 10 seconds (instructions for use, and Ref. 4 page 5)                                                                                                                                                                                                               | See note |
| Injection Site                                                                                                                                                                                                                | Periumbilical                                                                                                                                                                                                                                                      | 4 pg. 5  |
| Injection tissue and depth of injection                                                                                                                                                                                       | Subcutaneous, 8 mm (31 gauge)                                                                                                                                                                                                                                      | 4 pg. 5  |
| Audible / visual feedback                                                                                                                                                                                                     | Needs clarifications: "a means to differentiate the state when the pen is ready for injection and the state when the dose has been injected"                                                                                                                       | 4 pg. 10 |
| Cap Removal Force                                                                                                                                                                                                             | Min (b) (4) N and max (b) (4) N up to (b) (4) cycles                                                                                                                                                                                                               | 10 pg. 4 |
| Activation Force                                                                                                                                                                                                              | (b) (4) N                                                                                                                                                                                                                                                          | 4 pg. 15 |
| Visibility of medication container                                                                                                                                                                                            | The drug is visible.                                                                                                                                                                                                                                               |          |
| Last Dose Specifications and Safety Features                                                                                                                                                                                  | <ul style="list-style-type: none"> <li>- The pen cannot be dialed to "80" if not enough volume remains in the cartridge.</li> <li>- a means to prevent the delivery of a second dose after the delivery of the first dose without a second pre-setting.</li> </ul> | 4 pg. 10 |
| Needle Specifications <ul style="list-style-type: none"> <li>• Length(s)</li> <li>• Gauge(s)</li> <li>• Connection type <ul style="list-style-type: none"> <li>○ ISO 11608-2:2012</li> <li>○ Prestaked</li> </ul> </li> </ul> | mylife® Clickfin ® 31 gauge x 8mm, claimed compliance with ISO 11608-2:2012.                                                                                                                                                                                       | 4 pg. 3  |
| Type of Use (e.g. single use, disposable, reusable, other)                                                                                                                                                                    | Fixed dose, multiple dose, disposable                                                                                                                                                                                                                              | 4 pg. 5  |
| Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)                                                                                               | Self-administration after instruction from a professional. "The pen is suitable for a wide range of patients, but the intended population for abaloparatide is post-menopausal women with osteoporosis"                                                            | 4 pg. 5  |
| Injection mechanism (e.g., manual piston, spring, gas, etc.)                                                                                                                                                                  | Manual                                                                                                                                                                                                                                                             |          |
| Method of actuation                                                                                                                                                                                                           | (b) (4)                                                                                                                                                                                                                                                            |          |
| Automated Functions                                                                                                                                                                                                           | None                                                                                                                                                                                                                                                               | 4 pg. 4  |
| Residual Medication                                                                                                                                                                                                           | "After 30 doses the entire product is disposed."                                                                                                                                                                                                                   | 4 pg. 6  |
| Delivered Volume (for single dose or selectable volume)                                                                                                                                                                       | 40 µL of a 2 mg/mL solution (80 µg dose)                                                                                                                                                                                                                           | 4 pg. 4  |

| range for multidose pens)                                                       |                                                                                                                                                                                                                                                                                                                                                                                 |                 |                     |         |                     |         |  |  |  |                |
|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|---------------------|---------|---------------------|---------|--|--|--|----------------|
| Drug Container Type                                                             | (b) (4) clear (b) (4) glass, Type I, compliant with USP <660>, Ph Eur 3.2.1, and ISO 11608-3, supplier - (b) (4)                                                                                                                                                                                                                                                                | 5 pg. 1         |                     |         |                     |         |  |  |  |                |
| Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)                   | “80” unit corresponds to 40 µL of a 2 mg/mL solution.                                                                                                                                                                                                                                                                                                                           | 4 pg. 4         |                     |         |                     |         |  |  |  |                |
| Environments of use                                                             | Home or clinical                                                                                                                                                                                                                                                                                                                                                                |                 |                     |         |                     |         |  |  |  |                |
| Storage conditions and expiry                                                   | Pen subassemblies (b) (4)<br>Assembled pen and cartridge (b) (4)<br>Room temperature during the 30 day in-use period                                                                                                                                                                                                                                                            | 4 pg. 5         |                     |         |                     |         |  |  |  |                |
| Graduation marks / fill lines                                                   | None - Cartridge Holder Labeling Justification                                                                                                                                                                                                                                                                                                                                  | 4 pg.22         |                     |         |                     |         |  |  |  |                |
| Preparation and administration (describe all that are applicable)               | See instructions for use (above)                                                                                                                                                                                                                                                                                                                                                |                 |                     |         |                     |         |  |  |  |                |
| Safety Features <ul style="list-style-type: none"> <li>Needle safety</li> </ul> | <p>- The needle does not retract. No safety guard feature.</p> <p><b>Table 5: Safety Functions of the Abaloparatide Pen</b></p> <table border="1"> <thead> <tr> <th>Safety function</th> <th>Description</th> <th>Comment</th> <th>Design Verification</th> </tr> </thead> <tbody> <tr> <td colspan="4" style="background-color: #cccccc;">(b) (4)</td> </tr> </tbody> </table> | Safety function | Description         | Comment | Design Verification | (b) (4) |  |  |  | 4 pg. 6 and 11 |
| Safety function                                                                 | Description                                                                                                                                                                                                                                                                                                                                                                     | Comment         | Design Verification |         |                     |         |  |  |  |                |
| (b) (4)                                                                         |                                                                                                                                                                                                                                                                                                                                                                                 |                 |                     |         |                     |         |  |  |  |                |
| Electronics / Data transmission                                                 | none                                                                                                                                                                                                                                                                                                                                                                            | 4 pg. 4         |                     |         |                     |         |  |  |  |                |
| Material composition of injector                                                | <b>Table 4: Materials of Construction</b><br>(b) (4)                                                                                                                                                                                                                                                                                                                            | 4 pg. 9         |                     |         |                     |         |  |  |  |                |

|         | Component | Physical contact with patient | Color of visible parts | Material |  |  |
|---------|-----------|-------------------------------|------------------------|----------|--|--|
| (b) (4) |           |                               |                        |          |  |  |

**IV. Design Control Review**

**A. Design Review Summary**

The Sponsor has adequately demonstrated the device functions as specified in the instructions for use document, and per specifications provided. The device meets requirements in ISO 11608-1 and 11608-2 with exception to the dose accuracy.

**B. Design Control Documentation Check**



**C. Design Verification and Validation Review**

Summary of Design V&V Attributes:



(b) (4)

(b) (4)



**Table 16: Verification of Specified Use Related Forces**

| Requirement | Type | Result |
|-------------|------|--------|
| (b) (4)     |      | Passed |
| (b) (4)     |      | Passed |
| (b) (4)     |      | Passed |
| (b) (4)     |      | Passed |
| (b) (4)     |      | Passed |
| (b) (4)     |      | Passed |
| (b) (4)     |      | Passed |
| (b) (4)     |      | Passed |
| (b) (4)     |      | Passed |
| (b) (4)     |      | Passed |

The following table outlining ISO 11608-1 requirement verification is provided by the Sponsor on page 19 of reference 4:

Table 11: Verification of General Requirements According to ISO 11608-1

| ISO 11608-1 Chapter 5.5 <sup>a</sup> | Requirement                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Pen Feature | Conformance with requirement | ISO 11608-1 Chapter 5.5 <sup>a</sup> | Requirement                                                                                                                                                                                                                                                                                                                                                                                                                                       | Pen Feature | Conformance with requirement                                                                        |
|--------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------------------------------|--------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-----------------------------------------------------------------------------------------------------|
| a                                    | The container holder shall allow visibility of the deliverable volume. The manufacturer shall determine, by risk analysis, if a residual scale is required and how much of the deliverable volume shall be visible.                                                                                                                                                                                                                                                                                                 | (b) (4)     | Yes                          | j                                    | Variable multi-dose NISs (system designations A and C) shall be designed so that they:<br>1) do not allow a larger dose to be pre-set than is left in the container, or<br>2) do not allow dose delivery if the pre-set amount exceeds the amount of medicinal product left in the container, or<br>3) indicate the amount of medicinal product delivered, or<br>4) indicate the amount of medicinal product not delivered (of the pre-set dose). | (b) (4)     | Yes                                                                                                 |
| b                                    | With the exception of system designations B2 and D2, needle-based injection systems (NIS) shall be designed in such a way that they are able to accurately deliver the entire labeled volume from the container for which they are designed.                                                                                                                                                                                                                                                                        | (b) (4)     | Yes                          | k                                    | Fixed multi-dose NISs shall not allow pre-setting of the dose if a volume that is insufficient for the full fixed dose remains.                                                                                                                                                                                                                                                                                                                   | (b) (4)     | Yes                                                                                                 |
| d                                    | When the injection system requires the user to pre-set the dose, the injector shall provide an indication of the dose that has been set. This information can be displayed in drug-specific units (e.g. milliliters, milligrams, international units) or in a setting specified by the physician (e.g. number, letter, percentage) as appropriate for the drug to be delivered. When the dose has been pre-set by the manufacturer, the dose can be indicated by the device or the system labeling, as appropriate. | (b) (4)     | Yes                          | l                                    | The NIS shall be designed to function with its specified needles. ISO 11608-2 provides guidance for needles.                                                                                                                                                                                                                                                                                                                                      | (b) (4)     | Yes                                                                                                 |
| e                                    | There shall be an indication of the pre-setting by visual and either tactile and/or audible means.                                                                                                                                                                                                                                                                                                                                                                                                                  | (b) (4)     | Yes                          | m                                    | The NIS shall be designed to function with its specified containers. ISO 11608-3 provides guidance for containers.                                                                                                                                                                                                                                                                                                                                | (b) (4)     | Yes                                                                                                 |
| f                                    | The NIS shall indicate, at least by visual means, that it is ready for injection.                                                                                                                                                                                                                                                                                                                                                                                                                                   | (b) (4)     | Yes                          | q                                    | If designed with small parts that might be swallowed, the NIS labeling shall include warnings preventing access by children under the age of 3 years.                                                                                                                                                                                                                                                                                             | (b) (4)     | Yes                                                                                                 |
| g                                    | The state of the NIS, when ready to deliver a dose, shall be different from its state when the dose has been delivered. The difference shall be visible.                                                                                                                                                                                                                                                                                                                                                            | (b) (4)     | Yes                          | u                                    | Adverse effects of the medicinal product contact with the NIS shall be assessed and mitigated through risk assessment.                                                                                                                                                                                                                                                                                                                            | (b) (4)     | Yes                                                                                                 |
| h                                    | The NIS shall indicate, by visual, audible or tactile means, or any combination of these, that the injection stroke has been completed.                                                                                                                                                                                                                                                                                                                                                                             | (b) (4)     | Yes                          | v                                    | Biological requirements of the NIS shall be established in accordance with ISO 10993-1.                                                                                                                                                                                                                                                                                                                                                           | (b) (4)     | Yes                                                                                                 |
|                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | (b) (4)     |                              | w                                    | Where requirements in this part of ISO 11608 provide a test method without acceptance criteria, the manufacturer shall establish a specification and acceptance criteria appropriate for the intended use of the device, using a risk-based approach (consistent with ISO 14971 and IEC 62366).                                                                                                                                                   | (b) (4)     | Not applicable<br>ISO 11608-1 provides definitions for acceptance criteria for all performed tests. |

<sup>a</sup> The following clauses of chapter 5.5 "General Requirements" are not applicable for the abaloparatide pen, because it is neither a single-dose pen nor does it contain electronic or electromechanical components or software or batteries: c), i), n), o), p), r), s), and t).  
NIS = Needle-based injection system

**Dose accuracy verification:**

The following verification is documented in reference 13:

(b) (4)



[Page 25 - 46] Expiry – Pass

**Needle compatibility testing:**

[Ref. 9 page 31]



(b) (4)

**Table 13: Test Summary of Needle Compatibility Testing**

| Trade name                        | Description | Acceptance criteria | Test result |
|-----------------------------------|-------------|---------------------|-------------|
| Clickfine pen needle<br>31G x 8mm | [Redacted]  | [Redacted]          | passed      |
|                                   |             |                     | passed      |
|                                   |             |                     | passed      |

(b) (4)



(b) (4)

| Manufacturer | Trade name | Pen needle type |
|--------------|------------|-----------------|
| Ypsomed      | Clickfine  | 31G x 8mm       |



(b) (4)

**4.1 Results of torque to attach and remove needle**

| Tradename | Description | Acceptance criteria | Results |     |     | Conclusion |
|-----------|-------------|---------------------|---------|-----|-----|------------|
|           |             |                     | Mean    | Min | Max |            |
| Clickfine | [Redacted]  | [Redacted]          | (b) (4) |     |     | passed     |
|           |             |                     |         |     |     | passed     |

(b) (4)

**4.2 Results of dose accuracy measurements**

| Tradename | Dose       | Specification | Acceptance criteria | Results     |                      | Conclusion |
|-----------|------------|---------------|---------------------|-------------|----------------------|------------|
|           |            |               |                     | Mean, StDev | Upper STI, Lower STI |            |
| Clickfine | [Redacted] | [Redacted]    | [Redacted]          | (b) (4)     |                      | passed     |

(b) (4)

## **D. Risk Analysis**

| <b>Risk Analysis Attributes</b>                                                         | <b>Yes</b> | <b>No</b> | <b>N/A</b> |
|-----------------------------------------------------------------------------------------|------------|-----------|------------|
| Risk analysis conducted on the combination product                                      | X          |           |            |
| Hazards adequately identified                                                           | X          |           |            |
| Mitigations are adequate to reduce risk to health                                       | X          |           |            |
| Version history demonstrates risk management throughout design / development activities | X          |           |            |

### Summary of Risk Analysis

Risk analysis is completed by the device manufacture, Ypsomed (Ref.4 page 18). The vendor considered sixty-nine known and potential hazards which are applicable to similar devices, including potential use and misuse situations, during evaluation. After analysis, the vendor considers twenty-seven hazards applicable to the device. After implementation of proposed mitigation measures, the vendor states, two use errors remained (incomplete priming and incomplete hold time) and are considered to be mitigated as low as reasonable practicable (ALARP).

## **E. Labeling**

See reference 7 attached: Draft Medication Guide for warnings, and precautions.

(b) (4)

(b) (4)



Insert relevant Warnings / Precautions from User Manual or Package Insert

## **V. Device Assembly and Shipping**

The Sponsor has provided the following summary which outlines the assembly of the device from origination at the device manufacturer to completion at the drug facility. The drug manufacture completes the assembly of the finished device.

(b) (4)



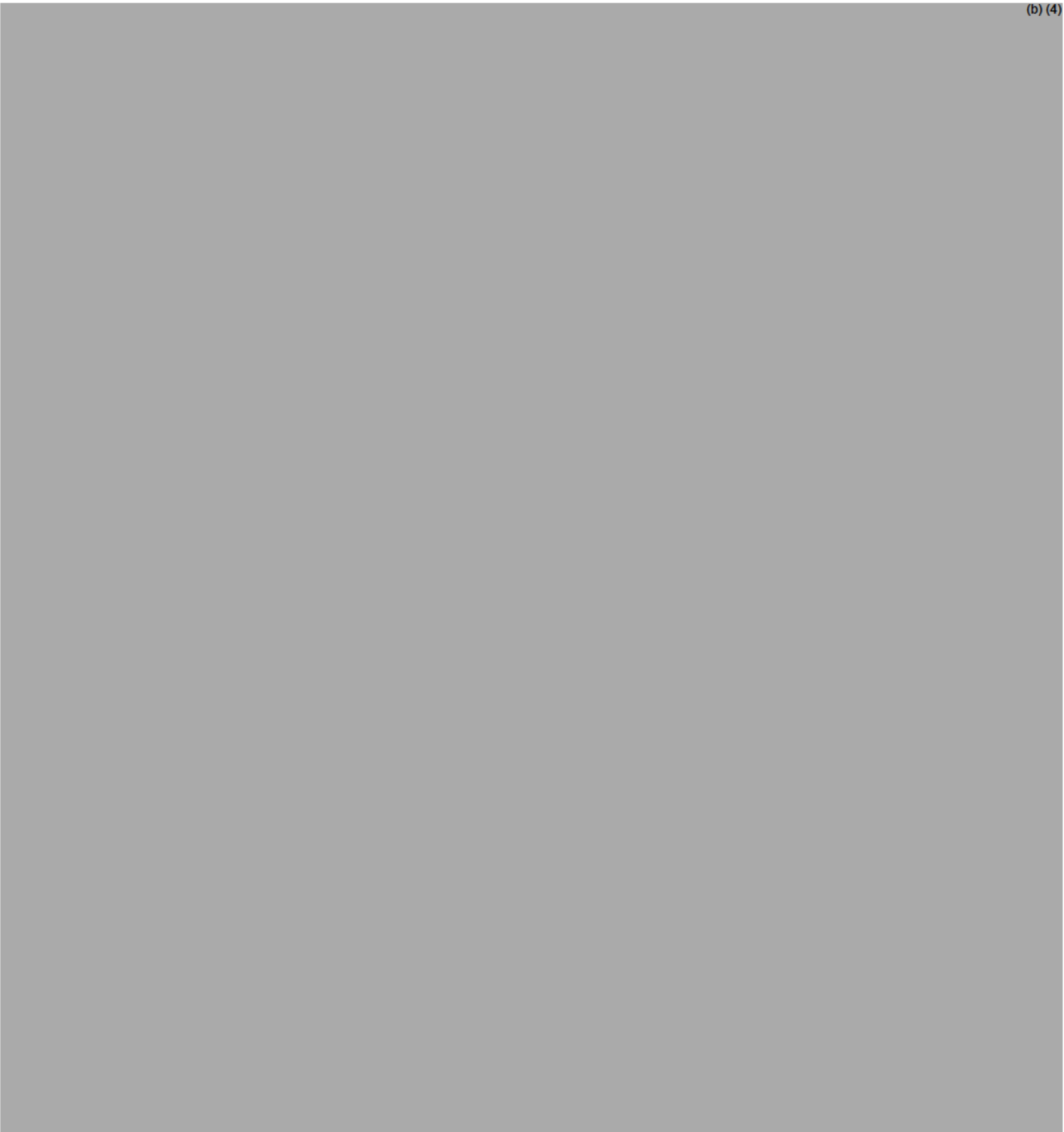


## **VI. Device Quality Control**

The components of the device are inspected at the vendor (Ypsomed) prior to shipping to the drug manufacture. The following tables outline attributes of the components which the vendor have identified as critical to the physical and performance aspects of the device (Ref. 4 page 15).



(b) (4)



## VII. Lot Release

In response to information request #3 the Sponsor provides the following lot release check list [Ref. 11] :

(b) (4)



### **VIII. Biocompatibility**

(b) (4)

### **IX. Information Requests – Sent 8/31/2016**

1. You have provided several container closure system documents which describe the Ypsomed pen injector which you are proposing to use for administration of the subject drug. Within these documents several specifications are included; however a full finished design specifications document is not provided. Please provide a design specifications document which lists all design features and associated specifications. Please include a column with this list which associates, when applicable, the design feature (output) to design input (why is the feature needed and specified as is, e.g. standard req., user input, etc.).

Sponsor's Response: The Sponsor provided reference document 10 listed above.

Reviewer's Response: The provided traceability table is adequate.

2. You have identified several design specifications and included summaries of associated testing verification. Please provide a traceability matrix which links all design features and specifications to associated verification documents or summaries. This matrix (table) may be interfaced with the specifications list you provide in response to information request number one (1).

Sponsor's Response: The Sponsor provided reference document 10 listed above.

Reviewer's Response: The provided traceability table is adequate.

3. Please provide clarification to the dose accuracy verification information you have included in the container closure system document; does the test method utilize the device as instructed? Please provide the test protocol, and clarify if new needles were used without priming for each measurement.

Sponsor's Response: *The test method for dose accuracy verification specifically requires that the instructions for use (IFU) for the abaloparatide pen are followed precisely for testing. The abaloparatide IFU requires the needle to be changed between injections. Only one dose per each pen tested was measured, regardless of the section of the cartridge from which the dose was taken. Priming was performed consistent with the IFU. Each pen was primed only once, at pen initiation, prior to the first dose.*

Reviewer's Response: The response is adequate.

4. In the container closure system document you have summarized risk management and analysis completed for the Ypsomed pen utilized. Please provide the table which list all identified hazards/ risks and the associated mitigation. All mitigation verification should be referenced to a document and page number, and all references should be included.

Sponsor's Response: The Sponsor provided a risk management table [Ref.15].

Reviewer's Response: The response is adequate.

5. You have provided insight regarding lot release procedures and specifications for components of the subject pen injector. Please provide a separate lot release document which outlines lot release criteria and procedures utilized to ensure future lots of finished assemblies are verified adequately prior to marketing. All functional parameters which are verified should be included and clearly noted to be identified through physical/ dimensional inspection or bench testing. If features are verified through bench testing then the associated protocols should be referenced or summarized

Sponsor's Response: The Sponsor provided the table included in the "Lot Release" criteria and summarized protocol.

Reviewer's Response: The response is adequate.

## X. Recommendation

CDRH recommends approval. The device constituents are adequately demonstrated to function as specified after adequate pre-conditions are applied to device. Note: **CDER Clinical team should be aware the dose accuracy is  $\pm \frac{(b)}{(4)}\%$  .040mL  $\pm \frac{(b)}{(4)}$  mL.**

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

/s/  
-----

THAO M VU  
12/13/2016  
upload on behalf of CDRH-ODE

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Pharmacovigilance Memo**

**Date:** December 8, 2016

**Reviewers:** Peter Waldron, MD, Medical Officer  
Samantha Cotter, PharmD, BCPS, FISMP, Safety Evaluator  
Division of Pharmacovigilance II

**Team Leader:** Neha Gada, PharmD, BCPS, Safety Evaluator Team Leader  
Division of Pharmacovigilance II

**Division Director (Acting):** S. Christopher Jones, PharmD, MPH, MS

**Product Name:** Abaloparatide

**Subject:** hereditary disorders and osteosarcoma

**Application Type/Number:** NDA 208743

**Applicant/Sponsor:** Radius Health Inc

**OSE RCM #:** 2016-2772

## 1 INTRODUCTION

The purpose of this memorandum is to provide justification to add the risk factor of “patients with a history of hereditary disorders predisposing to osteosarcoma” within the abaloparatide label. The majority of osteosarcoma cases within the general population occur in the absence of risk factors (Savage 2011). However, several risk factors are known and include: history of therapeutic radiation for a different cancer, individuals with certain cancer predisposition syndromes (e.g. Li-Fraumeni Syndrome, Werner Syndrome, Bloom Syndrome), and patients with Paget’s disease. Hereditary disorders may predispose individuals to the risk for osteosarcoma, in particular the younger population and may be less likely to contribute to the risk of osteosarcoma that develops in the older population (Savage 2011).

Abaloparatide is a recombinant 34-amino acid peptide, including 41% homology to human parathyroid hormone (PTH) 1-34 and 76% homology to human parathyroid hormone-related peptide 1-34. Abaloparatide binds to the PTH1 receptor (PTHR1) to activate the cAMP signaling pathway to increases bone formation, bone mass and bone strength. Abaloparatide is now undergoing FDA review (PDUFA date March 30, 2017), for the indication of treatment of postmenopausal women with osteoporosis to reduce vertebral and nonvertebral fractures. The recommended dose is 80 mcg administered subcutaneously once daily. Abaloparatide has not been approved outside the US. The sponsor of abaloparatide is seeking approval for use in the treatment of postmenopausal women with osteoporosis at high risk for fracture. Currently, there is one PTH analog available, teriparatide (Forteo), for the treatment of osteoporosis.

Preclinical studies show a dose- and treatment duration-dependent, increased risk for osteosarcoma in rats (but not in monkeys) at 3-58 times higher systemic exposure than in humans. The bone tumors in rats occurred in association with a large increase in bone mass and focal osteoblast hyperplasia which is the hypothetical, biological mechanism for the risk for osteosarcoma. It is also hypothesized that the rat skeleton is more sensitive than monkey or human skeletons to the pharmacological effects of parathyroid hormone (PTH) in the formation of new bone and osteosarcomas. Since bone metabolism in rats differs from that in humans, the relevance of the animal finding to humans is uncertain. However, FDA has previously approved two other parathyroid hormone agents: 1) teriparatide (Forteo) a recombinant human parathyroid hormone analog (1-34) for the treatment of osteoporosis, and 2) parathyroid hormone (Natpara) for the treatment of hypoparathyroidism (see Appendix A for relevant Natpara label information). Both of these agents also showed a higher risk of osteosarcoma in rodents. Both products have a boxed warning to mitigate the potential risk of osteosarcoma in humans.

### 1.1 DRAFT LABELING

The sponsor’s proposed Boxed Warning (BW) submitted with the NDA application on July 1, 2016, is pasted below. The BW and Warnings/Precautions language includes a description of those at increased risk for osteosarcoma including *those with Paget’s disease of bone or unexplained elevations of alkaline phosphatase,* (b) (4) *open epiphyses, or* (b) (4) *prior* (b) (4) *external beam or implant radiation therapy involving the skeleton.*

(b) (4)

The sponsor's proposed Warnings and Precaution submitted with the NDA application on July 1, 2016, is pasted below.

(b) (4)

## **2 SUMMARY OF REVIEWER'S COMMENTS AND RATIONALE**

Awareness and a reminder to clinicians of the risk factor for osteosarcoma of hereditary disorders may help to mitigate exposure to abaloparatide and therefore the potential risk for osteosarcoma in this at risk population. The principal inherited disorders with an increased risk for osteosarcoma, are Li- Fraumeni syndrome (constitutional mutation of the p53 gene) and inheritance of a mutated retinoblastoma (Rb) gene. Persons with those disorders develop osteosarcoma by age 60. There are six diseases that are most common among families with Li-Fraumeni syndrome (premenopausal breast cancer, soft tissue sarcoma, osteogenic sarcoma, brain tumors, leukemia). Unless a person knows their family carries this gene, it will take a careful history, and possibly referral for a genetics consultation to determine this risk. Similarly with the Rb gene mutations, there would typically be more than one family member with retinoblastoma and/or osteosarcoma. There are other rarer disorders with an osteosarcoma risk that cannot be easily communicated in the label. The label prompt of "hereditary disorders predisposing to osteosarcoma" may aid the practitioner in considering the heritable risks as part of the full picture of evaluating a person's risk for osteosarcoma and the benefit risk of a PTH analogue.

## **3 CONCLUSION/RECOMMENDATIONS**

DPV recommends the additional text of 'patients with hereditary disorders predisposing to osteosarcoma' to the list of risk factors for osteosarcoma when described in the label.

## 4 REFERENCES

1. Savage, Sharon and Mirabello, Lisa. Using Epidemiology and Genomics to Understand Osteosarcoma Etiology. *Sarcoma*. 2011; 2011: PMID: 548151.

## 5 APPENDIX A

| Approved Labeling – NATPARA® (parathyroid hormone) for injection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <p><b>WARNING: POTENTIAL RISK OF OSTEOSARCOMA</b></p> <p><i>See full prescribing Information for complete boxed warning</i></p> <ul style="list-style-type: none"><li>• In male and female rats, parathyroid hormone caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. A risk to humans could not be excluded (5.1, 13.1)</li><li>• Because of the potential risk of osteosarcoma, prescribe NATPARA only to patients who cannot be well-controlled on calcium and active forms of vitamin D and for whom the potential benefits are considered to outweigh the potential risk. (1, 5.1)</li><li>• Avoid use of NATPARA in patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, patients with hereditary disorders predisposing to osteosarcoma or patients with a history of prior external beam or implant radiation therapy involving the skeleton) (5.1)</li><li>• NATPARA is available only through a restricted program called the NATPARA REMS Program (5.2)</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |
| <p><b>5 WARNINGS AND PRECAUTIONS</b></p> <p><b>5.1 Potential Risk of Osteosarcoma</b></p> <p>In male and female rats, parathyroid hormone caused an increase in the incidence of osteosarcoma (a malignant bone tumor). The occurrence of osteosarcoma was observed to be dependent on parathyroid hormone dose and treatment duration. This effect was observed at parathyroid hormone exposure levels ranging from 3 to 71 times the exposure levels for humans receiving a 100 mcg dose of NATPARA. These data could not exclude a risk to humans [see <i>Nonclinical Toxicology</i> (13.1)].</p> <p>Because of a potential risk of osteosarcoma, use NATPARA only in patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone and for whom the potential benefits are considered to outweigh this potential risk [see <i>Limitations of Use</i> (1)].</p> <p>To further mitigate the potential risk of osteosarcoma, avoid use of NATPARA in patients who are at increased risk for osteosarcoma, such as patients with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, patients with hereditary disorders predisposing to osteosarcoma, or patients with a prior history of external beam or implant radiation therapy involving the skeleton. Instruct patients to promptly report clinical symptoms (e.g., persistent localized pain) and signs (e.g., soft tissue mass tender to palpation) that could be consistent with osteosarcoma.</p> <p>NATPARA is available only through a restricted program under a REMS [see <i>Warnings and Precautions</i> (5.2)].</p> |  |

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

/s/  
-----

PETER E WALDRON  
12/08/2016

SAMANTHA A COTTER  
12/08/2016

NEHA GADA  
12/08/2016

STEVEN C JONES  
12/08/2016



**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 Template  
Version: 2016-02-11**

Date: November 21, 2016

Reviewer(s): Jie (Jenni) Li, PhD  
Division of Epidemiology II

Wei Liu, PhD, MSc  
Division of Epidemiology II

Team Leader: Jie (Jenni) Li, PhD  
Division of Epidemiology II

Division Director: CAPT David Moeny, R.Ph., MPH, USPHS  
Division of Epidemiology II

Subject: ARIA Sufficiency Memo: Abaloparatide and Osteosarcoma

Drug Name(s): Abaloparatide-SC 80 mg

Application Type/Number: IND 073176

Applicant/sponsor: Radius Health, Inc.



**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                                  |   |
| -Exposure                                                          | X |
| -Outcome(s) of Interest                                            | X |
| -Covariate(s) of Interest                                          |   |
| -Surveillance Design/Analytic Tools                                |   |

## 1. BACKGROUND INFORMATION

### 1.1 Medical Product.

Abaloparatide is a recombinant 34-amino acid peptide, including 41% homology to human parathyroid hormone (PTH) 1-34 and 76% homology to human parathyroid hormone-related peptide 1-34. Abaloparatide binds to the PTH1 receptor (PTHR1) to activate the cAMP signaling pathway to increase bone formation, bone mass and bone strength. Abaloparatide is now undergoing FDA review (PDUFA date March 30, 2017), for the indication of treatment of postmenopausal women with osteoporosis to reduce vertebral and nonvertebral fractures. The recommended dose is 80 mcg administered subcutaneously once daily. Abaloparatide has not been approved outside the US (under review in the EU countries).

### 1.2 Describe the Safety Concern.

Preclinical studies show a dose- and treatment duration-dependent, increased risk for osteosarcoma in rats (but not in monkeys) at 3-58 times higher systemic exposure than in humans. The bone tumors in rats occurred in association with a large increase in bone mass and focal osteoblast hyperplasia which is the hypothetical, biological mechanism for the risk for osteosarcoma. It is also hypothesized that the rat skeleton is more sensitive than monkey or human skeletons to the pharmacological effects of parathyroid hormone (PTH) in the formation of new bone and osteosarcomas. Since bone metabolism in rats differs from that in humans, the relevance of the animal finding to humans is uncertain. Of 1332 postmenopausal women in premarketing clinical trials for abaloparatide, there were no instances of osteosarcoma, and the incidence of overall neoplasms and malignancies is generally balanced between abaloparatide (2.3%), teriparatide (3.6%) and placebo (3.4%) groups. The sponsor proposed a boxed warning in the label and a (b) (4) to minimize the potential risk for osteosarcoma in humans. The proposed label recommends against the use of abaloparatide in patients at a higher risk for osteosarcoma, such as patients with Paget's disease of bone unexplained elevations of alkaline phosphatase, (b) (4) open epiphyses, or (b) (4) prior (b) (4) external beam or implant radiation therapy involving the skeleton. Lifetime duration of use is to be limited to (b) (4) or 2 years (to be determined), since the clinical data on the safety and efficacy beyond (b) (4) of treatment has not been demonstrated.

FDA has previously approved two other parathyroid hormone agents: teriparatide (Forteo) is a recombinant human parathyroid hormone analog (1-34) for the treatment of osteoporosis, and Natpara a parathyroid hormone for the treatment of hypoparathyroidism. Same as abaloparatide, the two agents show a higher risk for osteosarcoma emerging from non-clinical rat studies (not in monkeys), but there are no human cases in pre-license trials. Both products now have a boxed warning and a REMS program to mitigate the potential risk of osteosarcoma. FDA requested two observational post-marketing safety studies for Forteo (one initiated in 2004 and the second in 2009). However, osteosarcoma is a rare cancer, with an incidence of 1.7-4.4 per million, depending on age, with an unknown latency period. In addition, the number of patients exposed to these products is low. For example, a recent study of the utilization patterns of osteoporosis drugs in Medicare identified just 9838 patients who received Forteo in 2013, among the total of 1.4 million receiving osteoporosis therapies<sup>a</sup>. In 2015, recognizing the challenges in studying this rare cancer outcome, FDA requested an enhanced pharmacovigilance program for Natpara, with no post-marketing observational study<sup>b</sup>. In Sections 3, 4

<sup>a</sup> Jha, S. & Bhattacharyya, Utilization and cost of anti-osteoporosis therapy among US Medicare beneficiaries , T. Arch Osteoporos (2016) 11: 28. doi:10.1007/s11657-016-0283-2 (<https://www.ncbi.nlm.nih.gov/pubmed/27576482>)

<sup>b</sup> PMR/PMC Development Template, accessed at:

and 7, we will discuss our conclusions and recommendations for abaloparatide, using the two approved agents as examples.

### 1.3 Osteosarcoma

Osteosarcoma is a rare type of cancerous bone tumor and represents less than 1% of all cancers diagnosed in the United States, and there is a paucity of comprehensive population-based data on its occurrence and outcome.<sup>c</sup> In the US, the incidence of osteosarcoma is age-dependent, with the primary peak in children and adolescents aged 0-24 (4.4 per million person per year) and a second peak in the elderly >60 (about 4.2 per million person per year).<sup>c</sup> The 5-year survival rate of osteosarcoma was reported as 24.2% in cases aged 60+. The survival rate drops drastically from approximately 50% for patients in their 50s to 17% for those in their mid-late 60s, and was the lowest for those age 80–84 (10.8%). In elderly patients, tumors occur more commonly in axial locations and in areas that have been previously irradiated or have underlying bone abnormalities. In elderly patients, osteosarcoma pathology was largely unspecified in SEER data (87%); the proportions for the pathologies that are specified were: chondroblastic (6.3%), fibroblastic (3.6%), telangiectatic (1.2%), and parosteal (1.4%).

#### FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARTS

*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 of the proposed inferential analysis is to determine the risk of osteosarcoma associated with the use of abaloparatide in human. FDA seeks to answer the question, "Given the increased risk observed in the pre-licensure rat study, can ARIA programs in Sentinel determine whether abaloparatide use is associated with a higher rate of osteosarcoma in humans, compared to patients treated with non-peptide anti-osteoporosis agents?" Osteosarcoma may develop after a long latency period following the abaloparatide treatment; a desired study design would allow long-term follow-up, e.g. 5-10 years.

It is important to note that the risk of osteosarcoma is already labeled for the other peptide anti-osteoporosis agent (Forteo), and it is anticipated that, if approved, abaloparatide will carry the same language in a boxed warning and in the Warnings and Precautions. Therefore, the level of evidence required for regulatory action is high, as the information gained may be used to provide more precise risk estimates, to quantify whether this drug is substantively different from non-peptide anti-osteosarcoma treatments, and potentially, revise or eliminate the Boxed Warning. In this regulatory context, because the event of interest is rare, the ARIA sufficiency determination primarily rests upon the need for large number of exposed patients and a valid cancer outcome algorithm.

[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2015/125511Orig1s000OtherR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125511Orig1s000OtherR.pdf)

<sup>c</sup> Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. *Cancer*. 2009;115(7):1531-1543.

## 2. SURVEILLANCE OR DESIRED STUDY POPULATION

Skipped, given the responses in Sections 3 and 4.

## 3. EXPOSURES

**3.1 Treatment Exposure(s)** The exposure of interest is abaloparatide.

**3.2 Comparator Exposure(s)** Other anti-osteoporosis medications (Table 1, below).

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

ARIA is judged to be insufficient to identify adequate numbers of exposed patients to study the rare outcome of osteosarcoma (see Section 4). Although the prescription dispensing (distributed through mail-order and outpatient pharmacies) will be captured in Sentinel, DEPI and DBRUP are concerned about the likely slow market uptake and low utilization of abaloparatide in the US patient population, for following reasons.

- First, abaloparatide is one of a number of marketed anti-osteoporosis drugs in the US. **Table 1** lists the various classes of FDA approved medications indicated for osteoporosis.
- Some agents, such as bisphosphonates, are approved for a broader indication (both prevention and treatment for osteoporosis among men and women) than abaloparatide (limited to treatment only, and only for women with high risk for fractures).
- Some agents are in more convenient dosage forms (e.g., annual intravenous or oral intake) than abaloparatide (daily subcutaneous injection). Convenient dosage forms are generally considered to lead to higher levels of product uptake and better compliance than less convenient forms such as daily subcutaneous injections.
- Further, generic anti-osteoporosis agents are now available at a lower price than the reference NDA products.
- Therefore, abaloparatide is unlikely to become a preferential choice over many other established drugs, some of which have been marketed for more than a decade, such as bisphosphonates.

Real world examples of the impacts of the issues discussed above are the PMR studies for Forteo. Forteo is comparable to abaloparatide as it is another peptide agent (daily injection), indicated for osteoporosis treatment among menopausal women. Forteo faced the challenge of declining utilization in the US when other anti-osteoporosis drugs in injectable form became available. Figure 1 below displays the nationally estimated number of packages sold for injectable osteoporosis products from manufacturers to U.S. retail and non-retail channels of distribution, years 2007 through year-to-date November 2012. Annual sales of Forteo decreased by (b) (4) % from (b) (4) pen devices sold in 2007 to (b) (4) pen devices sold in year 2011. DEPI reported that (Patty Greene, January 17, 2013, AIMS #2012-2712) the annual number of patients receiving a dispensed prescription for Forteo decreased by (b) (4) % from (b) (4) patients in year 2007 to approximately (b) (4) patients in year 2011 in the US outpatient retail pharmacy setting (mail-order/specialty pharmacy not captured). The low use of Forteo has become a barrier to complete Forteo's two observational PMR studies, in addition to other challenges of conducting the studies (details in Section 7). To identify a 3-fold increase in risk of

osteosarcoma, the prospective Forteo patient registry has to recruit approximately 1.7 million PYs of follow-up time.<sup>d</sup> Even if Sentinel can identify every single user in the US, an observational study may still be under-powered due to the expected small number of users and the rareness of the cancer outcome (to be discussed further in Sections 4 and 6 on power and sample size).

Table 1. Approved anti-osteoporosis medications cited in the Clinician’s Guide to Prevention and Treatment of Osteoporosis 2014.<sup>e</sup>

|                                   |                                                                                                                                                                                                                                                                                                                            |
|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bisphosphonates                   | Fosamax (alendronate Sodium),<br>Fosamax Plus D (alendronate Sodium with vitamin D),<br>Didronel (etidronate Disodium),<br>Boniva (ibandronate Sodium),<br>Aredia (pamidronate Disodium),<br>Actonel (risedronate Sodium),<br>Atelvia (risedronate Sodium),<br>Skelid (tiludronate Disodium),<br>Reclast (zoledronic Acid) |
| Calcitonin                        | (b) (4), Fortical, generic calcitonin                                                                                                                                                                                                                                                                                      |
| Estrogens/Hormone therapy         | Climara, Estrace, Estratab, Ogen, Premarin,<br>(b) (4), Activella, Femhrt, Premphase, Prempro                                                                                                                                                                                                                              |
| Estrogen agonist/antagonist       | Evista and generic raloxifene                                                                                                                                                                                                                                                                                              |
| Tissue-selective estrogen complex | Duavee                                                                                                                                                                                                                                                                                                                     |
| Parathyroid hormone (PTH 1-34)    | Forteo                                                                                                                                                                                                                                                                                                                     |
| RANKL inhibitor                   | Prolia, Xgeva                                                                                                                                                                                                                                                                                                              |

<sup>d</sup> Rate of osteosarcoma, 2.7 per million population per year (95% CI: 2.4, 3.0), age-adjusted to the 2000 US Standard Population (19 age groups; Census P25-1130) standard, from Surveillance, Epidemiology, and End Results (SEER) Program ([www.seer.cancer.gov](http://www.seer.cancer.gov)) SEER\*Stat Database: Incidence - SEER 17 Regs Public-Use, Nov 2005 Sub (2000-2003), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch. Released April 2006, based on the November 2005 submission. The background rate will be adjusted to the age/gender distribution of enrolled Forteo users for comparison purposes.

<sup>e</sup> Clinician’s guide to prevention and treatment of osteoporosis. 2014 Issue, version 1. Released April 2014.

#### **4. OUTCOME(S)**

**4.1 Outcomes of Interest.** The outcome of interest is osteosarcoma.

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

ARIA is deemed insufficient to assess short term osteosarcoma risk, as well as long term risk, among abaloparatide users for four main reasons: (1) limited duration of follow-up in claims data, (2) unknown validity of claims-based algorithms to ascertain osteosarcoma, (3) rareness of the cancer outcome, and (4) lack of histological data in the Sentinel data environment.

First, an average of 2 to 3 years of follow-up period in the US claims data may be insufficient to study long-term safety outcomes such as cancer. Due to the lack of human cases following abaloparatide exposure in pre-marketing trials, the latency period is unknown. If osteosarcoma develops after a long latency period following the abaloparatide treatment, a desired study design would allow long-term follow-up, e.g. 5-10 years. ARIA is unable to satisfy the regulatory need for long-term safety assessment for osteosarcoma.

Second, the validity of ICD-9 and ICD-10 codes (e.g., C40-C41, malignant neoplasm of bone and articular cartilage of limbs, or other sites) to identify osteosarcoma in claims data is unknown. A literature search identified no study on the validation of claims-based algorithms for osteosarcoma, using either ICD-9 or ICD-10 diagnosis codes. There is no prior study of osteosarcoma conducted in the Sentinel data environment. Although chart review may be able to provide adjudication of events for the subset of patients with available charts, it may not yield a claims-based algorithm for osteosarcoma with adequate validity that could be applied to all potential cases, and chart review does not fall within the ARIA paradigm.

Third, the rareness of the cancer, plus the anticipated low use in the US, likely makes ARIA insufficient. In the US, the incidence of osteosarcoma is about 4.2 per million person per year in the elderly >60 years old. A power estimate (provided in section 6.1 below), based on the calculations

provided for the Forteo PMR studies, shows that a PMR study is likely under-powered to detect the risk for osteosarcoma with abaloparatide use.

Lastly, histological type, International Classification of Disease for Oncology (ICD-O-3) diagnosis codes, cancer grade, and bony site data are not available in the Sentinel database to confirm the cancer diagnosis or to shed light on the biology/biologic mechanism of the cancer risk in humans.

## 5. COVARIATES

**5.1 Covariates of Interest.** Skip this section given our responses to Sections 3 and 4.

**5.2 Is ARIA sufficient to assess the covariates of interest?** Skip this section given our responses to Sections 3 and 4.

## 6. SURVEILLANCE DESIGN / ANALYTIC TOOLS

### 6.1 Estimated Sample Size Desired

To identify a 3-fold increase in risk of osteosarcoma, a safety study has to recruit approximately 1.7 million PYs of follow-up time.<sup>f</sup> The DEPI reviewer estimates that, with an estimated number of new users of (b) (4) per year (estimated nationwide outpatient sales distribution, (b) (4)), it would take approximately 20 years to gain 1.7 million person years of follow-up, assuming an average of 2 years follow-up in the Sentinel data environment.

## 7. NEXT STEPS

DBRUP and DEPI deem ARIA insufficient for short-term osteosarcoma risk, as well as long-term risk, with abaloparatide use, given our prior experience with the Forteo PMR observational studies. After 14 years post-approval, Forteo studies have led to only inconclusive study results on the risk for osteosarcoma. FDA requested two PMR studies on the safety of teriparatide in the US, a case-series study in 2004 and later a prospective voluntary Forteo-user registry in 2009. As of 2014, the retrospective case-series study identified 2,474 osteosarcoma patients, of which 802 were interviewed, and none osteosarcoma patient has been linked with a history of teriparatide treatment.<sup>h</sup> A similar European study faced the same challenge as the US study (112 osteosarcoma patients interviewed and 0 exposed patient). Subsequently, a prospective Forteo users registry was initiated in 2009 in the US, and by 2014, it enrolled 40,561 Forteo-exposed patients (person years not provided), with no cases of osteosarcoma identified from the enrolled patients.<sup>h</sup> The voluntary patient participation may partly be responsible for the low enrollment (apart from the low use overall) in the patient registry; but the safety

<sup>f</sup> Rate of osteosarcoma, 2.7 per million population per year (95% CI: 2.4, 3.0), age-adjusted to the 2000 US Standard Population (19 age groups; Census P25-1130) standard, from Surveillance, Epidemiology, and End Results (SEER) Program ([www.seer.cancer.gov](http://www.seer.cancer.gov)) SEER\*Stat Database: Incidence - SEER 17 Regs Public-Use, Nov 2005 Sub (2000-2003), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch. Released April 2006, based on the November 2005 submission. The background rate will be adjusted to the age/gender distribution of enrolled Forteo users for comparison purposes.

(b) (4)

Briefing document submitted by the sponsor for the Type C meeting on July 16, 2014. Proposed Updates to the Forteo Osteosarcoma Postmarketing Safety Assessment Program (teriparatide) NDA 21318.

signal arising from solely animal data (rats) does not warrant a mandatory patient registry (according to DBRUP). Given these challenges, DEPI and DBRUP are considering releasing the sponsor from the current Forteo PMRs. Yet the boxed warning is to remain as there is no sufficient data to refute the risk for osteosarcoma.

DBRUP and OSE are currently discussing potential paths forward for post-marketing safety approaches for abaloparatide (if approved). Under consideration is requesting that the sponsor implement enhanced pharmacovigilance to better characterize reported osteosarcoma cases. This approach is based on FDA's approval of Natpara, requesting the sponsor to conduct an enhanced pharmacovigilance program to monitor the risk for osteosarcoma among Natpara users, with no observational study post-marketing requirement. The enhanced pharmacovigilance program for Natpara will be conducted for a period of 15 years from FDA approval; and case reports of osteosarcoma will also be reviewed every quarter by the Natpara External Safety Committee.

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

/s/  
-----

JIE J LI  
11/28/2016

DAVID G MOENY  
11/29/2016

MICHAEL D BLUM  
11/29/2016

ROBERT BALL  
11/29/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service Food and Drug  
Administration Center for Devices and  
Radiological Health  
Office of Compliance, Division of Manufacturing & Quality  
Respiratory, ENT, General Hospital, Ophthalmic Device Branch (REGO)

---

**Date:** November 15, 2016

**To:** Krishna Ghosh, CDER/OPQ/OLDF  
Krishnakali.Ghosh@fda.hhs.gov

Juandria Williams,  
CDER/OPQ/OLDF  
[Juandria.Williams@fda.hhs.gov](mailto:Juandria.Williams@fda.hhs.gov)  
[v](#)

Office of combination products at [combination@fda.gov](mailto:combination@fda.gov)

**RPM:** Krishnakali Ghosh

**Through:** Ronald Swann, Branch Chief, ASDB, DMQ, OC, CDRH. WO-66, Room 3456

Ronald L. Swann -S  
2016.11.18 16:25:17 -05'00'

---

**From:** Latoya Oliver-Powell, ASDB, DMQ, OC, CDRH. WO-66, Room 3464

**Applicant:** Radius Health, Inc.  
950 Winter St.  
Waltham, MA 02451  
FEI# 3012498539

**Application #** NDA208743

**Consult #** ICC#1600236

**Product Name:** Abaloparatide-SC

**Documentation Review:** No Additional Information Required

**Final Recommendation:** **Approval**

---

The Office of Compliance at CDRH received a consult request from CDER to identify and evaluate the relevant device constituent manufacturing facilities and determine acceptability to support the current application.

## **REGULATORY HISTORY**

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

### Inspection Recommendation

1. Vetter Pharma-Fertigung GmbH & Co. KG  
Ravensburg, Baden-Wurttemberg, 88214 Germany  
FEI# 3005987757

Responsibility – This firm is involved in the manufacturing of the Abaloparatide-SC combination product.

Inspectional History – The most recent inspection was conducted July 18-July 26, 2016. This was a comprehensive Preapproval and GMP inspection which was conducted in accordance with Compliance Program Guidance Manual 7356.002 Drug Manufacturing Inspections; 7356.002A Sterile Drug Process Inspections; and 7382.845, Inspection of Medical Device Manufactures. No deficiencies were noted.

2. Ypsomed, AG  
Weissensteinstrasse 26  
Solothum, CH-4503 Switzerland  
FEI# 3005170966

Responsibility – This firm is involved in the manufacturing of the Abaloparatide-SC combination product.

Inspectional History – The most recent inspection was conducted August 22-August 25, 2016. This was a comprehensive inspection conducted in accordance with 7382.845, Inspection of Medical Device Manufactures. No deficiencies were noted.

### Inspection Recommendation

3. Vetter Pharma-Fertigung GmbH & Co. KG  
Eisenbahnstrasse 2-4  
Langenargen, Germany  
FEI# 3002808846

Responsibility – This firm is involved in the manufacturing of the Abaloparatide-SC combination product.

Inspectional History – The most recent inspection was conducted February 13-February 20, 2016. This was a comprehensive inspection which was conducted in accordance with Compliance Program Guidance Manual 7356.002 Drug Manufacturing Inspections. No deficiencies were noted during this inspection; however the most recent device inspection is unknown. Therefore, CDRH cannot attest to the compliance of the firm as it relates to 21 CFR 820.

### Inspection Recommendation

4. Vetter Pharma Holbeinstrasse (HOL), 40 88212  
Ravensburg, Germany

3003882331

Responsibility – This firm is involved in the manufacturing of the Abaloparatide-SC combination product.

Inspectional History – No EIR was provided for review; therefore CDRH cannot attest to the compliance of the firm as it relates to 21 CFR 820. CDRH Office of Compliance defers to CDER as it relates to the approvability of the application given the lack of information for this firm.

**OVERALL RECOMMENDATION**

As documented above, the consult request noted the need for an evaluation for four firms. Three EIR's were provided out of the four sites listed. Two EIR's documented device inspections and the other documented a drug inspection, only. There was no EIR provided for the last site.

Based on the information provided to the Office of Compliance for review, it appears that the application is approvable from the perspective of the compliance of Baden-Wurttemberg, Germany, VetterPharm, and Ypsomed site. CDRH defers to CDER as it relates to the approvability of the application based on the lack of information available for the Langenargen, Germany, and Ravensburg, Germany sites.

Latoya Oliver  
powell -A

Digitally signed by Latoya Oliver  
powell -A  
DN: c=US, o=U S Government  
ou=HHS, ou=FDA, ou=People  
0.9.2342.19200300.100.1.1=200035  
4592, cn=Latoya Oliver powell -A  
Date: 2016.11.17 16:54:20 -0500'

---

Latoya Oliver-Powell

Prepared: LOliver-Powell: 11/3/16  
Reviewed: FMLast name: RSwann: 11/18/2016

CTS No.: ICC1600174  
NDA (b) (4)

APPEARS THIS WAY ON ORIGINAL

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

/s/  
-----

THAO M VU  
11/22/2016  
upload on behalf of CDRH

---

## MEMORANDUM

### REVIEW OF HUMAN FACTORS VALIDATION PROTOCOL

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:** November 4, 2016

**Requesting Office or Division:** Division of Bone, Reproductive, and Urologic Products (DBRUP)

**Application Type and Number:** NDA 208743

**Product Name and Strength:** Proprietary name pending (abaloparatide) Injection  
80 mcg per dose

**Submission Date:** November 1, 2016

**Applicant/Sponsor Name:** Radius Health Inc.

**OSE RCM #:** 2016-1715

**DMEPA Primary Reviewer:** Walter Fava, RPh., MEd.

**DMEPA Associate Director for Human Factors:** Quynh Nhu Nguyen, MS

---

#### 1 PURPOSE OF MEMO

The Division of Bone, Reproductive, and Urologic Products requested that we review the revised human factors validation protocol for abaloparatide (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we communicated during a mid-cycle teleconference with the Applicant on September 22, 2016<sup>a</sup>. Our recommendations were to revise the priming step and needle removal step proposed in their proposed Instructions for Use (IFU) and re-validate these steps in another human factors validation study. The Applicant submitted their proposed revised human factors validation protocol and IFU for our review.

#### 2 CONCLUSION

We agree with the changes made to the IFU, but cannot determine how effective they are until the results of the human factors validation testing are available. We note that the

---

<sup>a</sup> Bell, S. Mid-Cycle Communication for abaloparatide (NDA 208743). Silver Spring (MD): FDA, CDER, CDRH, OSE, OSI, OCP, OPQ, OTS (US): 2016 Oct 19.

methodology for the validation study proposes to use a total of 15 study participants which will be a mix of experienced and inexperienced pen users. We expect each distinct group to have a minimum of 15 study subjects and provide specific recommendations to the Applicant in Section 3.

### **3 RECOMMENDATIONS FOR RADIUS HEALTH INC.**

We recommend the following be implemented prior to conducting your human factors validation study for the abaloparatide pen:

- A. Increase the number of study subjects to 30 to include 15 experienced and 15 inexperienced pen users as distinct user groups. Alternatively, you can provide data to support your proposed methodology of using 15 participants total.

**APPENDIX A. HUMAN FACTORS VALIDATION PROTOCOL AND INSTRUCTIONS FOR USE  
SUBMITTED ON OCTOBER 31, 2016**

The Revised Validation Study Protocol and IFU is located in DARRTS, received on November 1, 2016, eCTD Sequence Number0014.

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

/s/  
-----

WALTER L FAVA  
11/04/2016

QUYNHNHU T NGUYEN  
11/04/2016

**MEMORANDUM**

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

---

DATE: November 4, 2016

TO: Hylton Joffe, MD, M.M.Sc.  
Director  
Division of Bone, Reproductive, and Urologic Products

FROM: Michael F. Skelly, Ph.D.  
Lead Pharmacologist  
Division of Generic Drug Bioequivalence Evaluation  
(DGDBE)  
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.  
Director  
Division of Generic Drug Bioequivalence Evaluation  
(DGDBE)  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of EIR for Bioanalytical Inspection at (b) (4)  
(b) (4)  
NDA 208743 (Abaloparatide), sponsored by Radius Health,  
Inc.

**Inspection Summary:**

At the request of the Division of Bone, Reproductive, and Urologic Products, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the bioanalytical portion of study BA-058-05-016 at (b) (4)

(b) (4) The Form FDA 483 issued at the close of the inspection observed that (b) (4) used indirectly estimated concentrations of quality control (QC) samples, and wider limits for accepting bioanalytical runs than recommended in FDA guidance, impacting acceptance of run 147933 in the audited study. This reviewer recommends excluding data from run 147933, and accepting all other study data.

**Study Audited during this Inspection:**

**Study number:** BA058-05-016

**Study Title:** "A Randomized, Open Label, Single-Dose, 2-Way Crossover Study to Determine the Bioequivalence of Abaloparatide Administered Subcutaneously from Two Similar Pen Injectors to Healthy Postmenopausal Women"

**Sample Analysis:** January 19 to February 24, 2016

OSIS scientist Michael F. Skelly, Ph.D. conducted the inspection of the bioanalytical portion of study BA-058-05-016 from (b) (4), at the firm's present location, (b) (4). Parts of the method validation were conducted under the firm's original name, (b) (4), at the firm's original location at (b) (4). The audit covered the partial bioanalytical method validation and sample analyses for BA058 (abaloparatide) in plasma from study BA058-05-016. The study compared pharmacokinetics of abaloparatide after subcutaneous injection from two pen injectors. Thus, it was not a conventional bioequivalence study subject to 21 CFR 320.29(a). The method was transferred to (b) (4) from its developer (Ipsen Pharma) and another CRO (b) (4). (b) (4) conducted only a partial method validation.

The audit included a thorough review of facilities and equipment, review of study records and correspondence, and interviews and discussions with (b) (4) management and staff. As a global assessment of the firm's bioanalytical operations, I selected key components in other method validations to evaluate the firm's general bioanalytical operations.

At the conclusion of the inspection, I issued Form FDA 483 (**Attachment 1**). The Form FDA 483 observation, the firm's response dated October 12, 2016 (**Attachment 2**), and my evaluation follow.

**Observation:**

- 1. The run acceptance criteria used to demonstrate accuracy and precision were not appropriate. Specifically, you used indirectly estimated concentrations and pre-study variabilities to set criterial for quality control (QC) sample acceptance, instead of the actual concentrations and fixed percentage ranges. Run 147933 would have been rejected for failure of both high QC samples (actual concentration (b) (4) pg/mL) with fixed 20% acceptance criteria. These QCs were measured at (b) (4) % and (b) (4) % of the actual concentration.**

**Firm's Response:** (b) (4) acknowledged the observation and agreed that they did not use conventional run acceptance criteria. They will follow the FDA guidance in the future.

**OSIS Evaluation:** (b) (4) run acceptance criteria resembled the routine practices at diagnostic laboratories. During pre-study partial validation, (b) (4) measured abaloparatide concentrations in QC samples by comparison to calibrators. During the study, (b) (4) used these indirectly measured concentrations as criteria to decide run acceptance or rejection. FDA's guidance for Bioanalytical Method Validation recommends demonstration of accuracy and precision using simultaneous measurements of QC samples for run acceptance, with  $\pm 20\%$  acceptance ranges compared to nominal QC concentrations (for ligand binding assays), to test pharmacokinetic hypotheses. (b) (4) indirectly measured QC concentrations and wider acceptance ranges could have allowed less accurate and less precise measurements to be accepted. However, recalculated raw data from (b) (4) records revealed that all runs except 147933 would have passed using the more stringent conventional criteria.

Study BA058-05-016 was the first pharmacokinetic study by (b) (4) received at FDA, so there is no impact to other pharmacokinetic studies at this site.

**Recommendation:**

Following review of the EIR, I recommend that the bioanalytical data from study BA058-05-016, with the exception of run 147933, be accepted for further Agency review.

**Final Classification:**

VAI: (b) (4)

CC:

OTS/OSIS/Kassim/Taylor/Haidar/Fenty-Stewart/Nkah/Miller/Kadavil

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

OTS/OSIS/DGDBE/Cho/Skelly/Choi/Au

CDER/OND/DBRUP/Joffe

Draft: MFS 11/4/2016

Edit: KAS 11/4/2016; XC 11/4/2016; SC 11/4/2016

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE

Program/Bioanalytical Sites/ (b) (4)

FACTS: [REDACTED] (b) (4)

**Attachments:**

Attachment 1. Form FDA 483

Attachment 2. [REDACTED] (b) (4) Response to Form FDA 483

Michael F. Skelly, Ph.D.  
DGDBE, OSIS

Seongeun (Julia) Cho, Ph.D.  
Director  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance (OSIS)

4 Pages 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/  
-----

MICHAEL F SKELLY  
11/04/2016

SEONGEUN CHO  
11/04/2016

## Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

|                                    |                                                     |
|------------------------------------|-----------------------------------------------------|
| <b>IND or NDA</b>                  | 208743                                              |
| <b>Brand Name</b>                  | Not determined                                      |
| <b>Generic Name</b>                | Abaloparatide for injection                         |
| <b>Sponsor</b>                     | Radius Health, Inc.                                 |
| <b>Indication</b>                  | Treatment of postmenopausal women with osteoporosis |
| <b>Dosage Form</b>                 | Subcutaneous injection                              |
| <b>Drug Class</b>                  | Parathyroid hormone-related peptide                 |
| <b>Therapeutic Dosing Regimen</b>  | 80 µg                                               |
| <b>Duration of Therapeutic Use</b> | Chronic                                             |
| <b>Maximum Tolerated Dose</b>      | 240 µg                                              |
| <b>Submission Number and Date</b>  | 001 / 3/30/2016                                     |
| <b>Review Division</b>             | DBRUP                                               |

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

### 1 SUMMARY

#### 1.1 OVERALL SUMMARY OF FINDINGS

Transient and marginal increases in the QTc interval were observed in this TQT study. Based on QTcF, the largest upper bound of the 2-sided 90% CI for the mean difference between abaloparatide-SC 240 µg and placebo is 12.5 ms (Table 1). Abaloparatide increases heart rate significantly, with a mean peak increase of 15 bpm and 20 bpm at the first time point (15 minutes) after dosing with 80 µg and 240 µg, respectively. It is likely that the observed increases in QTc were due to the increased heart rate at the early time points.

The largest lower bound of the two-sided 90% CI for the  $\Delta\Delta$ QTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 6, indicating that assay sensitivity was established.

In this randomized, partially double-blind, placebo- and positive-controlled, 4-periods crossover study, 55 healthy subjects received abaloparatide-SC 80 µg, abaloparatide-SC 240 µg, moxifloxacin and placebo. Overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Abaloparatide-SC ( 80 µg and 240 µg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

| Treatment               | Time (hour) | ΔΔQTcF (ms) | 90% CI (ms) |
|-------------------------|-------------|-------------|-------------|
| Abaloparatide SC 80 µg  | 0.5         | 6.9         | (4.1, 9.7)  |
| Abaloparatide SC 240 µg | 0.5         | 9.7         | (6.9, 12.5) |
| *Moxifloxacin 400 mg*   | 2           | 10.9        | (8.8, 13.0) |

\*Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 8.0 ms.

The suprathreshold dose (240 µg) produces mean C<sub>max</sub> 2.2-fold that for the therapeutic dose (80 µg). Abaloparatide is a peptide and the likelihood of drug-drug interactions and hepatic impairment on PK is considered low. The concentrations achieved with the suprathreshold dose in this TQT study are above those for the predicted worst case scenario (severe renal impairment). Based on the concentration-QTc analysis, no QT-interval prolongations of clinical concern is expected at the therapeutic concentration range.

## 2 PROPOSED LABEL

The following is the sponsor’s proposed labeling language related to QT.

### 12.2. Pharmacodynamics

(b) (4)

A thorough QT/QTc study (4-way cross over) was conducted in 55 healthy subjects who received single doses of placebo, subcutaneous doses of abaloparatide at 80 mcg, (b) (4) (b) (4) 240 mcg (b) (4) and moxifloxacin 400 mg orally. (b) (4) abaloparatide increased heart rate, with a mean peak increase of 15 bpm and 20 bpm at the first time point (15 minutes) after dosing with 80 mcg and 240 mcg, respectively, (b) (4) there was no clinically meaningful (b) (4) or cardiac electrophysiology.

*The sponsor’s proposed labeling language is acceptable. QT-IRT’s proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.*

### **3 BACKGROUND**

#### **3.1 PRODUCT INFORMATION**

Parathyroid hormone-related peptide (PTHrP) acts as a biological signal in several tissues, including bone. It is thought to play a pivotal role as an endogenous stimulator of bone formation, which acts on committed osteoblast precursors in order to enhance their differentiation and also to reduce osteoblast apoptosis. Abaloparatide is a synthetic 34 amino acid analog of PTHrP (1-34), with specific amino acid substitutions. Based on the biology of PTHrP, abaloparatide is designed to have a greater net bone anabolic effect and also less resorptive and hypercalcemic effects than does PTH.

#### **3.2 MARKET APPROVAL STATUS**

Abaloparatide is not approved for marketing in any country.

#### **3.3 PRECLINICAL INFORMATION**

The cardiovascular effects of abaloparatide have been studied both in vitro (rabbit Purkinji fiber and Human Embryonic Kidney 293 [HEK-293]) cells and in vivo (anesthetized and unanesthetized beagle dogs).

In the study in rabbit Purkinje fibers, there was no significant effect on resting membrane potential, maximal rate of depolarization, amplitude of action potential, and action potential duration at 30% (ADP30) at all doses evaluated. The study in HEK-293 cells revealed a slight decrease in human ether-à-go-go-related gene current with maximal effect of 14% at 30  $\mu$ M.

The study in anesthetized dogs demonstrated increases in cardiac output secondary to changes in aortic blood pressure, total peripheral resistance, and heart rate (HR) following administration of abaloparatide. In these animals, a dose-dependent shortening of PR intervals (PR) and QT intervals (QT) at doses of 0.3  $\mu$ g/kg and above was observed without direct effects on the electrocardiogram (ECG) or prolongation of corrected QT intervals (QTc). In the study in conscious dogs, there were similar results; administration of abaloparatide increased HR and decreased arterial blood pressure but did not lengthen QTc and did not modify the morphology of the ECG.

#### **3.4 PREVIOUS CLINICAL EXPERIENCE**

See Appendix 6.1

#### **3.5 CLINICAL PHARMACOLOGY**

Appendix 6.1 summarizes the key features of abaloparatide's clinical pharmacology.

### **4 SPONSOR'S SUBMISSION**

#### **4.1 OVERVIEW**

The QT-IRT reviewed the protocol prior to conducting this study under IND 73176. The sponsor submitted the study report BA058-05-012 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

## 4.2 TQT STUDY

### 4.2.1 Title

A Randomized, Partially Double-blind, Single-dose, Positive-controlled (Moxifloxacin) and Placebo-controlled 4-way Crossover Study to Evaluate the Effects of Abaloparatide on the QT/QTc Interval in Healthy Subjects

### 4.2.2 Protocol Number

BA058-05-012

### 4.2.3 Study Dates

Date first subject enrolled: 22 January 2015

Date last subject completed: 16 March 2015

### 4.2.4 Objectives

The primary objective of the study was to assess the effect of a single-dose subcutaneous (SC) administration of abaloparatide on the (QT) interval corrected for heart rate (HR) using Fridericia's formula (QTcF).

The secondary objectives of the study were:

- To assess the relationship between plasma concentrations of abaloparatide and its effects, if any, on the QT/ QTc interval
- To study the effect of abaloparatide on the other electrocardiogram (ECG) parameters (HR, RR interval, PR interval, QRS duration, QT interval, and waveform morphology)
- To assess the effect of a positive control (oral moxifloxacin) on the QT/QTc interval in healthy subjects
- To confirm pharmacokinetic (PK) parameters for abaloparatide

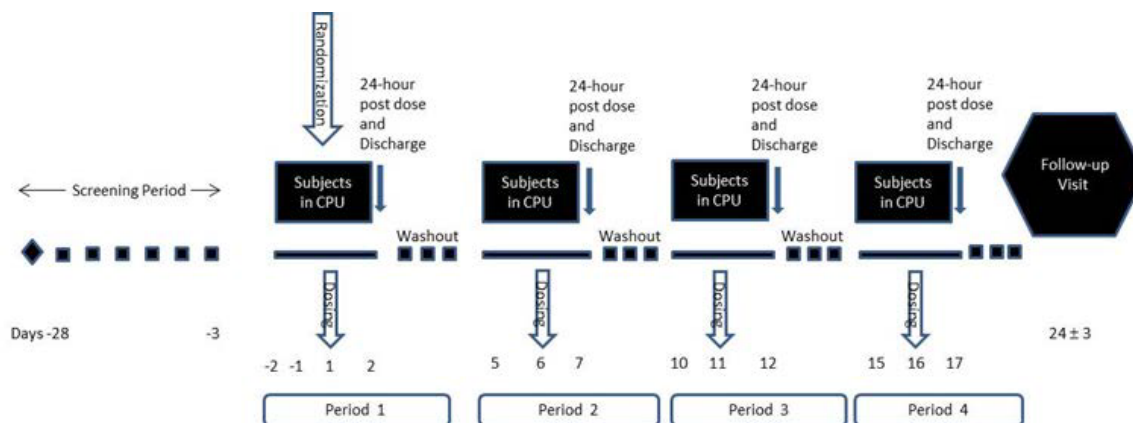
### 4.2.5 Study Description

#### 4.2.5.1 Design

This was a randomized, partially double-blind, single-dose, positive-controlled and placebo-controlled, 4-way crossover study in healthy male and female subjects using a therapeutic dose (80 µg) and a suprathreshold dose (240 µg) of abaloparatide for injection-SC (abaloparatide-SC), matching placebo administered SC, and orally administered moxifloxacin (400 mg) in 4 separate treatment periods. Subjects were confined to the clinical pharmacology unit (CPU) from day -2 of period 1 and from the day prior to dosing for subsequent periods (days 5, 10, and 15) until completion of PK sample collection, pharmacodynamic (PD) Holter ECGs, and safety assessments on the day following dosing (on days 2, 7, 12, and 17) in each of the 4 respective treatment periods. There was a 5-day washout period following administration of each treatment. A follow-up visit occurred 7±3 days after CPU discharge in period 4 (day 24 ±3 days).

An overview of the study design is presented in Figure 1.

**Figure 1 : Study Design Schematic**



#### 4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

#### 4.2.5.3 Blinding

The positive (moxifloxacin) control was administered open label.

#### 4.2.6 Treatment Regimen

##### 4.2.6.1 Treatment Arms

Subjects received the following 4 single-dose treatments according to a randomly assigned treatment sequence, in separate treatment periods:

- Placebo, administered-SC, double-blind; subjects were randomly assigned to receive an 80 µg or 240 µg equivalent placebo dose
- Therapeutic dose, abaloparatide-SC 80 µg, double-blind
- Supratherapeutic dose, abaloparatide-SC 240 µg, double-blind
- Moxifloxacin (400 mg) orally administered, open-label (1 tablet)

##### 4.2.6.2 Sponsor's Justification for Doses

A Phase 1 bioavailability/single-ascending dose (SAD) study (Study BA058-05-010) was conducted to select the supratherapeutic or maximum tolerated dose (MTD) for use in this QT/QTc study. In this study, the MTD was defined as being 1 dose level below an intolerable dose. An intolerable dose is defined as a dose that met 1 or more of the following criteria:

1. If 50% or more of the study subjects in a cohort experienced the same AE of moderate severity or greater that cannot be unequivocally shown as not related to study drug.
2. If 50% or more of the study subjects in a cohort experience orthostatic hypotension defined as a decrease in systolic blood pressure of 20 mmHg or a decrease in diastolic blood pressure of 10 mmHg within 3 minutes of standing when compared with blood pressure from a supine position.
3. If 50% or more of the subjects in a cohort experience hypercalcemia (defined as serum total calcium  $\geq 2.8$  mmol/L [11.2 mg/dL]) that is persistent during the

treatment period. The results of this study indicated that a dose of 280 µg was not tolerated; therefore, a dose of 240 µg was selected as the MTD for the present QT/QTc study.

*Reviewer's Comment: Acceptable. In this TQT study, the  $C_{max}$  and AUC of the 240-ug dose are about 2.2- and 2.3- fold those of the proposed therapeutic dose of 80 µg. Abaloparatide is a peptide and the likelihood of drug-drug interactions and hepatic impairment on PK is considered low. The concentrations achieved with the supratherapeutic dose in this TQT study are above those for the predicted worst case scenario (severe renal impairment).*

#### **4.2.6.3 Instructions with Regard to Meals**

Doses of abaloparatide, placebo, and moxifloxacin were administered in the morning after an overnight fast of at least 8 hours on days 1, 6, 11, and 16, according to the randomization scheme. Dosing for each subject occurred at the same time ( $\pm 5$  minutes) across treatment periods.

A standard lunch was served at a minimum of 4 hours after administration of treatment. A standard dinner was served approximately 6 hours later and an evening snack was provided. Meals schedules were the same for the same subject across all 4 treatment periods. There was no breakfast served on dosing days or on day -1.

*Reviewer's Comment: Acceptable. No significant food effect on PK is expected because abaloparatide is administered subcutaneously.*

#### **4.2.6.4 ECG and PK Assessments**

From the Holter recordings beginning on Days 1, 6, 11, and 16, triplicate ECGs will be extracted from flashcards at each of the following PD ECG time points, nominally designated as the following on the day of dosing: 0.75, 0.5, and 0.25 hours predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 4, 6, 8, 12, and 24 hours post dose.

PK blood samples was collected based on the sampling schedule in the **Table 2**.

**Table 2: Pharmacokinetic Sampling Schedule**

| Sample collection time |                | Time                          |
|------------------------|----------------|-------------------------------|
| Study day              | Time (event)   | (Relative to dosing)<br>h:min |
| Days 1, 6, 11, 16      | 0 h (pre-dose) | -0:15 <sup>a</sup>            |
|                        | 15 min         | 0:15 <sup>a</sup>             |
|                        | 30 min         | 0:30 <sup>a</sup>             |
|                        | 45 min         | 0:45 <sup>a</sup>             |
|                        | 1 h            | 01:00 <sup>a</sup>            |
|                        | 1 h 30 min     | 01:30 <sup>a</sup>            |
|                        | 2 h            | 02:00 <sup>a</sup>            |
|                        | 2 h 30 min     | 02:30 <sup>a</sup>            |
|                        | 4 h            | 04:00 <sup>a</sup>            |
|                        | 6 h            | 06:00 <sup>c</sup>            |
|                        | 8 h            | 08:00 <sup>b</sup>            |
| Days 2, 7, 12, 17      | 12 h           | 12:00 <sup>b</sup>            |
|                        | 24 h           | 24:00 <sup>c,d</sup>          |

<sup>a</sup> Collected within a time window of  $\pm 5$  minutes.

<sup>b</sup> Collected within a time window of  $\pm 10$  minutes.

<sup>c</sup> Collected within a time window of  $\pm 15$  minutes.

<sup>d</sup> Collected prior to discharge.

*Reviewer's Comment: The timing of ECG/PK sampling is acceptable. abaloparatide showed a median  $t_{max}$  of 0.35 h, which could be captured by the sampling schedule.*

#### 4.2.6.5 Baseline

Applicant used an averaged pre-dose QTc values as baseline.

#### 4.2.1 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

#### 4.2.2 Sponsor's Results

##### 4.2.2.1 Study Subjects

A total of 148 subjects were screened, and 55 of these subjects were enrolled in the study. A total of 49/55(89.1%) subjects completed the study.

Of the 55 subjects enrolled in the study, 55 (100.0%) subjects were included in the safety population, 53 (96.4%) subjects were included in the PK population, and 52 (94.5%) subjects were included in the PD population.

##### 4.2.2.2 Statistical Analyses

###### 4.2.2.2.1 Primary Analysis

The primary endpoint was baseline-adjusted mean difference between abaloparatide-SC (80  $\mu$ g and 240  $\mu$ g) and placebo in  $\Delta$ QTcF. The sponsor used an analysis of covariance model. The model included period, sequence, treatment, time, and treatment by time interaction as fixed effects; subject as a random effect; and the baseline as covariate. The sponsor concluded that abaloparatide has no QTcF prolongation effect, as the upper

bounds of the 2-sided 90% CIs for the mean differences between abaloparatide (80 µg and 240 µg) and placebo were below 10 ms. The Applicant's results are presented in Table 3 and Table 4. The Applicant's concluded that Abaloparatide-SC did not cause an effect on the QTcI interval of clinical concern and an effect exceeding 10 ms could be excluded at all post-dosing time points. The largest placebo-corrected ΔQTcI was observed 30 minutes after dosing and reached 5.3 ms (90% CI: 2.7 to 8.0) and 7.1 ms (90% CI: 4.4 to 9.7) in the 80 µg and 240 µg group, respectively.

**Table 3: Placebo-Adjusted Change from Baseline - Estimates from Mixed Effects General Linear Model QTc Individual (ms) - Electrocardiographic Analysis Set**

| Time     | Abaloparatide-SC<br>80 ug<br>(n=52) |                       |                       | Abaloparatide-SC<br>240 ug<br>(n=52) |                       |                       | Moxifloxacin<br>400 mg/day<br>(n=50) |                       |                       |
|----------|-------------------------------------|-----------------------|-----------------------|--------------------------------------|-----------------------|-----------------------|--------------------------------------|-----------------------|-----------------------|
|          | Estimate<br>[1]                     | Lower<br>Bound<br>[2] | Upper<br>Bound<br>[2] | Estimate<br>[1]                      | Lower<br>Bound<br>[2] | Upper<br>Bound<br>[2] | Estimate<br>[1]                      | Lower<br>Bound<br>[2] | Upper<br>Bound<br>[2] |
| 15 Min   | 2.9                                 | 0.3                   | 5.6                   | 4.0                                  | 1.3                   | 6.6                   | 1.6                                  | -2.0                  | 5.2                   |
| 30 Min   | 5.3                                 | 2.7                   | 8.0                   | 7.1                                  | 4.4                   | 9.7                   | 3.9                                  | 0.2                   | 7.5                   |
| 45 Min   | 4.0                                 | 1.3                   | 6.6                   | 5.0                                  | 2.4                   | 7.6                   | 6.3                                  | 2.7                   | 10.0                  |
| 1 Hr     | 1.5                                 | -1.1                  | 4.2                   | 2.4                                  | -0.2                  | 5.1                   | 7.6                                  | 3.9                   | 11.2                  |
| 1.5 Hr   | 0.2                                 | -2.4                  | 2.9                   | -2.2                                 | -4.8                  | 0.4                   | 7.2                                  | 3.6                   | 10.8                  |
| 2 Hr     | -0.3                                | -2.9                  | 2.3                   | -3.4                                 | -6.1                  | -0.8                  | 10.7                                 | 7.1                   | 14.4                  |
| 2.5 Hr   | -0.9                                | -3.5                  | 1.7                   | -3.8                                 | -6.4                  | -1.2                  | 10.5                                 | 6.9                   | 14.1                  |
| 4 Hr     | -2.5                                | -5.1                  | 0.1                   | -4.5                                 | -7.2                  | -1.9                  | 11.2                                 | 7.6                   | 14.8                  |
| 6 Hr     | -4.6                                | -7.3                  | -2.0                  | -6.0                                 | -8.6                  | -3.4                  | 7.2                                  | 3.6                   | 10.8                  |
| 8 Hr     | -4.2                                | -6.8                  | -1.6                  | -4.2                                 | -6.8                  | -1.5                  | 5.6                                  | 1.9                   | 9.2                   |
| 12 Hr    | 1.1                                 | -1.5                  | 3.7                   | -0.3                                 | -3.0                  | 2.3                   | 5.6                                  | 2.0                   | 9.3                   |
| 24 Hr    | 1.1                                 | -1.5                  | 3.7                   | 0.5                                  | -2.1                  | 3.2                   | 4.7                                  | 1.0                   | 8.3                   |
| Time Ave | 0.3                                 | -1.5                  | 2.2                   | -0.4                                 | -2.2                  | 1.4                   | 6.8                                  | 4.3                   | 9.3                   |

[1] Mixed Effect General Linear Model is fit for time-matched changes from baseline and includes terms for treatment, time, and interactions: treatment by time.

[2] Lower/Upper Bound = lower or upper 2-sided 90% (i.e. 1-sided 95%). Note: Presented bounds are multiplicity adjusted for moxifloxacin only.

Source: Abaloparatide-SC QT/QTc Expert Report, Table 5.4, page 34/313

**Table 4: Placebo-Adjusted Change from Baseline - Estimates from Mixed Effects General Linear Model QTc Fridericia's (ms) - Electrocardiographic Analysis Set**

| Time     | Abaloparatide-SC<br>80 ug<br>(n=52) |                       |                       | Abaloparatide-SC<br>240 ug<br>(n=52) |                       |                       | Moxifloxacin<br>400 mg/day<br>(n=50) |                       |                       |
|----------|-------------------------------------|-----------------------|-----------------------|--------------------------------------|-----------------------|-----------------------|--------------------------------------|-----------------------|-----------------------|
|          | Estimate<br>[1]                     | Lower<br>Bound<br>[2] | Upper<br>Bound<br>[2] | Estimate<br>[1]                      | Lower<br>Bound<br>[2] | Upper<br>Bound<br>[2] | Estimate<br>[1]                      | Lower<br>Bound<br>[2] | Upper<br>Bound<br>[2] |
| 15 Min   | 4.5                                 | 2.1                   | 6.8                   | 6.4                                  | 4.1                   | 8.8                   | 1.9                                  | -1.4                  | 5.1                   |
| 30 Min   | 6.8                                 | 4.5                   | 9.2                   | 9.6                                  | 7.3                   | 12.0                  | 4.0                                  | 0.7                   | 7.2                   |
| 45 Min   | 5.0                                 | 2.6                   | 7.3                   | 7.2                                  | 4.8                   | 9.5                   | 6.3                                  | 3.0                   | 9.5                   |
| 1 Hr     | 3.4                                 | 1.1                   | 5.8                   | 4.9                                  | 2.6                   | 7.3                   | 7.9                                  | 4.6                   | 11.1                  |
| 1.5 Hr   | 1.2                                 | -1.2                  | 3.6                   | -0.0                                 | -2.4                  | 2.3                   | 7.6                                  | 4.4                   | 10.9                  |
| 2 Hr     | 0.2                                 | -2.2                  | 2.5                   | -1.3                                 | -3.6                  | 1.1                   | 10.9                                 | 7.6                   | 14.1                  |
| 2.5 Hr   | -0.4                                | -2.7                  | 2.0                   | -2.1                                 | -4.5                  | 0.3                   | 10.0                                 | 6.8                   | 13.3                  |
| 4 Hr     | -2.2                                | -4.6                  | 0.2                   | -3.4                                 | -5.8                  | -1.1                  | 10.5                                 | 7.3                   | 13.7                  |
| 6 Hr     | -4.8                                | -7.2                  | -2.5                  | -4.9                                 | -7.3                  | -2.6                  | 6.0                                  | 2.8                   | 9.3                   |
| 8 Hr     | -3.9                                | -6.3                  | -1.6                  | -3.7                                 | -6.1                  | -1.4                  | 5.3                                  | 2.0                   | 8.5                   |
| 12 Hr    | 1.2                                 | -1.1                  | 3.6                   | 0.3                                  | -2.1                  | 2.6                   | 5.5                                  | 2.3                   | 8.8                   |
| 24 Hr    | 0.2                                 | -2.2                  | 2.5                   | 0.2                                  | -2.1                  | 2.6                   | 4.1                                  | 0.9                   | 7.4                   |
| Time Ave | 1.0                                 | -0.5                  | 2.5                   | 1.1                                  | -0.4                  | 2.7                   | 6.7                                  | 4.6                   | 8.8                   |

[1] Mixed Effect General Linear Model is fit for time-matched changes from baseline and includes terms for treatment, time, and interactions: treatment by time.

[2] Lower/Upper Bound = lower or upper 2-sided 90% (i.e. 1-sided 95%). Note: Presented bounds are multiplicity adjusted for moxifloxacin only.

Source: Abaloparatide-SC QT/QTc Expert Report, Table 5.4, page 35/313

Reviewer's Comments: We will provide our independent analysis results in section 5.2. Our results are similar with the applicant's QTcF results.

#### 4.2.2.2.2 Assay Sensitivity

The moxifloxacin QT response demonstrated assay sensitivity for the study, since the lower bound of the Bonferroni-adjusted 90% CIs of  $\Delta\Delta$ QTcI exceeded 5 ms at 3 of 4 pre-defined time points (see Table 3 and Table 4) and the  $\Delta\Delta$ QTc profile was as expected.

Reviewer's Comments: We will provide our independent analysis results in section 5.2.

#### 4.2.2.2.3 Categorical Analysis

No subjects with QTcI or QTcF > 480 ms or  $\Delta$ QTcI or  $\Delta$ QTcF > 60 ms.

**Table 5: Applicant's Categorical Analysis**

|                                               | Abaloparatide<br>80 µg | Abaloparatide<br>240 µg | Moxifloxacin<br>400 mg | Placebo |
|-----------------------------------------------|------------------------|-------------------------|------------------------|---------|
| Total N                                       | 52                     | 52                      | 50                     | 51      |
| Heart Rate in bpm (mean change from baseline) | 8.7                    | 12.2                    | 3.1                    | 2.4     |
| Heart Rate tachycardic outliers, n (%)        | 2 (4%)                 | 6 (12%)                 | 1 (2%)                 | 0       |
| Heart Rate bradycardic outliers, n (%)        | 0                      | 0                       | 0                      | 0       |
| PR outliers, n (%)                            | 0                      | 0                       | 0                      | 0       |
| QRS outliers, n (%)                           | 0                      | 0                       | 0                      | 0       |
| QT new >500 ms, n (%)                         | 0                      | 0                       | 0                      | 0       |
| QTcI new >500 ms, n (%)                       | 0                      | 0                       | 0                      | 0       |
| QTcI new >480 ms, n (%)                       | 0                      | 0                       | 0                      | 0       |
| Increase in QTcI >30-60 ms, N (%)             | 2 (4%)                 | 4 (8%)                  | 0                      | 0       |
| Increase in QTcI >60 ms, n (%)                | 0                      | 0                       | 0                      | 0       |
| QTcF new >500 ms, n (%)                       | 0                      | 0                       | 0                      | 0       |
| QTcF new >480 ms, n (%)                       | 0                      | 0                       | 0                      | 0       |
| Increase in QTcF >30-60 ms, n (%)             | 1 (2%)                 | 1 (2%)                  | 0                      | 0       |
| Increase in QTcF >60 ms, n (%)                | 0                      | 0                       | 0                      | 0       |

bpm = beats per minute; ms=milliseconds; QTcI: Individual correction; QTcF= Fridericia correction; Source: Selected data from Tables 14.2.3.1 through 14.2.3.7 Appendix 1

#### 4.2.2.3 (Safety Analysis)

No deaths, SAEs, or other significant AEs occurred during the study. There were no severe TEAEs reported in subjects who received abaloparatide 80 µg; there was one (1) severe TEAE reported in a subject who received abaloparatide 240 µg. All TEAEs were transient and resolved by the end of the study.

#### 4.2.2.4 Clinical Pharmacology

##### 4.2.2.4.1 Pharmacokinetic Analysis

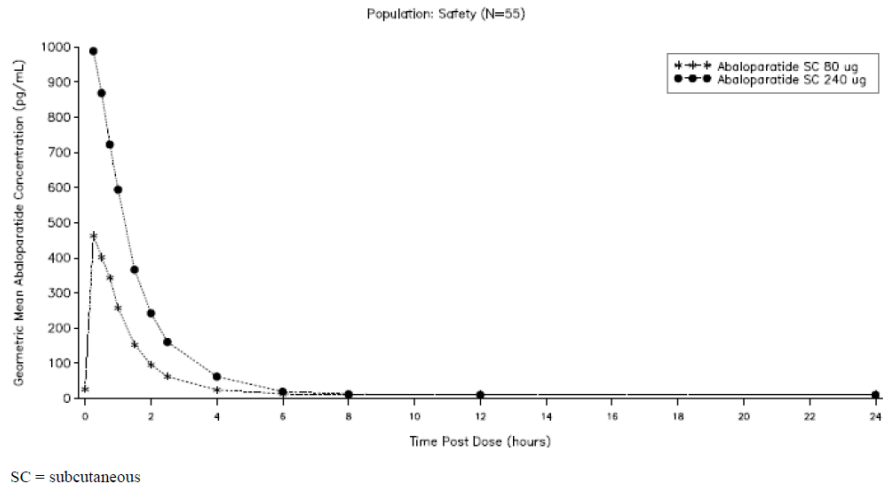
The PK results of abaloparatide are presented in Figure 2 and Table 6. The geometric mean of C<sub>max</sub> and AUC values following administration of 240 µg abaloparatide Supra were 2.2-fold and 2.3-fold respectively those with 80 µg, the intended clinical dose.

**Table 6: Summary of Abaloparatide Plasma Concentration Parameters (PK Population)**

|                                        | Abaloparatide-SC 80 µg<br>(N = 52) | Abaloparatide-SC 240 µg<br>(N = 52) |
|----------------------------------------|------------------------------------|-------------------------------------|
| <b>PK Parameter</b>                    |                                    |                                     |
| <b>C<sub>max</sub> (pg/mL)</b>         |                                    |                                     |
| n                                      | 52                                 | 52                                  |
| Mean                                   | 511.5                              | 1125.5                              |
| SD                                     | 150.44                             | 453.53                              |
| CV%                                    | 29.4                               | 40.3                                |
| Median                                 | 493.0                              | 1014.0                              |
| Q1, Q3                                 | 404.0, 567.0                       | 842.0, 1351.0                       |
| Min, Max                               | 230, 928                           | 534, 3000                           |
| GeoMean                                | 490.6                              | 1057.6                              |
| <b>T<sub>max</sub> (h)</b>             |                                    |                                     |
| n                                      | 52                                 | 52                                  |
| Mean                                   | 0.4506                             | 0.5096                              |
| SD                                     | 0.19543                            | 0.27179                             |
| CV%                                    | 43.4                               | 53.3                                |
| Median                                 | 0.3333                             | 0.3333                              |
| Q1, Q3                                 | 0.3333, 0.5833                     | 0.3333, 0.5833                      |
| Min, Max                               | 0.333, 1.083                       | 0.333, 1.583                        |
| <b>C<sub>last</sub> (pg/mL)</b>        |                                    |                                     |
| n                                      | 52                                 | 52                                  |
| Mean                                   | 31.27                              | 36.85                               |
| SD                                     | 8.953                              | 13.676                              |
| CV%                                    | 28.6                               | 37.1                                |
| Median                                 | 30.00                              | 35.00                               |
| Q1, Q3                                 | 23.00, 38.00                       | 26.00, 43.00                        |
| Min, Max                               | 20.0, 52.0                         | 20.0, 82.0                          |
| GeoMean                                | 30.06                              | 34.71                               |
| <b>AUC<sub>last</sub> (h*pg/mL)</b>    |                                    |                                     |
| n                                      | 52                                 | 52                                  |
| Mean                                   | 724.7                              | 1713.7                              |
| SD                                     | 385.98                             | 974.76                              |
| CV%                                    | 53.3                               | 56.9                                |
| Median                                 | 637.9                              | 1514.2                              |
| Q1, Q3                                 | 491.3, 895.1                       | 1138.8, 1894.8                      |
| Min, Max                               | 195, 2288                          | 503, 5979                           |
| GeoMean                                | 644.6                              | 1523.8                              |
| <b>AUC<sub>(0-inf)</sub> (h*pg/mL)</b> |                                    |                                     |
| n                                      | 50                                 | 52                                  |
| Mean                                   | 774.0                              | 1771.4                              |
| SD                                     | 396.20                             | 992.60                              |
| CV%                                    | 51.2                               | 56.0                                |
| Median                                 | 678.1                              | 1581.3                              |
| Q1, Q3                                 | 528.3, 984.6                       | 1187.3, 1950.4                      |
| Min, Max                               | 225, 2325                          | 520, 6044                           |
| GeoMean                                | 694.5                              | 1581.1                              |
| <b>t<sub>½</sub> (h)</b>               |                                    |                                     |
| n                                      | 51                                 | 52                                  |
| Mean                                   | 0.9631                             | 1.0744                              |
| SD                                     | 0.40991                            | 0.25696                             |
| CV%                                    | 42.6                               | 23.9                                |
| Median                                 | 0.8774                             | 1.0039                              |
| Q1, Q3                                 | 0.6471, 1.1729                     | 0.9060, 1.1739                      |
| Min, Max                               | 0.427, 2.975                       | 0.497, 1.881                        |

CV% = coefficient of variation; GeoMean = geometric mean; hr = hour; Max = maximum; Min = minimum; Q = quartile; SD = standard deviation; SC = subcutaneous

**Figure 2: Plot of Geometric Mean Abaloparatide Plasma Concentrations versus Time on a Linear Scale**



**4.2.2.4.2 Exposure-Response Analysis**

The relationships between the individually observed abaloparatide concentrations and  $\Delta\Delta QTcI$  and  $\Delta\Delta QTcF$  are presented in Figure 3 and Figure 4.

**Figure 3: Placebo-Corrected Change from Baseline QTcI vs Exposure**

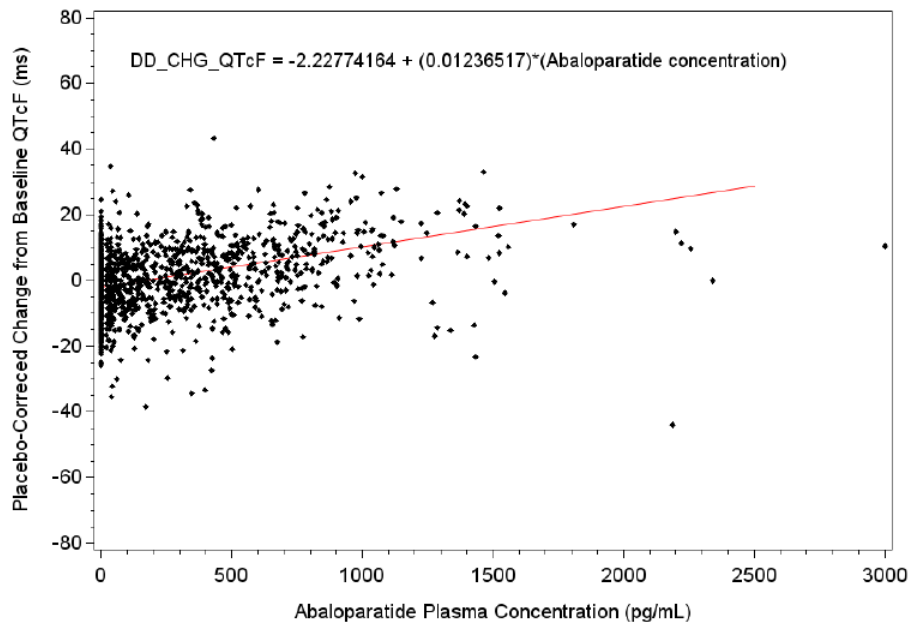


**Figure 4: Placebo-Corrected Change from Baseline QTcF vs Exposure**

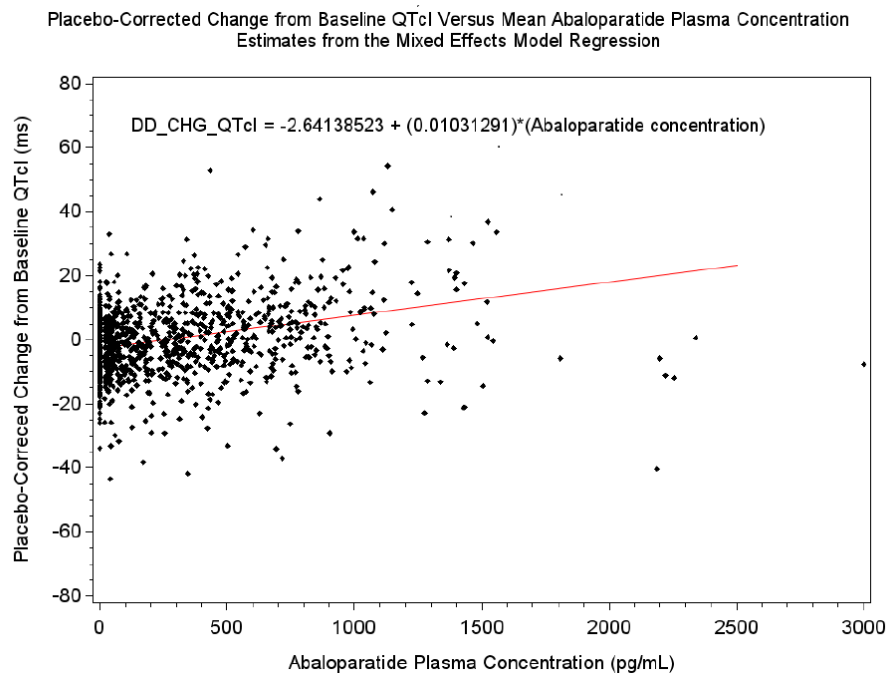


Table 7 shows results of the pharmacokinetic-pharmacodynamic model, using all available data, for the slopes of the relationships for placebo adjusted change from baseline in QTcI and QTcF versus abaloparatide plasma concentration.

**Table 7: Concentration-QTc Effect Analysis - Placebo Adjusted Change from Baseline versus the 80µg Abaloparatide-SC Concentrations Estimates from Linear Mixed Model – QTc Individual and QTc Fridericia Pharmacokinetic-Pharmacodynamic Population**

| QT Parameter | Slope (90%CI)of Plasma Conc. Effect on $\Delta\Delta QTc$ [1] | Standard Error of Slope of Plasma Conc. Effect on $\Delta\Delta QTc$ {1} | p-value Slope of Plasma Conc. Effect on $\Delta\Delta QTc$ [1] | Overall Model Fit [1] |
|--------------|---------------------------------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------|-----------------------|
| QTcI         | 0.01031291<br>(0.007572, 0.013054)                            | 0.00166640                                                               | <.0001                                                         | <0.0001               |
| QTcF         | 0.01236517<br>(0.010139, 0.014601)                            | 0.00135908                                                               | <.0001                                                         | <0.0001               |

[1] Linear mixed effects model is fit for change from baseline versus the abaloparatide plasma concentration. Subject random effects on the intercept and slope (i.e., concentration) are also included. Model fit p-value is based on a Null Model Log Likelihood Ratio Test

The predicted QT effect ( $\Delta\Delta QTcI$ ) at the observed mean (511.5 pg/mL) and maximum  $C_{max}$  (928 pg/mL) after 80 µg abaloparatide-SC were 2.6 and 6.9 ms, respectively, with the upper bound of the 1-sided 95% CI below 10 ms at the highest dose (9.5 ms).

*Reviewer's Analysis: The reviewer's independent analysis is presented in Section 5.3. Similar to the sponsor's analysis, shallow but significant relationships between observed abaloparatide concentrations and  $\Delta\Delta QTcI$  and  $\Delta\Delta QTcF$  were observed.*

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

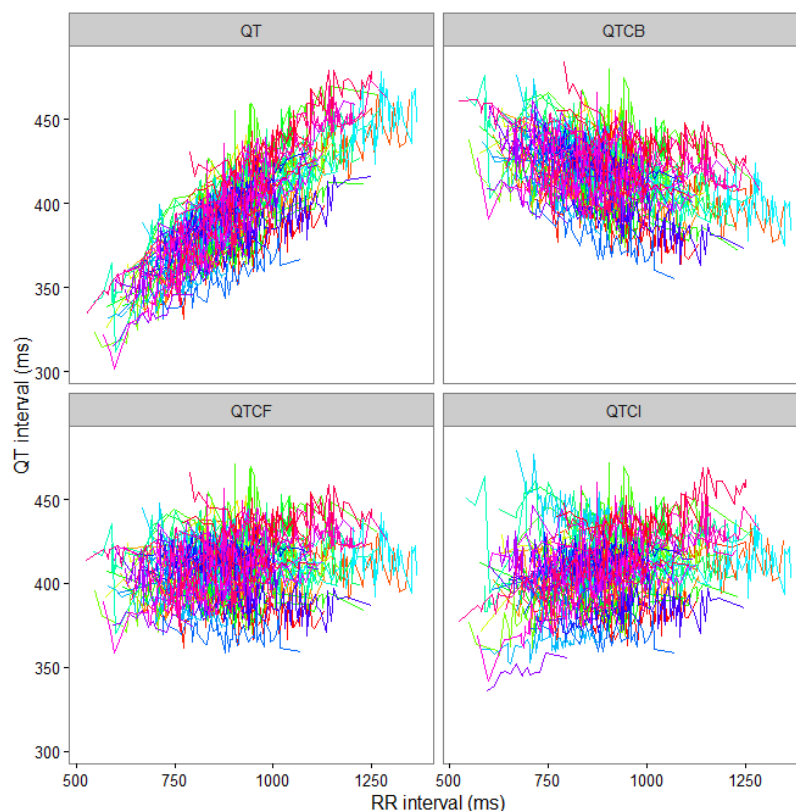
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 8 and Figure 5, it appears that QTcF is better than QTcI in both treatment groups. This reviewer use QTcF as primary statistical analysis and QTcI as supplemental information. The sponsor used QTcI as primary outcome.

**Table 8: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

| Treatment Group         | Correction Method |        |      |        |      |        |
|-------------------------|-------------------|--------|------|--------|------|--------|
|                         | QTcI              |        | QTcB |        | QTcF |        |
|                         | N                 | MSSS   | N    | MSSS   | N    | MSSS   |
| Abaloparatide SC 240 ug | 52                | 0.0041 | 52   | 0.0183 | 52   | 0.0035 |
| Abaloparatide SC 80 ug  | 52                | 0.0031 | 52   | 0.0128 | 52   | 0.0022 |
| Moxifloxacin 400 mg     | 50                | 0.0021 | 50   | 0.0072 | 50   | 0.0025 |
| Placebo                 | 51                | 0.0029 | 51   | 0.0060 | 51   | 0.0023 |
| All                     | 55                | 0.0018 | 55   | 0.0069 | 55   | 0.0007 |

The relationship between different correction methods and RR is presented in Figure 5.

**Figure 5: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1.1 The Primary Analysis for Abaloparatide SC

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcF effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in

Based on QTcF and QTcI intervals, marginal QTc prolongation effect of abaloparatide at the suprathreshold dose (SC 240  $\mu$ g) are observed in this TQT study, although this could be the impact of inadequate heart rate correction for both outcomes since abaloparatide significantly increases heart rate (Section **Error! Reference source not found.**).

**Table 9.** The largest upper bounds of the 2-sided 90% CI for the mean differences between Abaloparatide-SC 80 ug and placebo, and between Abaloparatide-SC 240 ug are 9.7 ms and 12.5 ms, respectively. This reviewer also used the same model to analyze  $\Delta$ QTcI and the results are listed in Table 10. The largest upper bound of the 2-sided 90% CI for the mean difference between Abaloparatide SC 80 ug and placebo is 8.7 ms. However, the largest upper bound for the mean difference between Abaloparatide SC 240 ug exceed 10 ms (10.4 ms) of the regulatory concern as described in ICG E14 guidelines. Based on QTcF and QTcI intervals, marginal QTc prolongation effect of abaloparatide at the suprathreshold dose (SC 240  $\mu$ g) are observed in this TQT study, although this could

be the impact of inadequate heart rate correction for both outcomes since abaloparatide significantly increases heart rate (Section **Error! Reference source not found.**).

**Table 9: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Abaloparatide SC 80 ug, Abaloparatide SC 240 ug and Moxifloxacin 400 mg**

| Time (h) | Treatment Group |                         |         |                     |              |                        |         |                     |              |                     |         |                     |             |              |
|----------|-----------------|-------------------------|---------|---------------------|--------------|------------------------|---------|---------------------|--------------|---------------------|---------|---------------------|-------------|--------------|
|          | Placebo         | Abaloparatide SC 240 ug |         |                     |              | Abaloparatide SC 80 ug |         |                     |              | Moxifloxacin 400 mg |         |                     |             |              |
|          | $\Delta$ QTcF   | $\Delta$ QTcF           |         | $\Delta\Delta$ QTcF |              | $\Delta$ QTcF          |         | $\Delta\Delta$ QTcF |              | $\Delta$ QTcF       |         | $\Delta\Delta$ QTcF |             |              |
|          | LS Mean         | N                       | LS Mean | LS Mean             | 90% CI       | N                      | LS Mean | LS Mean             | 90% CI       | N                   | LS Mean | LS Mean             | 90% CI      | *Adj. 90% CI |
| 0.25     | -1.1            | 52                      | 5.4     | 6.5                 | (4.1, 8.9)   | 52                     | 3.5     | 4.6                 | (2.2, 6.9)   | 50                  | 0.8     | 1.9                 | (-0.6, 4.3) | (-1.4, 5.2)  |
| 0.5      | -1.0            | 52                      | 8.7     | 9.7                 | (6.9, 12.5)  | 52                     | 6.0     | 6.9                 | (4.1, 9.7)   | 50                  | 3.0     | 4.0                 | (1.1, 6.8)  | (0.1, 7.8)   |
| 0.75     | -0.3            | 52                      | 6.9     | 7.2                 | (4.8, 9.6)   | 52                     | 4.7     | 5.0                 | (2.7, 7.4)   | 50                  | 5.9     | 6.2                 | (3.8, 8.7)  | (2.9, 9.5)   |
| 1        | -0.4            | 52                      | 4.6     | 5.0                 | (2.7, 7.2)   | 52                     | 3.2     | 3.6                 | (1.3, 5.8)   | 50                  | 7.5     | 7.9                 | (5.6, 10.1) | (4.8, 11.0)  |
| 1.5      | 0.2             | 52                      | 0.1     | -0.1                | (-2.2, 2.0)  | 52                     | 1.4     | 1.2                 | (-1.0, 3.3)  | 50                  | 7.7     | 7.5                 | (5.3, 9.6)  | (4.6, 10.4)  |
| 2        | 0.3             | 52                      | -0.9    | -1.2                | (-3.3, 0.9)  | 52                     | 0.6     | 0.3                 | (-1.8, 2.3)  | 50                  | 11.2    | 10.9                | (8.8, 13.0) | (8.0, 13.8)  |
| 2.5      | -0.4            | 52                      | -2.4    | -2.0                | (-4.3, 0.2)  | 52                     | -0.6    | -0.3                | (-2.6, 2.0)  | 50                  | 9.7     | 10.0                | (7.7, 12.3) | (6.9, 13.2)  |
| 4        | 0.3             | 51                      | -3.2    | -3.4                | (-5.6, -1.2) | 52                     | -2.0    | -2.3                | (-4.4, -0.1) | 50                  | 10.6    | 10.3                | (8.1, 12.5) | (7.3, 13.3)  |
| 6        | -3.6            | 51                      | -8.4    | -4.9                | (-7.5, -2.3) | 52                     | -8.5    | -4.9                | (-7.5, -2.3) | 50                  | 2.4     | 6.0                 | (3.4, 8.6)  | (2.4, 9.5)   |
| 8        | -4.5            | 52                      | -8.3    | -3.8                | (-6.1, -1.5) | 52                     | -8.5    | -4.0                | (-6.3, -1.7) | 49                  | 0.7     | 5.2                 | (2.9, 7.5)  | (2.0, 8.3)   |
| 12       | -3.9            | 52                      | -3.7    | 0.2                 | (-2.5, 3.0)  | 52                     | -2.7    | 1.2                 | (-1.6, 3.9)  | 50                  | 1.6     | 5.5                 | (2.7, 8.3)  | (1.7, 9.3)   |
| 24       | -2.2            | 52                      | -1.9    | 0.3                 | (-1.9, 2.5)  | 52                     | -2.0    | 0.2                 | (-2.0, 2.5)  | 48                  | 1.7     | 3.9                 | (1.7, 6.2)  | (0.8, 7.0)   |

\* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

**Table 10 : Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI for Abaloparatide-SC 80 ug, Abaloparatide-SC 240 ug and Moxifloxacin 400 mg**

| Time (h) | Treatment Group |                         |         |                     |              |                        |         |                     |              |                     |         |                     |             |  |
|----------|-----------------|-------------------------|---------|---------------------|--------------|------------------------|---------|---------------------|--------------|---------------------|---------|---------------------|-------------|--|
|          | Placebo         | Abaloparatide SC 240 ug |         |                     |              | Abaloparatide SC 80 ug |         |                     |              | Moxifloxacin 400 mg |         |                     |             |  |
|          | $\Delta$ QTcI   | $\Delta$ QTcI           |         | $\Delta\Delta$ QTcI |              | $\Delta$ QTcI          |         | $\Delta\Delta$ QTcI |              | $\Delta$ QTcI       |         | $\Delta\Delta$ QTcI |             |  |
|          | LS Mean         | N                       | LS Mean | LS Mean             | 90% CI       | N                      | LS Mean | LS Mean             | 90% CI       | N                   | LS Mean | LS Mean             | 90% CI      |  |
| 0.25     | -1.1            | 52                      | 2.9     | 4.1                 | (1.0, 7.2)   | 52                     | 1.9     | 3.0                 | (-0.0, 6.1)  | 50                  | 0.5     | 1.6                 | (-1.5, 4.7) |  |
| 0.5      | -1.2            | 52                      | 6.0     | 7.2                 | (4.0, 10.4)  | 52                     | 4.3     | 5.4                 | (2.2, 8.7)   | 50                  | 2.7     | 3.9                 | (0.6, 7.1)  |  |
| 0.75     | -0.7            | 52                      | 4.3     | 5.1                 | (2.0, 8.1)   | 52                     | 3.3     | 4.0                 | (1.0, 7.0)   | 50                  | 5.6     | 6.3                 | (3.2, 9.3)  |  |
| 1        | -0.5            | 52                      | 2.1     | 2.6                 | (-0.2, 5.3)  | 52                     | 1.2     | 1.6                 | (-1.1, 4.3)  | 50                  | 7.1     | 7.6                 | (4.8, 10.3) |  |
| 1.5      | 0.2             | 52                      | -2.0    | -2.2                | (-4.4, -0.0) | 52                     | 0.5     | 0.3                 | (-2.0, 2.5)  | 50                  | 7.4     | 7.1                 | (4.9, 9.4)  |  |
| 2        | -0.0            | 52                      | -3.4    | -3.4                | (-5.7, -1.1) | 52                     | -0.2    | -0.2                | (-2.5, 2.1)  | 50                  | 10.7    | 10.7                | (8.4, 13.0) |  |
| 2.5      | -0.5            | 52                      | -4.3    | -3.8                | (-6.2, -1.4) | 52                     | -1.4    | -0.9                | (-3.3, 1.5)  | 50                  | 9.9     | 10.5                | (8.0, 12.9) |  |
| 4        | -0.4            | 51                      | -4.8    | -4.4                | (-6.8, -2.0) | 52                     | -2.9    | -2.5                | (-4.9, -0.1) | 50                  | 10.7    | 11.1                | (8.7, 13.6) |  |
| 6        | -5.3            | 51                      | -11.3   | -6.0                | (-8.8, -3.2) | 52                     | -10.0   | -4.7                | (-7.5, -2.0) | 50                  | 1.7     | 7.0                 | (4.3, 9.8)  |  |
| 8        | -5.5            | 52                      | -9.7    | -4.2                | (-6.6, -1.9) | 52                     | -9.7    | -4.2                | (-6.6, -1.9) | 49                  | -0.1    | 5.4                 | (3.0, 7.8)  |  |
| 12       | -4.7            | 52                      | -5.2    | -0.5                | (-3.3, 2.3)  | 52                     | -3.7    | 1.0                 | (-1.8, 3.8)  | 50                  | 0.8     | 5.5                 | (2.6, 8.3)  |  |
| 24       | -2.8            | 52                      | -2.3    | 0.5                 | (-1.7, 2.8)  | 52                     | -1.7    | 1.1                 | (-1.1, 3.4)  | 48                  | 1.7     | 4.5                 | (2.2, 6.8)  |  |

### 5.2.1.2 Assay Sensitivity Analysis

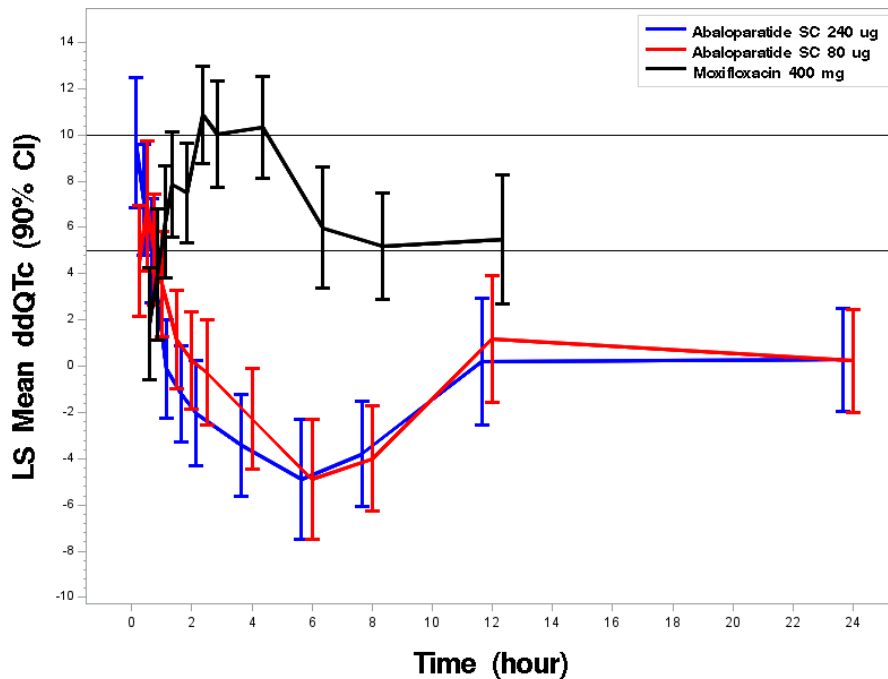
The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. Based on QTcF and QTcI intervals, marginal QTc prolongation effect of abaloparatide at the supratherapeutic dose (SC 240 µg) are observed in this TQT study, although this could be the impact of inadequate heart rate correction for both outcomes since abaloparatide significantly increases heart rate (Section Error! Reference source not found.).

**Table 9.** The largest unadjusted 90% lower confidence interval is 8.8 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 8.0 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

### 5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of  $\Delta\Delta$ QTcF for different treatment groups.

**Figure 6: Mean and 90% CI  $\Delta\Delta$ QTcF Time Course**



### 5.2.1.4 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose QTcF values are  $\leq 450$  ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and  $> 500$  ms. No subject's QTcF is above 480 ms.

**Table 11: Categorical Analysis for QTcF**

| Treatment Group         | Total N | Value $\leq$ 450 ms | 450 ms $<$ Value $\leq$ 480 ms | 480 ms $<$ Value $\leq$ 500 ms | Value $>$ 500 |
|-------------------------|---------|---------------------|--------------------------------|--------------------------------|---------------|
| Abaloparatide SC 240 ug | 52      | 49 (94.2%)          | 3 (5.8%)                       | 0 (0.0%)                       | 0 (0.0%)      |
| Abaloparatide SC 80 ug  | 52      | 51 (98.1%)          | 1 (1.9%)                       | 0 (0.0%)                       | 0 (0.0%)      |
| Moxifloxacin 400 mg     | 50      | 45 (90.0%)          | 5 (10.0%)                      | 0 (0.0%)                       | 0 (0.0%)      |
| Placebo                 | 51      | 50 (98.0%)          | 1 (2.0%)                       | 0 (0.0%)                       | 0 (0.0%)      |

Table 12 lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline is above 60 ms.

**Table 12: Categorical Analysis of  $\Delta$ QTcF**

| Treatment Group         | Total N | Value $\leq$ 30 ms | 30 ms $<$ Value $\leq$ 60 ms | 60 ms $<$ Value $\leq$ 90 ms | Value $>$ 90 ms |
|-------------------------|---------|--------------------|------------------------------|------------------------------|-----------------|
| Abaloparatide SC 240 ug | 52      | 51 (98.1%)         | 1 (1.9%)                     | 0 (0.0%)                     | 0 (0.0%)        |
| Abaloparatide SC 80 ug  | 52      | 51 (98.1%)         | 1 (1.9%)                     | 0 (0.0%)                     | 0 (0.0%)        |
| Moxifloxacin 400 mg     | 50      | 50 (100%)          | 0 (0.0%)                     | 0 (0.0%)                     | 0 (0.0%)        |
| Placebo                 | 51      | 51 (100%)          | 0 (0.0%)                     | 0 (0.0%)                     | 0 (0.0%)        |

### 5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze  $\Delta$ HR effect. The model includes treatment as a fixed effect and baseline value as a covariate. The analysis results are listed in Table 13. The largest upper bounds of the 2-sided 90% CI for the mean differences between Abaloparatide SC-80 ug and placebo, and between Abaloparatide-SC 240 ug are 16.1 bpm and 22.1 bpm, respectively.

The sponsor concluded that abaloparatide-SC caused a clear dose-related increase of heart rate, which peaked at the first post-dosing time point (15 minutes) at  $\sim 15$  bpm and  $\sim 20$  bpm after dosing of 80  $\mu$ g and 240  $\mu$ g, respectively.

Table 14 presents the categorical analysis of HR. Eight subjects who experienced HR interval greater than 100 bpm are in Abaloparatide-SC group.

**Table 13: Analysis Results of  $\Delta$ HR and  $\Delta\Delta$ HR for Abaloparatide SC-80 ug, Abaloparatide SC-240 ug and Moxifloxacin 400 mg**

|          |         | Treatment Group         |         |                   |              |                        |         |                   |              |                     |         |                   |             |
|----------|---------|-------------------------|---------|-------------------|--------------|------------------------|---------|-------------------|--------------|---------------------|---------|-------------------|-------------|
|          |         | Abaloparatide SC 240 ug |         |                   |              | Abaloparatide SC 80 ug |         |                   |              | Moxifloxacin 400 mg |         |                   |             |
|          |         | $\Delta$ HR             |         | $\Delta\Delta$ HR |              | $\Delta$ HR            |         | $\Delta\Delta$ HR |              | $\Delta$ HR         |         | $\Delta\Delta$ HR |             |
| Time (h) | LS Mean | N                       | LS Mean | LS Mean           | 90% CI       | N                      | LS Mean | LS Mean           | 90% CI       | N                   | LS Mean | LS Mean           | 90% CI      |
| 0.25     | 0.0     | 52                      | 20.5    | 20.4              | (18.8, 22.1) | 52                     | 14.6    | 14.5              | (12.9, 16.1) | 50                  | 0.3     | 0.3               | (-1.3, 1.9) |
| 0.5      | 0.5     | 52                      | 20.1    | 19.6              | (17.9, 21.4) | 52                     | 13.7    | 13.3              | (11.5, 15.0) | 50                  | 1.8     | 1.3               | (-0.4, 3.0) |
| 0.75     | 0.3     | 52                      | 18.3    | 18.0              | (16.2, 19.8) | 52                     | 10.8    | 10.5              | (8.7, 12.3)  | 50                  | 2.4     | 2.1               | (0.3, 3.9)  |
| 1        | 0.8     | 52                      | 15.0    | 14.3              | (12.5, 16.0) | 52                     | 9.5     | 8.7               | (7.0, 10.5)  | 50                  | 2.8     | 2.0               | (0.3, 3.8)  |
| 1.5      | -0.2    | 52                      | 10.5    | 10.7              | (8.9, 12.5)  | 52                     | 7.1     | 7.3               | (5.5, 9.2)   | 50                  | 1.2     | 1.4               | (-0.4, 3.3) |
| 2        | 0.6     | 52                      | 10.3    | 9.7               | (7.7, 11.6)  | 52                     | 6.0     | 5.5               | (3.5, 7.4)   | 50                  | 2.2     | 1.6               | (-0.4, 3.6) |
| 2.5      | -0.4    | 52                      | 9.8     | 10.2              | (7.8, 12.6)  | 52                     | 4.9     | 5.4               | (3.0, 7.7)   | 50                  | 0.4     | 0.8               | (-1.6, 3.3) |
| 4        | 1.1     | 51                      | 6.6     | 5.5               | (3.4, 7.6)   | 52                     | 5.1     | 4.0               | (1.9, 6.2)   | 50                  | 1.3     | 0.3               | (-1.9, 2.4) |
| 6        | 8.3     | 51                      | 13.4    | 5.1               | (2.7, 7.5)   | 52                     | 11.1    | 2.8               | (0.3, 5.2)   | 50                  | 9.2     | 0.9               | (-1.5, 3.4) |
| 8        | 3.9     | 52                      | 8.8     | 4.9               | (2.8, 7.1)   | 52                     | 8.1     | 4.2               | (2.1, 6.4)   | 49                  | 6.5     | 2.6               | (0.4, 4.8)  |
| 12       | 6.9     | 52                      | 10.0    | 3.1               | (0.8, 5.4)   | 52                     | 9.5     | 2.6               | (0.3, 4.9)   | 50                  | 8.6     | 1.7               | (-0.7, 4.0) |
| 24       | 3.5     | 52                      | 3.7     | 0.2               | (-1.2, 1.6)  | 52                     | 3.6     | 0.1               | (-1.3, 1.5)  | 48                  | 3.5     | 0.0               | (-1.4, 1.4) |

**Table 14: Categorical Analysis for HR**

| Treatment Group         | Total N | HR $\leq$ 100 bpm | HR $>$ 100 bpm |
|-------------------------|---------|-------------------|----------------|
| Abaloparatide SC 240 ug | 52      | 45 (86.5%)        | 7 (13.5%)      |
| Abaloparatide SC 80 ug  | 52      | 50 (96.2%)        | 2 (3.8%)       |
| Moxifloxacin 400 mg     | 50      | 48 (96.0%)        | 2 (4.0%)       |
| Placebo                 | 51      | 51 (100%)         | 0 (0.0%)       |

### 5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze  $\Delta$ PR effect. The model includes treatment as a fixed effect and baseline value as a covariate. The analysis results are listed in Table 15. The largest upper bounds of the 2-sided 90% CI for the mean differences between Abaloparatide-SC 80 ug and placebo, and between Abaloparatide-SC 240 ug are 3.1 ms and 3.1 ms, respectively. Table 16 presents the categorical analysis of PR. One subject who experienced PR interval greater than 200 ms is in Abaloparatide-SC group.

**Table 15: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Abaloparatide-SC 80 ug, Abaloparatide-SC 240 ug and Moxifloxacin 400 mg**

|             |         | Treatment Group         |         |                   |              |                        |         |                   |              |                     |         |                   |             |
|-------------|---------|-------------------------|---------|-------------------|--------------|------------------------|---------|-------------------|--------------|---------------------|---------|-------------------|-------------|
| Placebo     |         | Abaloparatide SC 240 ug |         |                   |              | Abaloparatide SC 80 ug |         |                   |              | Moxifloxacin 400 mg |         |                   |             |
| $\Delta$ PR |         | $\Delta$ PR             |         | $\Delta\Delta$ PR |              | $\Delta$ PR            |         | $\Delta\Delta$ PR |              | $\Delta$ PR         |         | $\Delta\Delta$ PR |             |
| Time (h)    | LS Mean | N                       | LS Mean | LS Mean           | 90% CI       | N                      | LS Mean | LS Mean           | 90% CI       | N                   | LS Mean | LS Mean           | 90% CI      |
| 0.25        | -0.2    | 51                      | -6.2    | -6.0              | (-7.8, -4.2) | 52                     | -4.0    | -3.8              | (-5.6, -2.0) | 50                  | -0.4    | -0.2              | (-2.0, 1.6) |
| 0.5         | -0.4    | 52                      | -6.4    | -6.0              | (-7.8, -4.2) | 52                     | -3.5    | -3.1              | (-4.9, -1.3) | 50                  | -0.4    | -0.1              | (-1.9, 1.8) |
| 0.75        | -0.6    | 52                      | -5.7    | -5.2              | (-6.9, -3.4) | 52                     | -2.8    | -2.2              | (-4.0, -0.5) | 50                  | -0.1    | 0.5               | (-1.3, 2.2) |
| 1           | -0.6    | 52                      | -6.6    | -6.0              | (-7.8, -4.2) | 52                     | -3.7    | -3.1              | (-4.9, -1.3) | 50                  | -1.3    | -0.7              | (-2.5, 1.0) |
| 1.5         | -0.2    | 52                      | -4.6    | -4.4              | (-5.9, -2.9) | 52                     | -2.8    | -2.6              | (-4.1, -1.1) | 50                  | -1.1    | -0.9              | (-2.4, 0.6) |
| 2           | -0.2    | 52                      | -4.7    | -4.5              | (-6.3, -2.7) | 52                     | -2.1    | -1.9              | (-3.7, -0.1) | 50                  | -1.1    | -0.8              | (-2.7, 1.0) |
| 2.5         | -1.0    | 52                      | -4.3    | -3.4              | (-5.2, -1.5) | 52                     | -2.3    | -1.3              | (-3.2, 0.5)  | 50                  | -2.3    | -1.3              | (-3.2, 0.6) |
| 4           | -1.0    | 51                      | -4.3    | -3.3              | (-5.1, -1.6) | 52                     | -2.8    | -1.8              | (-3.6, -0.1) | 50                  | -2.7    | -1.7              | (-3.5, 0.1) |
| 6           | -4.5    | 51                      | -5.3    | -0.8              | (-2.7, 1.0)  | 52                     | -4.7    | -0.2              | (-2.1, 1.6)  | 50                  | -5.6    | -1.1              | (-3.0, 0.8) |
| 8           | -5.7    | 52                      | -6.4    | -0.7              | (-2.6, 1.2)  | 52                     | -5.9    | -0.2              | (-2.1, 1.6)  | 49                  | -6.5    | -0.9              | (-2.8, 1.1) |
| 12          | -4.9    | 52                      | -4.1    | 0.8               | (-1.4, 3.1)  | 52                     | -4.1    | 0.8               | (-1.4, 3.1)  | 50                  | -4.6    | 0.3               | (-2.0, 2.6) |
| 24          | -1.0    | 52                      | -0.8    | 0.1               | (-1.6, 1.9)  | 52                     | -0.9    | 0.1               | (-1.7, 1.8)  | 48                  | -1.5    | -0.5              | (-2.3, 1.3) |

**Table 16: Categorical Analysis for PR**

| Treatment Group         | Total N | PR $\leq$ 200 ms | PR $>$ 200 ms |
|-------------------------|---------|------------------|---------------|
| Abaloparatide SC 240 ug | 52      | 52 (100%)        | 0 (0.0%)      |
| Abaloparatide SC 80 ug  | 52      | 51 (98.1%)       | 1 (1.9%)      |
| Moxifloxacin 400 mg     | 50      | 48 (96.0%)       | 2 (4.0%)      |
| Placebo                 | 51      | 49 (96.1%)       | 2 (3.9%)      |

#### 5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze  $\Delta$ QRS effect. The model includes treatment as a fixed effect and baseline value as a covariate. The analysis results are listed in Table 17. The largest upper bounds of the 2-sided 90% CI for the mean differences between Abaloparatide-SC 80 ug and placebo, and between Abaloparatide-SC 240 ug are 0.8 mg and 0.6 mg, respectively. Table 18 presents the categorical analysis of QRS. Two subjects who experienced QRS interval greater than 110 ms are in Abaloparatide-SC group.

**Table 17: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Abaloparatide-SC 80 ug, Abaloparatide-SC 240 ug and Moxifloxacin 400 mg**

|          |         | Treatment Group         |         |                    |              |                        |         |                    |              |                     |         |                    |              |
|----------|---------|-------------------------|---------|--------------------|--------------|------------------------|---------|--------------------|--------------|---------------------|---------|--------------------|--------------|
|          |         | Abaloparatide SC 240 ug |         |                    |              | Abaloparatide SC 80 ug |         |                    |              | Moxifloxacin 400 mg |         |                    |              |
|          |         | $\Delta$ QRS            |         | $\Delta\Delta$ QRS |              | $\Delta$ QRS           |         | $\Delta\Delta$ QRS |              | $\Delta$ QRS        |         | $\Delta\Delta$ QRS |              |
| Time (h) | LS Mean | N                       | LS Mean | LS Mean            | 90% CI       | N                      | LS Mean | LS Mean            | 90% CI       | N                   | LS Mean | LS Mean            | 90% CI       |
| 0.25     | 0.2     | 52                      | -1.6    | -1.8               | (-2.6, -1.0) | 52                     | -0.7    | -0.9               | (-1.7, -0.1) | 50                  | 0.1     | -0.0               | (-0.8, 0.7)  |
| 0.5      | -0.2    | 52                      | -1.1    | -1.0               | (-1.7, -0.2) | 52                     | -0.6    | -0.4               | (-1.2, 0.3)  | 50                  | -0.0    | 0.2                | (-0.6, 0.9)  |
| 0.75     | -0.0    | 52                      | -0.9    | -0.9               | (-1.6, -0.2) | 52                     | -0.5    | -0.5               | (-1.2, 0.2)  | 50                  | -0.0    | -0.0               | (-0.7, 0.7)  |
| 1        | -0.3    | 52                      | -0.5    | -0.2               | (-0.9, 0.5)  | 52                     | -0.4    | -0.1               | (-0.8, 0.6)  | 50                  | -0.2    | 0.1                | (-0.6, 0.8)  |
| 1.5      | 0.0     | 52                      | -0.6    | -0.6               | (-1.1, 0.0)  | 52                     | -0.4    | -0.4               | (-1.0, 0.2)  | 50                  | -0.3    | -0.3               | (-0.9, 0.3)  |
| 2        | -0.3    | 52                      | -0.3    | 0.0                | (-0.6, 0.6)  | 52                     | -0.4    | -0.1               | (-0.7, 0.5)  | 50                  | -0.1    | 0.2                | (-0.4, 0.7)  |
| 2.5      | -0.0    | 52                      | -0.4    | -0.4               | (-1.1, 0.3)  | 52                     | 0.2     | 0.2                | (-0.5, 0.8)  | 50                  | -0.5    | -0.5               | (-1.1, 0.2)  |
| 4        | 0.2     | 51                      | -0.7    | -0.9               | (-1.5, -0.3) | 52                     | -0.6    | -0.8               | (-1.4, -0.2) | 50                  | -0.7    | -0.9               | (-1.5, -0.3) |
| 6        | 0.5     | 51                      | -0.9    | -1.4               | (-2.3, -0.5) | 52                     | -0.2    | -0.7               | (-1.6, 0.1)  | 50                  | -0.7    | -1.3               | (-2.2, -0.4) |
| 8        | -0.4    | 52                      | -1.3    | -0.9               | (-1.7, -0.1) | 52                     | -1.2    | -0.9               | (-1.7, -0.1) | 49                  | -1.3    | -1.0               | (-1.8, -0.1) |
| 12       | 0.3     | 52                      | -0.2    | -0.6               | (-1.3, 0.1)  | 52                     | -0.4    | -0.7               | (-1.4, 0.0)  | 50                  | -0.7    | -1.0               | (-1.7, -0.3) |
| 24       | 0.2     | 52                      | -0.4    | -0.6               | (-1.3, 0.2)  | 52                     | -0.3    | -0.5               | (-1.2, 0.2)  | 48                  | -0.4    | -0.6               | (-1.4, 0.1)  |

**Table 18: Categorical Analysis for QRS**

| Treatment Group         | Total N | QRS $\leq$ 110 ms | QRS $>$ 110 ms |
|-------------------------|---------|-------------------|----------------|
| Abaloparatide SC 240 ug | 52      | 51 (98.1%)        | 1 (1.9%)       |
| Abaloparatide SC 80 ug  | 52      | 50 (96.2%)        | 2 (3.8%)       |
| Moxifloxacin 400 mg     | 50      | 49 (98.0%)        | 1 (2.0%)       |
| Placebo                 | 51      | 50 (98.0%)        | 1 (2.0%)       |

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between  $\Delta$ QTc and abaloparatide and  $\Delta$ QTc was investigated separately by linear mixed-effects modeling. The model used QTcF change from baseline ( $\Delta$ QTcF), as well as QTcI change from baseline ( $\Delta$ QTcI), as the dependent variable and observed drug concentrations as the continuous variable (0 for the placebo treatment), treatment (active (IND=1) or placebo (IND=0)), day and nominal time postdose as categorical factors, and random effects on intercept and slope. The general model formula is shown below.

$$\Delta QT_{c,l,k,d,t} = \mu_l + p_t + qC_{l,k,d,t} + V_k C_{l,k,d,t} + W_k + \varepsilon_{l,k,d,t}$$

$\mu_l$  = Fixed effect, treatment specific ( $l$ ) intercept (active ( $l=1$ ), placebo ( $l=0$ ))

$p_t$  = Fixed effect, Study Time ( $t$ ) specific intercept (as factor)

$q$  = Fixed effect, slope parameter

$Cl_{,,}$  = Independent variable, Concentration for time point( $t$ ), treatment( $l$ ), Study Day ( $d$ ), and subject ( $k$ )

$V_k$  = Random effect, random subject level ( $k$ ) effect on slope ( $q$ )

$W_k$  = Random effect, random subject level ( $k$ ) effect on intercept ( $\mu$ )

$\epsilon l_{,,}$  = Random effect, residual error for time point( $t$ ), treatment( $l$ ), Study Day ( $d$ ), and subject ( $k$ )

A log-transformed instead of linear abaloparatide concentrations was employed to in the FDA reviewer's exposure-response analysis for QTc. The selection of exposure format was on the basis of AIC[QTcF: 10861.6(log) vs. 10879.1(linear); QTcI: 11207.8 (log) vs. 11220.4 (linear)].

The relationships between  $\Delta$ QTc and abaloparatide concentrations are listed in Table 19. The results showed a shallow but statistically significant positive exposure-response relationship.

**Table 19: Concentration-QTc Effect Analysis. Estimates from Linear Mixed Model – QTc Individual and QTc Fridericia Pharmacokinetic-Pharmacodynamic Population**

| Parameters | Slope of Plasma Conc. (log) Effect on $\Delta$ QTc | Standard Error of Slope of Plasma Conc. (log) Effect on $\Delta$ QTc | P value Slope of Plasma Conc. (log) Effect on $\Delta$ QTc |
|------------|----------------------------------------------------|----------------------------------------------------------------------|------------------------------------------------------------|
| QTcF       | 2.3768                                             | 0.2678                                                               | <0.0001                                                    |
| QTcI       | 1.5979                                             | 0.2980                                                               | 0.0005                                                     |

The relationship between  $\Delta\Delta$ QTcF and  $\Delta\Delta$ QTcI and abaloparatide concentrations is visualized from Figure 7 to Figure 12. Although for both QTcF and QTcI, shallow exposure-response relationships were observed, the estimated QTc changes from placebo and baseline and its 90% CI upper bound at the mean  $C_{max}$  of the suprathreshold abaloparatide SC 240  $\mu$ g are less than 10 ms for both criteria.

**Figure 7:  $\Delta\Delta$  QTcF vs. Abaloparatide Concentration**

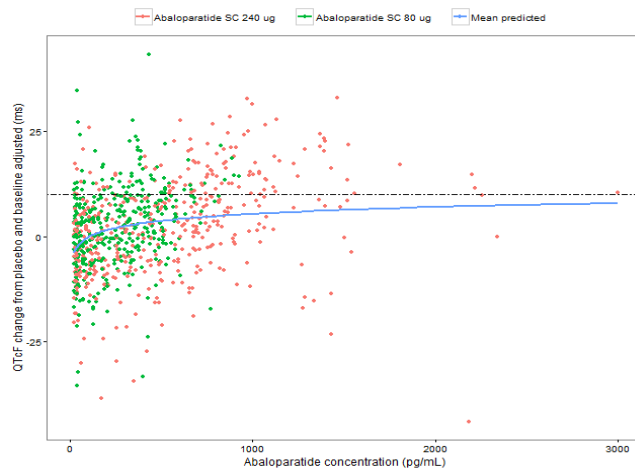


**Figure 8:  $\Delta\Delta$  QTcF vs. Abaloparatide Quantiles**

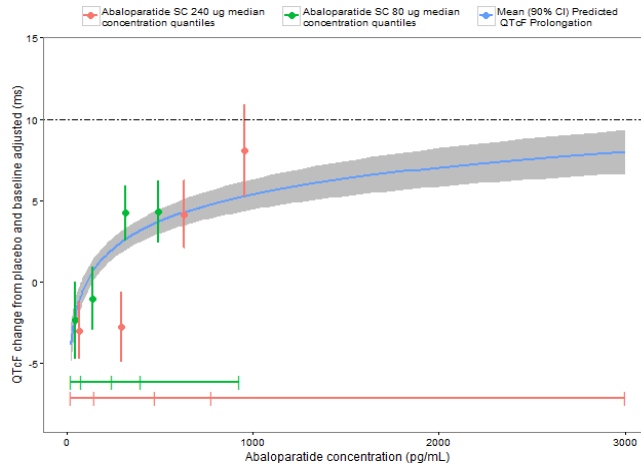


**Figure 9: Predicted  $\Delta\Delta$  QTcF at Abaloparatide Mean Cmax**

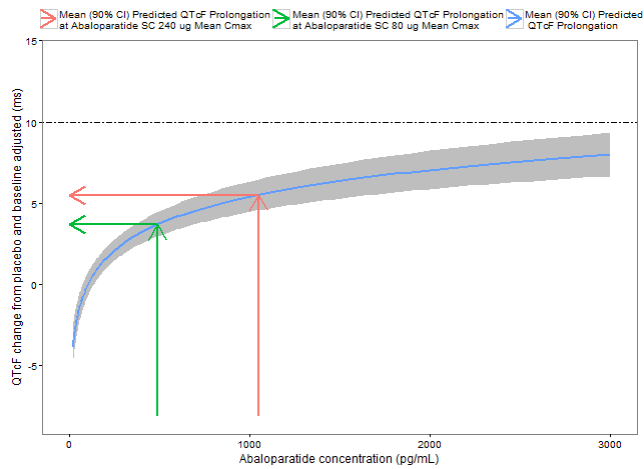


**Figure 10:  $\Delta\Delta$  QTcI vs. Abaloparatide Concentration**

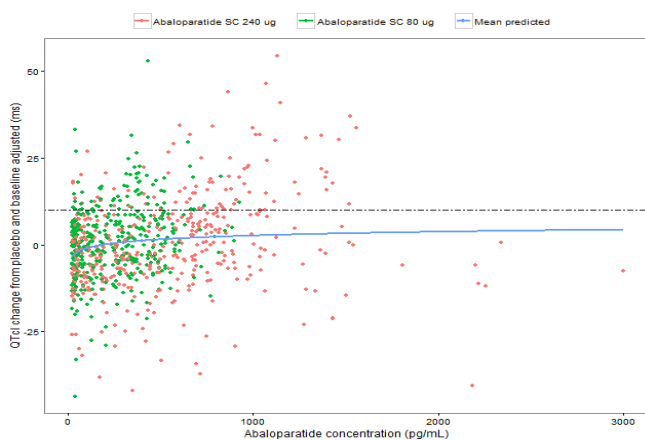


**Figure 11:  $\Delta\Delta$  QTcI vs. Abaloparatide Quantiles**

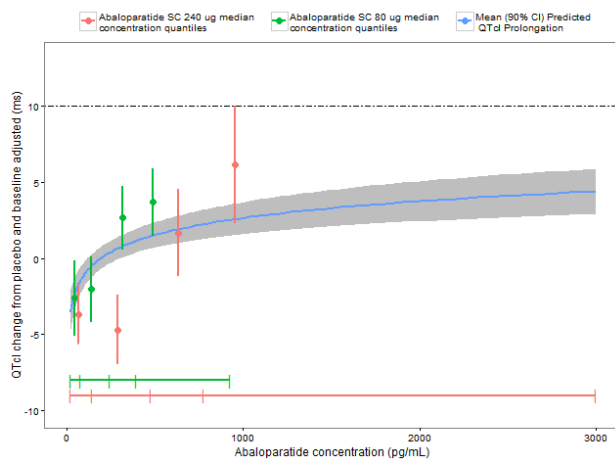
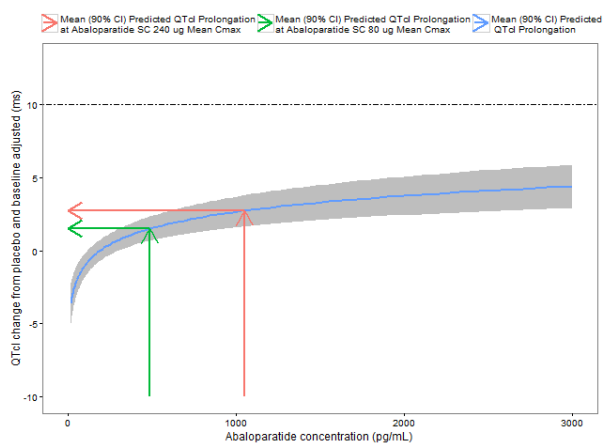


**Figure 12: Predicted  $\Delta\Delta$  QTcI at Abaloparatide Mean Cmax**



In addition, the relationship between  $\Delta\Delta\text{HR}$  and abaloparatide concentrations was also explored using linear mixed effect model and visualized in Figure 13. A significant relationship between  $\Delta\Delta\text{HR}$  and abaloparatide concentrations was observed.

**Figure 13: Predicted  $\Delta\Delta\text{HR}$  vs. Abaloparatide Concentration**



## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

Abaloparatide increased heart rate in a dose-dependent manner. At the highest dose level, 13.5% subjects experienced heart rate  $>100$  bpm. Two subjects reported palpitations and one subject experienced sinus tachycardia.

One subject (ID 1026) experienced syncope after receiving abaloparatide 240  $\mu\text{g}$  that was considered by the Investigator as severe. The event was not considered to be a SAE, no concomitant treatment was given to the subject, it resulted in an outcome of recovered/resolved, and the subject completed the study.

Abaloparatide did not exert a clinically meaningful effect of cardiac conduction (the PR and QRS interval). The observed PR interval shortening is consistent with the drug's effect on heart rate.

### 5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

|                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Therapeutic dose         | 80 µg administered once daily subcutaneously (SC)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Maximum tolerated dose   | 240 µg                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Principal adverse events | <p><b>Include most common adverse events; dose limiting adverse events</b></p> <p>Across studies, the majority of TEAEs in the abaloparatide-SC treated subjects were mild to moderate in severity. In study 2-52-52127-001, a total of 76 subjects received abaloparatide-SC, while 20 received a placebo. AEs reported in two or more subjects in included nausea, vomiting, asthenia, dizziness, headache, hyperhidrosis, and orthostatic hypotension. In Study BA058-05-001, 39 subjects received study drug with doses ranging from 5 µg to 80 µg. AEs reported in two or more subjects included ear pain, constipation, hard feces, nausea, asthenia, injection site erythema, injection site hemorrhage, musculoskeletal stiffness, and pruritis. In Study BA058-05-001B, evaluating Abaloparatide-SC 80 µg, 100 µg, and 120 µg doses, 30 subjects were enrolled and more Abaloparatide-SC treated subjects experienced gastrointestinal system AEs (i.e., constipation, nausea, vomiting, diarrhea) than placebo-treated subjects. In Study BA058-05-002 in which doses of 20 µg (N=43), 40 µg (N=43), and 80 µg (N=45) were administered through 24 weeks, the adverse events reported most commonly by the abaloparatide-SC treated subjects were influenza, headache, nasopharyngitis, injection site haematoma, hypercalciuria, back pain, bronchitis, arthralgia, diarrhea, and dizziness.</p> <p>The MTD of abaloparatide has been evaluated in Study BA058-05-010, in which single SC doses of abaloparatide were administered to healthy subjects at doses ranging from 80 to 320 µg, with 8 subjects receiving active drug and 2 subjects receiving placebo in each cohort<sup>1</sup>. Subcutaneous doses of 80 µg (Cohort 1) and 120 µg (Cohort 2) were well tolerated. In Cohort 3 (240 µg), a total of 22 adverse events occurred in 7 subjects; 3 of these events were considered to be of moderate severity and the remaining events were judged by the Investigator to be mild. Dizziness (3 mild, 2 moderate), headache (5 mild), and nausea (4 mild) were the most frequently reported AEs. Four subjects who experienced dizziness were unable to stand for orthostatic blood pressure assessments. Moderate severity orthostatic tachycardia was also reported in 1 subject. The Investigator considered the 240 µg dose to be tolerated.</p> <p>At the 320 µg dose level (Cohort 4), 21 AEs occurred in 7 subjects, with dizziness (1 mild, 5 moderate), headache (all mild), nausea (1 mild, 2 moderate), and dyspnea (all mild) being the most frequently reported. Five of</p> |

<sup>1</sup> Subject treatment completed, data analysis ongoing.

|                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                     |
|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                           | <p>the events of dizziness resulted in the subjects being unable to stand for their orthostatic blood pressure measurements. Moderate severity presyncope was also reported in 1 subject. There were 2 clinically significant findings in vital signs; 1 subject experienced clinically significant orthostatic hypotension 6 hours post dose, and 1 subject experienced a nonclinically significant mildly prolonged QT corrected for HR using Bazett's formula interval. The Investigator determined that the 320 µg dose was not tolerated.</p> <p>In the subsequent cohort (Cohort 5), the planned dose of 400 µg was reduced to 280 µg. A total of 23 AEs occurred in 9 subjects, with dizziness (1 mild, 5 moderate), headache (5 mild), nausea (1 mild, 2 moderate), tachycardia (3 mild), and dyspnea (2 mild). There were also 3 subjects who experienced clinically significant abnormalities in their vital signs; 2 subjects experienced tachycardia (orthostatic HRs which increased by more than 30 bpm, with values of ≥ 100 bpm) and a third subject who experienced both tachycardia and orthostatic hypotension. The Investigator determined that this dose was not tolerated.</p> |                                                                                                                                                                                                                                                                                     |
| Maximum dose tested                       | Single Dose                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 320 µg                                                                                                                                                                                                                                                                              |
|                                           | Multiple Dose                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 120 µg administered daily for 7 consecutive days                                                                                                                                                                                                                                    |
| Exposures Achieved at Maximum Tested Dose | Single Dose                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <p><b>Mean (%CV) Cmax and AUC</b></p> <p>For 120 µg (SC) X 1 day: Cmax: 952 ± 285 pg/mL, AUC: 1552.2 ± 659.34 (pg*hr/mL)</p> <p>The MTD (240 µg) Cmax and AUC (exposure) are about 3.5-fold greater than that observed with the proposed therapeutic dose of 80 µg.<sup>2</sup></p> |
|                                           | Multiple Dose                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <p><b>(%CV) Cmax and AUC</b></p> <p>For 120 µg (SC) X 7 days, Day 7:</p> <p>Cmax: 956 ± 338 pg/mL</p> <p>AUC: 1600.7 ± 675.18 (pg*hr/mL)</p>                                                                                                                                        |
| Range of linear PK                        | <p><b>Specify dosing regimen</b></p> <p>The range and extent of absorption (as evidenced by Cmax and AUC) were generally dose proportional over the dosage range of 20 to 120 µg.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                     |
| Accumulation at steady state              | <p><b>Mean (%CV); specify dosing regimen</b></p> <p>Single and multiple dose exposure to abaloparatide were comparable between Day 1 and Day 7 following dosing, the mean accumulation index (AI) values</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                     |

<sup>2</sup> A MTD study of abaloparatide is ongoing. In this study doses of up to 320 µg have been administered, however, only preliminary PK results are available.

|              |                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|              | ranged from 0.8 to 1.2, indicating that drug accumulation was negligible following administration of multiple doses, consistent with the rapid metabolism of a peptide.                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Metabolites  | Nonclinical ADME information suggests that abaloparatide follows the same metabolic pathway as other short chain peptides and is likely eliminated by breakdown at the cellular level into its constituent amino acids. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Absorption   | Absolute/<br>Relative<br>Bioavailability                                                                                                                                                                                | <b>Mean (%CV) Ipsen Phase 1</b><br><br>With regard to the absorption phase, the absolute bioavailability estimated after SC administration was complete (mean individual Bayesian value of $1.01 \pm 0.06$ ); the first order absorption rate constant of BIM44058 was $0.373 \text{ h}^{-1}$ with an inter-individual variability of 17%; and a short lag-time before absorption of approximately 4 minutes was estimated. Finally, a proportional error model described better the pattern of residual error (23%). <sup>3</sup> |
|              | Tmax                                                                                                                                                                                                                    | <ul style="list-style-type: none"> <li>• <b>Median (range) for parent</b><br/>0.522 (0.257, 2.03) hour</li> <li>• <b>Median (range) for metabolites</b><br/>Not applicable</li> </ul>                                                                                                                                                                                                                                                                                                                                              |
| Distribution | Vd/F or Vd                                                                                                                                                                                                              | <b>Mean (%CV)</b><br><br>Plasma clearance of BIM44058 was estimated in the population analysis as 27.4 L/h associated with a low unexplained degree of inter-subject variability (12%). The final model gave mean estimates for the two volumes of distribution: central (Vc) and peripheral compartment (VP1) of 3.99 and 20.0 L, respectively. Therefore, the steady-state volume of distribution (Vss) is approximately 24 L.                                                                                                   |
|              | % bound                                                                                                                                                                                                                 | <b>Mean (%CV)</b><br>Not determined                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Elimination  | Route                                                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>• <b>Primary route; percent dose eliminated</b></li> </ul> <p>In vivo tissue distribution and main routes of elimination were assessed in rats administered <sup>124</sup>I-abaloparatide and in vitro metabolic stability has been investigated using rat tissue homogenates and cathepsin B and chymotrypsin enzymes. The results of the studies suggest that metabolism is rapid, and that the primary route of metabolite excretion is urinary,</p>                                     |

<sup>3</sup> The bioavailability of the current formulation is being evaluated, only preliminary PK information is available.

|                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                            | and that clearance is 3-fold faster in kidney tissue compared to liver tissue.<br><ul style="list-style-type: none"> <li>• <b>Other routes</b></li> </ul> None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Terminal t <sub>1/2</sub>  | <ul style="list-style-type: none"> <li>• <b>Mean (%CV) for parent</b><br/>1.30±0.216 hr</li> <li>• <b>Mean (%CV) for metabolites</b><br/>Not applicable</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| CL/F or CL                 | <b>Mean (%CV)</b><br>CL/F: 68.64±23.16 L/hr                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Age                        | Specify mean changes in C <sub>max</sub> and AUC<br>There have been no studies or analyses performed to evaluate the effect of age on the PK of abaloparatide.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Sex                        | Specify mean changes in C <sub>max</sub> and AUC<br>In study 2-52-52127-001 comparison of PK parameters such as T <sub>max</sub> , C <sub>max</sub> /AUC, λ <sub>z</sub> , t <sub>1/2λz</sub> and MRT by means of the ANOVA test showed no statistically significant differences by dose in any of the parameters tested by gender.                                                                                                                                                                                                                                                                                                                   |
| Race                       | Specify mean changes in C <sub>max</sub> and AUC<br>There have been no studies or analyses performed to evaluate the effect of race on the PK of abaloparatide.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Hepatic & Renal Impairment | Specify mean changes in C <sub>max</sub> and AUC<br>Hepatic Impairment<br>Nonclinical ADME information suggests that abaloparatide follows the same metabolic pathway as other short chain peptides and is likely eliminated by breakdown at the cellular level into its constituent amino acids or by renal excretion. The agency has agreed that it will not be necessary to perform a PK study in patients with hepatic impairment. (Type A Post Meeting Minutes, March 21, 2012).<br>Renal Impairment<br>A Phase 1 study in subjects with varying degrees of renal dysfunction is planned. It is anticipated that treatment will begin in (b) (4) |
| Drug interactions          | Include listing of studied DDI studies with mean changes in C <sub>max</sub> and AUC<br>There have been no DDI studies conducted with abaloparatide to date.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Food Effects               | Specify mean changes in C <sub>max</sub> and AUC and meal type (i.e., high-fat, standard, low-fat)<br>There have been no food effects studies conducted with abaloparatide to date.                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

|                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Expected High Clinical Exposure Scenario</p> | <p><b>Describe worst case scenario and expected fold-change in C<sub>max</sub> and AUC. The increase in exposure should be covered by the supra-therapeutic dose.</b></p> <p>The MTD of abaloparatide has been evaluated. In Study BA058-05-010, single SC doses of abaloparatide were administered to healthy subjects at doses ranging from 80 to 320 µg, with 8 subjects receiving active drug and 2 subjects receiving placebo in each cohort. Subcutaneous doses of 80 µg (Cohort 1) and 120 µg (Cohort 2) were well tolerated. However, subcutaneous doses of 280 (Cohort 5) and 320 µg (Cohort 4), were not well tolerated as evidenced by episodes of moderate dizziness which led to &gt; 50% of the subjects in each Cohort being unable to stand for orthostatic vital signs.</p> <p>In Cohort 3 (240 µg), a total of 22 adverse events occurred in 7 subjects; 3 of these events were considered to be of moderate severity and the remaining events were judged by the Investigator to be mild. The Investigator considered the 240 µg dose to be tolerated. The MTD (240 µg) C<sub>max</sub> and AUC (exposure) are about 3.5-fold greater than that observed with the proposed therapeutic dose of 80 µg.<sup>4</sup></p> <p>One overdose has been reported in the Phase 2 study. The subject (abaloparatide-SC 40 µg group) received 10 times (400 µg) the prescribed dose of abaloparatide-SC on one occasion which was inadvertently administered by an untrained family member. Following the injection, the subject experienced asthenia, headache and nausea, which were moderate in severity, and mild vertigo. When measured on the following day, the subject's serum calcium was within the normal range. Nausea resolved that day; asthenia decreased to mild severity the following day and resolved and the headache resolved approximately one week later. Mild vertigo continued for approximately two weeks. All events were reported as possibly related to study treatment. An ECG conducted on the day of the overdose showed a ventricular rate of 60 bpm with QTcB of 429 msec; the ECG was reported as abnormal with an unspecified disorder of ventricular repolarization; the abnormality was not considered to be clinically significant. Dosing was withheld for 14 days after which the subject continued treatment, completed the 24-week study, and entered the 24-week extension period. She subsequently discontinued from the extension study due to an episode of syncope.</p> <p>The no observed adverse effect level in monkeys treated with abaloparatide for 14 consecutive days was 150 µg/kg. Scaled for a 65 kg human, and considering body surface area, this would be equivalent to a daily human SC dose of 3400 µg. When compared to the dose of 400 µg inadvertently administered to this subject, this represents an 8.5-fold safety margin.</p> |
| <p>Clinical Cardiac Safety</p>                  | <p><b>Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g.,</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

<sup>4</sup> A MTD study of abaloparatide is ongoing. In this study doses of up to 320 µg have been administered, however, only preliminary PK results are available.

QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).

To date, abaloparatide-SC has been evaluated in three completed Phase 1 clinical trials in which Abaloparatide-SC was administered as single and multiple doses in healthy subjects and one completed Phase 2 study. A Phase 3 study is currently ongoing.

In Study 2-52-52127-001, a total of 96 healthy elderly male and female subjects from 55 to 73 years of age were enrolled and administered single SC doses of 2, 5, 7.5, 10, 15, 20, 40, 60, 80, and 100 µg abaloparatide-SC, or placebo (Part A). In the cross-over segment (Part B), 16 eligible subjects received 2.5 µg abaloparatide IV and 15 µg SC. In total, 76 subjects received abaloparatide-SC, while 20 received a placebo. In this study there were no reported TEAEs of QT prolongation, seizures, ventricular arrhythmias, ventricular fibrillation, flutter, torsade de pointes, or sudden death. In Part A there was one event of supraventricular tachycardia (5 µg) and one report of syncope (80 µg). In Part B there was one report of ventricular tachycardia (2.5 µg IV).

Study BA058-05-001 assessed the safety, pharmacokinetics and pharmacodynamics of abaloparatide-SC administered daily as 5 µg, 20 µg, 40 µg, and 80 µg SC doses for seven days to healthy postmenopausal female subjects from 50 to 73 years old. Forty subjects were enrolled and 39 received study drug and completed treatment without any serious adverse effects. Doses of up to 80 µg were well tolerated in this study population. In this study there were no reports of QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden death.

Study BA058-05-001B assessed the safety, pharmacokinetics and pharmacodynamics of abaloparatide-SC administered daily as 80 µg, 100 µg, and 120 µg doses for seven consecutive days to healthy postmenopausal female subjects from 52 to 74 years old. Thirty subjects were enrolled and 29 completed treatment. In this study there were no reports of QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden death.

The Phase 2 trial of abaloparatide-SC, (Study BA058-05-002, 221 randomized patients) was conducted as a multi-national, randomized, placebo-controlled, parallel-group dose-finding study of abaloparatide-SC for the treatment of postmenopausal women with osteoporosis. Daily SC doses of abaloparatide-SC, abaloparatide-SC placebo or teriparatide were administered to postmenopausal females from 54 to 84 years old who were randomized equally to one of 5 treatment groups. Doses of abaloparatide-SC were 20 µg, 40 µg or 80 µg per day by SC self-administered injection using a 30-day multi-dose cartridge delivered via a pen injector device, for 24 weeks. Teriparatide was administered at a dose of 20 µg by SC injection. A 24-week

extension of their assigned treatment was offered to eligible subjects. In this study there were no reports of seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden death.

Two subjects were found to have had prolonged QTcB intervals >500 msec during the initial study period. These events were not reported as TEAE's. One subject in the 40 µg group had elevations that were likely equipment related; ECGs at the time were assessed as normal by the investigator. One subject in the teriparatide group had an ECG reported as abnormal due to a prolonged QTc at Week 28; her follow-up ECG was normal. One subject in the Abaloparatide-SC 40 µg group discontinued treatment during the extension period due to moderate syncope assessed as possibly related to abaloparatide-SC.

In Cohort 3 (240 µg), a total of 22 adverse events occurred in 7 subjects; 3 of these events were considered to be of moderate severity and the remaining events were judged by the Investigator to be mild. This included a report of moderate severity orthostatic tachycardia in 1 subject.

At the 320 µg dose level (Cohort 4), 21 AEs occurred in 7 subjects, with dizziness (1 mild, 5 moderate), headache (all mild), nausea (1 mild, 2 moderate), and dyspnea (all mild) being the most frequently reported. Moderate severity presyncope was reported in 1 subject, and 1 subject experienced a nonclinically significant mildly prolonged QT corrected for HR using Bazett's formula interval.

In the subsequent cohort (Cohort 5), the planned dose of 400 µg was reduced to 280 µg. A total of 23 AEs occurred in 9 subjects, which included three reports of mild tachycardia.

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

/s/  
-----

MOH JEE NG  
08/16/2016

QIANYU DANG  
08/26/2016

CHAO LIU  
08/26/2016

JIANG LIU  
08/26/2016

MICHAEL Y LI  
08/28/2016

CHRISTINE E GARNETT  
08/29/2016

## 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 # 208743<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:<br>Established/Proper Name: abaloparatide<br>Dosage Form: injectable; subcutaneous<br>Strengths: 80 mcg                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Applicant: Radius Health, Inc<br>Agent for Applicant (if applicable):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Date of Application: 3-30-16<br>Date of Receipt: 3-30-16<br>Date clock started after Unacceptable for Filing (UN):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| PDUFA/BsUFA Goal Date: 3-30-17                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                              | Action Goal Date (if different):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Filing Date: 5-29-16                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                              | Date of Filing Meeting: 5-18-16                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 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 checked="" 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<br><input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval)<br><input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval) |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Proposed indication(s)/Proposed change(s): Treatment of postmenopausal women with osteoporosis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 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><input type="checkbox"/> 505(b)(1)<br><input type="checkbox"/> 505(b)(2)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b><i>If 505(b)(2)NDA/NDA Supplement: 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 checked="" 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):

List referenced IND Number(s): 073176

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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                        |                                     |                          |                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|----------------|
| <i>to the supporting IND(s) if not already entered into electronic archive.</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"/> |                |
| <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>                                                                                                                                                                                                                                                                                         | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                               | <input checked="" type="checkbox"/> |                          |                |
| <b>If yes, explain in comment column.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                        |                                     |                          |                |
| <b>If affected by AIP, has OC been notified of the submission?</b><br><b>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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</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. Contact the User Fee Staff. If appropriate, send UN letter.</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 checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No                                                                                                                                                  |                                     |                          |                |
| <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 checked="" type="checkbox"/> |                          |                |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                     |                                     |                                     |                |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|----------------|--|
| cover letter, and annotated labeling). <b>If yes</b> , answer the bulleted questions below:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                     |                                     |                                     |                |  |
| • Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                     | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                |  |
| • 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)].                                                                                                                                                                                                                                                                                                                |                                     | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                |  |
| • 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)]?                                                                                                                                                                                                                                                                                                          |                                     | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                |  |
| <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>                                                                                                                                                                                                                                                                                                                                                                   |                                     |                                     |                                     |                |  |
| • Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                     | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                |  |
| <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>                                                                                                                                                                                                                                                                                                                                                                                                               |                                     |                                     |                                     |                |  |
| <b>If yes</b> , please list below:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                     |                                     |                                     |                |  |
| Application No.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Drug Name                           | Exclusivity Code                    | Exclusivity Expiration              |                |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                     |                                     |                                     |                |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                     |                                     |                                     |                |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                     |                                     |                                     |                |  |
| <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 orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i> |                                     |                                     |                                     |                |  |
| <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 checked="" type="checkbox"/> |                                     |                |  |
| <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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                     |                                     |                                     |                |  |
| <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 checked="" type="checkbox"/> | <input 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 checked="" 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"/> |  |

| Format and Content                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                   |                          |                          |                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|----------------|
| <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)<br><br><input checked="" 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:<br><br><input checked="" type="checkbox"/> legible | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                               | <input type="checkbox"/> |                          |                |

<sup>1</sup> <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                     |                          |                                     |                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|-------------------------------------|----------------|
| <input checked="" type="checkbox"/> English (or translated into English)<br><input checked="" type="checkbox"/> pagination<br><input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)                                                                                                                                                                                                                                                                                                                                                      |                                     |                          |                                     |                |
| <b>If no, explain.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                     |                          |                                     |                |
| <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, BLA #</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                     |                          |                                     |                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                     |                          |                                     |                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                     |                          |                                     |                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                     |                          |                                     |                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                     |                          |                                     |                |
| <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, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms include:</b> user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications include:</b> 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"/> |                                     |                |
| <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> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|----------------|
| <p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><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></p> | <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> |
| <p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><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></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>                                                                                                                                                                                                                                                                                                           | <input type="checkbox"/>            | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                |
| <b>Controlled Substance/Product with Abuse Potential</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <b>YES</b>                          | <b>NO</b>                           | <b>NA</b>                           | <b>Comment</b> |
| <p><u>For NMEs:</u><br/>Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u><br/><i>Date of consult sent to Controlled Substance Staff:</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/>            | <input checked="" type="checkbox"/> | <input type="checkbox"/>            |                |
| <b>Pediatrics</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <b>YES</b>                          | <b>NO</b>                           | <b>NA</b>                           | <b>Comment</b> |
| <p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <input checked="" type="checkbox"/> | <input type="checkbox"/>            |                                     |                |

2

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

Version: 4/12/2016

7

|                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                     |                                     |                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------|----------------|
| <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage 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"/>            |                |
| <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 type="checkbox"/>            | <input checked="" type="checkbox"/> |                |
| <b>BPCA:</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 type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <input checked="" type="checkbox"/> | <input type="checkbox"/>            |                |
| <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 checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <input 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 (Prescribing Information)(PI)<br><input type="checkbox"/> Patient Package Insert (PPI)<br><input checked="" type="checkbox"/> Instructions for Use (IFU)<br><input checked="" type="checkbox"/> Medication Guide (MedGuide)<br><input checked="" type="checkbox"/> Carton labeling<br><input checked="" type="checkbox"/> Immediate container labels<br><input type="checkbox"/> Diluent labeling<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 Physician Labeling Rule (PLR)                                                                                                                                                                                                                                                                                                                             | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/>            |                                     |                |

3

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

|                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                  |                                                          |                                                          |                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|----------------|
| format? <sup>4</sup>                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                  |                                                          |                                                          |                |
| <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 Pregnancy and Lactation Labeling Rule (PLLR) format?<br><br>Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?                                                                                                                             | <input checked="" type="checkbox"/><br><br><input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                   | <input type="checkbox"/><br><br><input type="checkbox"/> | <input type="checkbox"/><br><br><input type="checkbox"/> |                |
| <b>For applications submitted on or after June 30, 2015:</b><br><b>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 PLLR format before the filing date.</i> | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/>                                 | <input checked="" type="checkbox"/>                      |                |
| Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?                                                                                                                                                                                                                                                                                        | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/>                                 | <input type="checkbox"/>                                 |                |
| Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? ( <i>send WORD version if available</i> )                                                                                                                                                                                                                                                                                                | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/>                                 | <input type="checkbox"/>                                 |                |
| Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/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)<br><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?                                                                                                                                                                                                                                                                                                                                                                     | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/>                                 |                                                          |                |

4

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

|                                                                                                          |                                     |                          |                          |                |
|----------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|--------------------------|----------------|
| <i>If no, request in 74-day letter.</i>                                                                  |                                     |                          |                          |                |
| Are annotated specifications submitted for all stock keeping units (SKUs)?                               | <input type="checkbox"/>            | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <i>If no, request in 74-day letter.</i>                                                                  |                                     |                          |                          |                |
| If representative labeling is submitted, are all represented SKUs defined?                               | <input type="checkbox"/>            | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <i>If no, request in 74-day letter.</i>                                                                  |                                     |                          |                          |                |
| All labeling/packaging 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) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <i>If yes, specify consult(s) and date(s) sent:<br/>QT-IRT for Study BA058-05-012 sent on 5-19-16</i>    |                                     |                          |                          |                |
| <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> January 21, 2010                                           | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                          |                |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?<br><b>Date(s):</b> May 28, 2015; June 3, 2015 (CMC)           | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                          |                |
| Any Special Protocol Assessments (SPAs)?<br><b>Date(s):</b> July 15, 2009 (Carcinogenicity SPA)          | <input checked="" type="checkbox"/> |                          |                          |                |

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** May 18, 2016

**BACKGROUND:** Abaloparatide (BA058) is a new molecular entity that is an analogue of parathyroid hormone-related peptide (PTHrP). PTHrP is secreted endogenously by osteoblasts and, like parathyroid hormone, contributes to calcium homeostasis. Radius Health, Inc has submitted a 505(b)(1) application for the treatment of postmenopausal women with osteoporosis.

The applicant has submitted an 18-month Phase 3 trial (BA058-05-003) with a 24-month extension (BA058-05-005) as well as several Phase 2 studies in this application as clinical efficacy and safety data to support abaloparatide for the proposed indication.

**REVIEW TEAM:**

| Discipline/Organization                                     | Names          |                | Present at filing meeting? (Y or N) |
|-------------------------------------------------------------|----------------|----------------|-------------------------------------|
| Regulatory Project Management                               | RPM:           | Samantha Bell  | Y                                   |
|                                                             | CPMS/TL:       | Margaret Kober | Y                                   |
| Cross-Discipline Team Leader (CDTL)                         | Theresa Kehoe  |                | Y                                   |
| Division Director/Deputy                                    | Hylton Joffe   |                | Y                                   |
|                                                             | Audrey Gassman |                | Y                                   |
| Office Director/Deputy                                      | Julie Beitz    |                | Y                                   |
|                                                             | Amy Egan       |                | Y                                   |
| Clinical                                                    | Reviewer:      | Stephen Voss   | Y                                   |
|                                                             | TL:            | Theresa Kehoe  | 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:      | LaiMing Lee    | Y                                   |

|                   |           |                |   |
|-------------------|-----------|----------------|---|
|                   |           |                |   |
|                   | TL:       | Myong-Jin Kim  | Y |
| • Genomics        | Reviewer: |                |   |
| • Pharmacometrics | Reviewer: | Fang Li        | Y |
| Biostatistics     | Reviewer: | Jia Guo        | Y |
|                   | TL:       | Mahboob Sobhan | Y |

|                                                                            |           |                   |   |
|----------------------------------------------------------------------------|-----------|-------------------|---|
| Nonclinical<br>(Pharmacology/Toxicology)                                   | Reviewer: | Gemma Kuijpers    | Y |
|                                                                            | TL:       | Mukesh Summan     | Y |
| Statistics (carcinogenicity)                                               | Reviewer: |                   |   |
|                                                                            | TL:       |                   |   |
| Product Quality (CMC) Review Team:                                         | ATL:      | Mark Seggel       | Y |
|                                                                            | RBPM:     | Thao Vu           | Y |
| • Drug Substance                                                           | Reviewer: | Xavier Ysern      | Y |
| • Drug Product                                                             | Reviewer: | Hamid Shafiei     | Y |
| • Process                                                                  | Reviewer: | Yuesheng Ye       | Y |
| • Microbiology                                                             | Reviewer: | Yeissa Rosello    | Y |
| • Facility                                                                 | Reviewer: | Krishna Ghosh     | Y |
| • Biopharmaceutics                                                         | Reviewer: | Kelly Kitchens    | Y |
| • Immunogenicity                                                           | Reviewer: |                   |   |
| • Labeling (BLAs only)                                                     | Reviewer: |                   |   |
| • Other (e.g., Branch Chiefs, EA Reviewer)                                 |           |                   |   |
| OMP/OMPI/DMPP (MedGuide, PPI, IFU)                                         | Reviewer: |                   |   |
|                                                                            | TL:       |                   |   |
| OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling) | Reviewer: |                   |   |
|                                                                            | TL:       |                   |   |
| OSE/DMEPA (proprietary name, carton/container labeling)                    | Reviewer: | Walter Fava       | Y |
|                                                                            | TL:       | Danielle Harris   | Y |
| OSE/DRISK (REMS)                                                           | Reviewer: | Leah Hart         | Y |
|                                                                            | TL:       | Kimberly Lehrfeld | Y |
| OC/OSI/DSC/PMSB (REMS)                                                     | Reviewer: |                   |   |
|                                                                            | TL:       |                   |   |

|                                  |                                              |              |   |
|----------------------------------|----------------------------------------------|--------------|---|
| Bioresearch Monitoring (OSI)     | Reviewer:                                    | Roy Blay     | Y |
|                                  | TL:                                          |              |   |
| Controlled Substance Staff (CSS) | Reviewer:                                    |              |   |
|                                  | TL:                                          |              |   |
| Other reviewers/disciplines      |                                              |              |   |
| • <b>CDRH</b>                    | Reviewer:                                    | Robert Meyer | Y |
|                                  | TL:                                          |              |   |
| Other attendees                  | Bindi Nikhar, Office of Combination Products |              | 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><br><input type="checkbox"/> YES <input type="checkbox"/> NO<br><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 checked="" 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 type="checkbox"/> NO<br><input checked="" type="checkbox"/> To be determined<br><br>Reason:                                                      |
| <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 checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES<br><input 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 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 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 checked="" type="checkbox"/> YES<br><input 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 checked="" 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 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 checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO<br><br><input 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> Julie Beitz                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): 9-7-16                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <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 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 type="checkbox"/>                                                                                                  | Send review issues/no review issues by day 74                                                                                                                                                                                                                                                                                                                                                                                           |
| <input type="checkbox"/>                                                                                                  | Conduct a PLR format labeling review and include labeling issues in the 74-day letter                                                                                                                                                                                                                                                                                                                                                   |
| <input 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: April 2016

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

/s/  
-----

SAMANTHA S BELL  
05/23/2016

MARGARET M KOBER  
05/31/2016

**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 208743

**Application Type:** New NDA

**Drug Name(s)/Dosage Form(s):** abaloparatide/ injectable; subcutaneous

**Applicant:** Radius Health, Inc

**Receipt Date:** 3-30-16

**Goal Date:** 3-30-17

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

Radius Health, Inc has submitted a 505(b)(1) New Drug Application for abaloparatide for the treatment of postmenopausal women with osteoporosis. Radius Health is proposing a dose of 80 µg once daily administered by subcutaneous self-injection to the periumbilical region using a multi-dose prefilled pen.

### **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**

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

In addition, the following labeling issues were identified:

1. In Highlights, under Indications and Usage section: (b) (4) should be underlined and the bullet should be removed.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 1, 2016. The resubmitted PI will be used for further labeling review.

## Selected Requirements of Prescribing Information

---

### 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.

---

### 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 |
|---------|-------------------|
|---------|-------------------|

## Selected Requirements of Prescribing Information

|                                                   |                                                       |
|---------------------------------------------------|-------------------------------------------------------|
| • <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                                              |
| • <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

- YES** 12. All text in the BW must be **bolded**.

*Comment:*

**YES**

## Selected Requirements of Prescribing Information

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:**

- YES** 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:**

- YES** 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

- NO** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

**Comment:** *Remove bullet from the sentence in Dosage Forms and Strengths section in Highlights.*

### Contraindications in Highlights

**NO**

## Selected Requirements of Prescribing Information

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:** Remove bullet (b) (4)

### Adverse Reactions in Highlights

- NO** 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 (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.**”

**Comment:** Remove bullet. Move "SUSPECTED ADVERSE REACTIONS" paragraph currently presented at the end of Highlights to Adverse Reactions section of Highlights

### 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:*
- YES** 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:*
- YES** 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:*
- 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

- YES** 35. All text in the BW should be **bolded**.

*Comment:*

- YES** 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:*

#### 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:*

- 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

- NO** 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:** *Revise sentence under Patient Counseling Information section of the Full Prescribing Information from "Advise patients.." to "Advise the patient"...*

- YES** 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/  
-----

SAMANTHA S BELL  
05/23/2016