CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208743Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208743 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Tymlos Established/Proper Name: abaloparatide Dosage Form: injectable		Applicant: Radius Health, Inc Agent for Applicant (if applicable):
RPM: Samantha Bell		Division:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is June 30, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

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

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

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

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

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

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval 4/28/17
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	8/23/16; 11/22/16 8/23/16; 11/21/16
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 5/23/16 DMEPA: ☒ 2/17/17 DMPP/PLT (DRISK): 2/23/17 ☒ OPDP: ☒ 2/16/17 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	5/31/16 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 12/7/16 If PeRC review not necessary, explain:	
❖ Breakthrough Therapy Designation	☐ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	7/16/15; 7/2/14
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	7/13/15
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	N/A
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 5/28/15 CMC: 6/3/15
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 1/21/10
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A 9/22/16
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A 12/20/16
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 4/27/17
Division Director Summary Review *(indicate date for each review)*	☐ None 4/27/17
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 4/21/17
PMR/PMC Development Templates *(indicate total number)*	☐ None 4/27/17

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review 4/21/17
• Clinical review(s) *(indicate date for each review)*	12/8/16
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See 12/8/16 clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☐ None 8/29/16 QT-IRT, Immunogenicity 4/6/17
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None 11/4/16; 11/29/16; 12/8/16; 2/8/17; 2/15/17
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 3/31/17; 2/9/17; 1/31/17; 1/26/17
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 12/8/16
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 12/15/16
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested 11/4/16; 12/22/16; 12/27/16;

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

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 12/22/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 12/14/16
❖ ECAC/CAC report/memo of meeting	☐ None 9/14/17
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 12/14/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None CDRH 12/13/16
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	5/3/16
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	3/1/17, 11/18/16 ☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

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

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

SAMANTHA S BELL
04/28/2017

From: Bell, Samantha
Sent: Wednesday, April 26, 2017 2:02 PM
To: Desai, Deepa (Ddesai@radiuspharm.com)
Subject: NDA 208743 Revised PI and Medication Guide Labeling

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

Our proposed revisions to the Prescribing Information and Medication Guide are attached. We also intend to have revisions for the Instructions for Use which will be sent in a separate communication.

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

<< File: NDA 208743 PI FDA Final Track Change 042617.docx >> << File: NDA 208743 MedGuide 042617 FDA edits.docx >>

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/s/

SAMANTHA S BELL
04/26/2017

From: Bell, Samantha
Sent: Wednesday, April 26, 2017 3:32 PM
To: Desai, Deepa (Ddesai@radiuspharm.com)
Subject: NDA 208743 Revised Instructions for Use

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

Our proposed revisions to the Instructions for Use are attached. We are requesting a response for all of the labeling revisions by April 27, 2017.

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

<< File: NDA 208743 IFU FDA edits 042617.docx >>

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/s/

SAMANTHA S BELL
04/26/2017

From: Bell, Samantha
To: Desai, Deepa (Ddesai@radiuspharm.com)
Subject: NDA 208743 Revised PI
Date: Tuesday, April 11, 2017 2:47:00 PM
Attachments: NDA 208743 PI 041117 FDA edits.docx

Dear Ms. Desai,

Attached are the FDA edits and comments to the NDA 208743 Prescribing Information received on March 31, 2017. The FDA has no further comments for the Medication Guide and Instructions for Use received on March 31, 2017.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC

Regulatory Health Project Manager

FDA/Center for Drug Evaluation and Research

Division of Bone, Reproductive, and Urologic Products

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SAMANTHA S BELL
04/11/2017

From: Bell, Samantha
Sent: Tuesday, March 21, 2017 9:57 AM
To: Desai, Deepa (Ddesai@radiuspharm.com)
Subject: NDA 208743 Postmarketing Commitment

Dear Ms. Desai:

Please refer to your New Drug Application (NDA) 208743 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide.

We are reviewing your February 8, and March 6, 2017, responses to our requests for additional immunogenicity information and have the following comments and request for information:

Review of the safety data did not reveal safety concerns directly related to the immunogenicity of abaloparatide. However, immunogenicity responses as described in Section 6.2, Immunogenicity, of the Prescribing Information were only based on serum samples from a portion of patients. To provide a more accurate description of the immune response to abaloparatide, we are requesting that you test additional serum samples from patients enrolled in Study BA058-05-003 as a Postmarketing Commitment (PMC). Based on results from this testing, revisions to the prescribing information may be needed.

We recommend that this PMC study be conducted in two parts:

- Part 1: Test for abaloparatide binding antibodies in all collected serum samples not previously tested for abaloparatide binding antibodies. Test the confirmed positive samples for abaloparatide binding anti-drug antibody (ADA) titer, and abaloparatide drug neutralization.

- Part 2: Test all confirmed anti-abaloparatide positive serum samples for antibodies able to cross-react with or neutralize endogenous PTH or PTHrP.

To finalize the PMC, we will need to agree on timelines for final protocol submission, study completion, and submission of the complete study report to FDA. Submit your proposed timelines taking into consideration both parts of the PMC.

We are requesting a response by April 3.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
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samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
03/21/2017

From: Bell, Samantha
Sent: Friday, March 17, 2017 12:21 PM
To: Desai, Deepa (Ddesai@radiuspharm.com)
Subject: NDA 208743 Revised Labeling with FDA comments

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

Our proposed revisions to the prescribing information (PI), Medication Guide, and Instructions for Use (IFU) are attached.

We are requesting a response by March 29, 2017.

Sincerely,
Samantha Bell

<< File: NDA 208743 Tymlos track change PI 031717.docx >> << File: NDA 208743 Tymlos MG (Marked) 031717.docx >> << File: NDA 208743 Tymlos MG (Clean) 031717.docx >> << File: NDA 208743 IFU Tymlos (Marked) 031717.docx >> << File: NDA 208743 IFU Tymlos (Clean) 031717.docx >>

Samantha Bell, BS, BA, RAC
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/s/

SAMANTHA S BELL
03/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208743

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Radius Health, Inc.
Attention: Deepa Desai, M.S.
Director, Regulatory Affairs
950 Winter Street
Waltham, MA 02451

Dear Ms. Desai:

Please refer to your New Drug Application (NDA) dated and received March 30, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for abaloparatide.

On February 10, 2017, we received your February 8, 2017, submission that responded to our request for additional data and information regarding the immunogenicity of abaloparatide. We have determined that this submission is a major amendment to your application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is June 30, 2017. We will also use the time to fully review your subsequent submission of immunogenicity data received March 6, 2017.

If you have any questions, call Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

HYLTON V JOFFE
03/09/2017

From: Bell, Samantha
Sent: Monday, February 27, 2017 8:59 AM
To: Desai, Deepa (Ddesai@radiuspharm.com)
Subject: NDA 208743 Information Request

Dear Ms. Desai:
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide, NDA 208743.

We are reviewing your February 8, 2017, response to our requests for additional immunogenicity information and have the following additional comments and requests for information:

The PTH and PTHrP cross-reactivity binding assay validations require clarifications that can be addressed immediately and would provide information necessary to our evaluation. Pending these clarifications, slight revisions to the proposed immunogenicity labeling may be required;

1. The confirmatory cut points (CCP) used for scoring samples as positive for ADA cross-reactivity to PTH (b) (4) assay validation #50289) and PTHrP (b) (4) assay validation # 50322) both appear to incorporate a false-positive rate of 0.1%. Agency guidance recommends that confirmatory assays utilize a 1% false-positive rate, as opposed to a 0.1% false-positive rate, to avoid an increased rate of false negative results. Please recalculate the CCP for both the PTH and PTHrP cross-reactivity confirmatory assays per Agency guidelines, and revise the immunogenicity section of the labeling accordingly.
2. The data provided to support the (b) (4) PTH and PTHrP cross-reactivity binding assays minimum required dilution (MRD) validation for serum samples are not clear. The same data charts appear to have been reported for each assay; and in both cases insufficient reasoning is provided supporting use of the selected 1:6 MRD. Provide additional clarification regarding the MRD validation data and justification for use of the selected MRD.

We are requesting a response by March 2, 2017.

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
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samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
02/27/2017

From: Bell, Samantha
Sent: Monday, February 27, 2017 9:18 AM
To: Desai, Deepa (Ddesai@radiuspharm.com)
Subject: NDA 208743 Response to February 6, 2017, Information Request

Dear Ms. Desai:
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide, NDA 208743.

We acknowledge your February 9, 2017, response to our information request (IR). In the IR dated February 6, 2017, we asked you to provide an updated use related risk analysis (URRA) to justify the lack of a cleaning step (e.g. swabbing the rubber seal prior to attaching the needle) within the IFU.

We reviewed your updated URRA for evaluation of this use scenario and potential hazards and use errors. We also reviewed your justification for not including the cleaning step in the IFU. We note your justification includes a best practice approach to emphasize proper use and storage (e.g. replacing the cap after use) rather than to add cleaning instructions. In addition, we note your table of referenced products you submitted in support of your justification. We find your URRA and justification acceptable and we concur with your decision not to include a step to the IFU instructing users to swab the rubber seal before attaching the needle. We have no further comments at this time.

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
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10903 New Hampshire Avenue
Silver Spring, MD 20993

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/s/

SAMANTHA S BELL
02/27/2017

From: Bell, Samantha
Sent: Friday, February 24, 2017 11:55 AM
To: Desai, Deepa (Ddesai@radiuspharm.com)
Subject: NDA 208743 Information Request

Dear Ms. Desai:
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide, NDA 208743.

We have the following comments and requests for additional information regarding your February 10, 2017, submission for an enhanced pharmacovigilance (EPV) protocol, entitled, (b) (4)

We are requesting a response by March 3, 2017.

(b) (4)

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
02/24/2017

From: Bell, Samantha
Sent: Monday, February 06, 2017 11:24 AM
To: Desai, Deepa (Ddesai@radiuspharm.com)
Subject: NDA 208743 Information Request

Dear Ms. Desai:
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide, NDA 208743.

We note that the proposed Instructions for Use (IFU) for abaloparatide does not include instructions to swab the rubber seal prior to attaching the needle. If you have data to support excluding it from the IFU, provide your rationale in a use related risk hazard analysis. Alternatively, consider adding instructions for swabbing the rubber seal to the IFU prior to attaching the needle as an essential task for consistency with instructions found for other currently marketed pen products.

We are requesting a response by February 9, 2017.

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
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/s/

SAMANTHA S BELL
02/06/2017

From: Bell, Samantha
Sent: Friday, February 03, 2017 11:42 AM
To: Desai, Deepa (Ddesai@radiuspharm.com)
Subject: NDA 208743 Information Request

Dear Ms. Desai:
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide, NDA 208743.

Our review of your application has determined that additional data and information are necessary to complete our review of the immunogenicity of abaloparatide. Address the following items to facilitate our review:

1. Regarding ADA cross-reactivity against endogenous PTH and PTHrP assessed in ADA+ samples from your trial, we note three study subjects (1320106, 1810183 and 1810221) tested positive for anti-abaloparatide antibodies capable of neutralizing endogenous PTHrP activity as reported in the Interim 37 Month Anti-Abaloparatide Antibody Immunogenicity Summary (12-Sept-2016). The following should be provided:

    a. Long-term monitoring data for the endogenous PTHrP NAb+ subjects, including available ADA levels, adverse events and progression of osteoporosis.

    b. Analysis of ADA+ samples for cross-reactivity against endogenous PTH and PTHrP was limited to ADA+ samples at the 18 month time point. To capture accurate data on the incidence of ADA cross-reactive with these endogenous peptides throughout the study, all ADA+ samples collected at all visits should be tested for cross-reactivity against PTH and PTHrP. Specifically, provide information regarding the following:

        i. Availability of ADA+ samples from time points not tested for cross-reactive ADAs,

        ii. Timeline required for full cross-reactive ADA testing (binding and neutralizing antibodies and their titers, against endogenous PTH and PTHrP) for those ADA+ samples not previously tested for cross-reactive ADA.

2. Our review indicates that subjects were classified as ADA negative based upon the anti-BA-058 RIA analysis of their Visit 9 (18-month) samples, and that their samples from prior visits were not further analyzed for appearance of ADA. This strategy introduces a

potential for under-reporting ADA positive incidence. To capture accurate immunogenicity incidence, patient serum samples collected at all visits should be tested for appearance of ADA. Provide the following:

a. Availability of patient samples not tested for ADA,

b. Timeline required for full analysis of all samples from subjects initially classified as ADA negative. Analyses should include BA-058 binding antibodies, BA-058 NAb, ADA titer, and assays to determine cross-reactivity and neutralization against endogenous PTH and PTHrP.

3. Regarding validation of your anti-BA-058 binding antibody radioimmunoprecipitation assay (RIA):

a. Our review of the method validation for the binding antibody (BAb) assay indicates an apparent inconsistency. The Method Validation Report Addendum 2 for ICDIM 25 Project MTQ5, page 13 states that the working inhibition solution containing 500 ng/ml BA-058 will result in 125 ng/ml final, while the Experimental Design section (page 22) states that the inhibited sample will contain 500 ng/ml BA-058, or 375 ng/ml final. Provide information to resolve this apparent inconsistency.

b. Provide assay characterization information demonstrating the ability of your BAb assay to detect relevant Ig subclasses could not be found in the submission. Provide information on the ability of your RIA method to sensitively detect relevant Ig subclasses to ensure that all anti-BA-058 antibody responses in samples collected from participants in your clinical studies have been detected and reported.

4. Regarding validation report BAL-15-227-003-REP for the neutralizing anti-BA-058 antibody assay, as developed at (b) (4) and utilized for detection of neutralizing antibodies (NAb) in your Phase 3 clinical study samples, provide the following information:

a. Provide assay development data for your cell-based anti-BA-058 NAb assay to define the dose-response of the UMR-106 target cells for the BA-058 drug and to support the 3pg/mL concentration of BA-058 drug used for stimulation of the UMR-106 cells. The concentration of study drug should be optimized to enable sensitive detection of anti-BA-058 NAbs in ADA+ samples from the pivotal clinical study.

b. The validation study report for the BAL-15-227-003 NAb assay reports a BA-058 drug tolerance level for assay of 3pg/mL determined with the LPC1 and LPC2,

and up to 6pg/mL as determined with the HPC. This low tolerance level is at the BA-058 stimulation level for the cell-based assay, potentially leading to underestimation of the NAb incidence when on-board BA-058 drug levels in the samples are above 3pg/mL. Provide data to demonstrate that BA-058 drug levels in samples collected for ADA analysis are expected to, or have been determined to, possess BA-058 levels below this limit, allowing for accurate assessment of NAb activity.

c. Table 2 from Appendix 2 in the Anti-Abaloparatide Antibody Immunogenicity Testing Summary Interim Report (04-Nov-2015) summarizes validation parameters for the (b) (4) NAb assay. The Validation Parameter "BA-058 concentration" is reported as 248pg/mL. The derivation of this value cannot be found in the (b) (4) NAb assay validation report BAL-15-227-003-REP; provide this information.

d. Provide information on the stability of the labeled cAMP reporter reagent from the MSD cAMP assay kit used in the NAb assay for determining cellular response to BA-058; this could not be found in your submission and has potential to impact evaluation of samples for the presence of NAb.

5. We note that assay sensitivity data are reported throughout your validation study reports as titers. The Agency recommends that sensitivity data should be reported in mass units per volume, not as titers (see FDA 2016 Draft Guidance document on Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products). Provide sensitivity levels for your immunogenicity assays expressed as mass units per volume matrix.

We are requesting an initial response by February 7, 2017.

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
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/s/

SAMANTHA S BELL
02/03/2017

From: Bell, Samantha
Sent: Wednesday, February 01, 2017 7:53 AM
To: Desai, Deepa (Ddesai@radiuspharm.com)
Subject: NDA 208743 Information Request

Dear Ms. Desai:
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide, NDA 208743.

We refer to your Human Factors (HF) validation study report received on December 12, 2016. We have concerns regarding your validation study report which shows failure to prime and needle stick injury. We ask that you provide a response to the following comments and requests for additional information by February 6, 2017:

1. Failures relating to prime prior to first use
    a) Your study results show participants experienced priming errors. Specifically we note errors surrounding either skipping the priming step altogether, or re-priming the pen upon re-use. We note that for one of the priming errors, the user interpreted the presence of the (b) (4) next to the priming step in the Instructions for Use (IFU) to mean she should not prime the pen. Given that this user interface issue was identified from your HF study, we recommend that you consider using different symbols or statements.

2. Needle stick injuries/difficulties/use errors
    b) The results of your validation study noted 21 use difficulties and 7 use errors including one needle stick injury related to removing the needle. Subjective feedback from participants experiencing these use difficulties and use errors demonstrated that they did not understand the instructions i.e. (b) (4) for removing the needle. We agree that the use of disposable pens presents an inherent risk of unintended needle stick injuries to users, however, the instructions for attaching and/or removing needles should be optimized to minimize the occurrence of these errors. We recommend that you consider revising the instruction for removing the needle by including more specific instructions. As an example, you may consider clarifying the IFU in terms of how and where the user can hold the pen to grasp the needle and of how to turn it and remove it safely.

For issues 1 and 2 above, we ask that you provide to the Agency any revisions you plan to make to address them. Also, provide an updated use-related risk analysis based on your proposed revisions along with a justification regarding whether additional validation study is needed to demonstrate the effectiveness of your proposed revisions.

3. To better inform our review, clarify whether the UnoPen Platform from Ypsomed, is currently used for other drug combination products, and whether you have any postmarketing data related the use of the product, in particular, priming and needle removal. Provide the clarification and data (if available) for our review.

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
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/s/

SAMANTHA S BELL
02/01/2017

From: Bell, Samantha
Sent: Friday, January 27, 2017 9:11 AM
To: 'Desai, Deepa'; Osborne, Anne
Subject: NDA 208743 Comments Regarding Enhanced Pharmacovigilance Protocol

Dear Ms. Desai:
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide, NDA 208743.

We have the following comments and requests for additional information regarding your proposed enhanced pharmacovigilance (EPV) protocol, entitled (b) (4)

We are requesting a response by February 10, 2017.

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
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/s/

SAMANTHA S BELL
01/27/2017

From: Bell, Samantha
Sent: Tuesday, December 13, 2016 7:44 AM
To: Desai, Deepa (Ddesai@radiuspharm.com)
Subject: NDA 208743 Carton and Container Information Request

Dear Ms. Desai:
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide, NDA 208743.

We are reviewing the application and have the following comments and requests for information regarding your carton and container labeling:

We note the statement, [redacted] (b) (4) on the container and carton lacks clarity and can be improved upon. As such, there is a risk that the user will use your product beyond 30 days. Consider revising the statement to read: 'Date of first use _/_/_. Discard unused portion 30 days after first opening'.

We are requesting a response by December 20, 2016.

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
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SAMANTHA S BELL
12/13/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208743

LABELING PMR/PMC DISCUSSION COMMENTS

Radius Health, Inc.
Attention: Deepa Desai, M.S.
Director, Regulatory Affairs
950 Winter Street
Waltham, MA 02451

Dear Ms. Desai:

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

We also refer to our June 7, 2016, letter in which we notified you of our target date of December 9, 2016, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On March 30 and July 1, 2016, we received your proposed labeling submissions to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by January 6, 2017. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

These revisions have been reviewed and cleared to the level of Division Director.

At this time, we do not anticipate the need for any postmarketing requirements/commitments.

If you have any questions, call me at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Samantha Bell, B.S., B.A., R.A.C.
Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

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/s/

SAMANTHA S BELL
12/09/2016

From: Bell, Samantha
Sent: Thursday, December 08, 2016 11:18 AM
To: Desai, Deepa (Ddesai@radiuspharm.com)
Subject: NDA 208743 Carton and Container Labeling Information Request

Dear Ms. Desai:
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide, NDA 208743.

We are reviewing the application and have the following comments and requests for information regarding your carton and container labeling:

1. Immediate container label:
    a. The storage condition should be revised to: "Before first use, keep in refrigerator at 2°C – 8°C (36°F – 46°F). After first use, store for up to 30 days at 20°C – 25°C (68°F – 77°F). Do not Freeze or subject to heat".
    b. Name of manufacturer/distributor should be added to the label.
    c. Net content should be revised from (b) (4) to 3120 mcg/1.56 mL (2000 mcg/mL).

2. Carton label:
    a. The storage condition should be revised to: "Before first use, keep in refrigerator at 2°C – 8°C (36°F – 46°F). After first use, store for up to 30 days at 20°C – 25°C (68°F – 77°F). Do not Freeze or subject to heat".
    b. The statement of being sterile should be added to the label.
    c. The statement "for full prescribing information see the package insert" should be added to the label.
    d. Net content should be revised from (b) (4) to 3120 mcg/1.56 mL (2000 mcg/mL).

We are requesting a response by December 20, 2016.

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
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/s/

SAMANTHA S BELL
12/08/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208743

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Radius Health, Inc.
950 Winter Street
Waltham, MA 02451

ATTENTION: Deepa Desai, M.S.
Director, Regulatory Affairs

Dear Ms. Desai:

Please refer to your New Drug Application (NDA) dated March 30, 2016, received March 30, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abaloparatide Injection, 80 mcg/40 microliters.

We also refer to your August 30, 2016, correspondence, received August 30, 2016, requesting review of your proposed proprietary name, Tymlos.

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

If any of the proposed product characteristics as stated in your August 30, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta M. Jackson, MS, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-4952. For any other information regarding this application, contact Samantha Bell, Regulatory Project Manager in the Office of New Drugs, at 301-796-9687.

Sincerely,

{See appended electronic signature page}

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

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
11/22/2016

From: Bell, Samantha
Sent: Thursday, November 10, 2016 12:26 PM
To: Desai, Deepa (Ddesai@radiuspharm.com)
Subject: NDA 208743 Information Request

Dear Ms. Desai:
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide, NDA 208743.

We are reviewing the application and have the following requests for information:

For Study BA058-05-016, we are requesting that you reanalyze and report the pharmacokinetic parameters without subjects #1015 and #1016. In the updated analysis, include the statistical comparison of the BD II pen and UnoPen injectors without the two subjects.

Submit this updated analysis of your pivotal bioequivalence study by November 17, 2016.

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
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samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
11/10/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208743

GENERAL ADVICE

Radius Health, Inc.
Attention: Deepa Desai, M.S.
Director, Regulatory Affairs
950 Winter Street
Waltham, MA 02451

Dear Ms. Desai:

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

We also refer to your October 31, 2016, submission, containing a focused human factors summative study protocol and proposed Instructions for Use, which includes modifications to clarify priming and needle removal.

We recommend the following be implemented prior to conducting your human factors validation study:

1. Increase the number of study subjects to 30 to include 15 experienced and 15 inexperienced pen users as distinct user groups.

2. Alternatively, provide data to support your proposed methodology of using 15 participants total.

If you have any questions, call Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

HYLTON V JOFFE
11/08/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208743

MID-CYCLE COMMUNICATION

Radius Health, Inc.
Attention: Michael Macalush, M.S.
Director, Regulatory Affairs
950 Winter Street
Waltham, MA 02451

Dear Mr. Macalush:

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

We also refer to the teleconference between representatives of your firm and the FDA on September 22, 2016. The purpose of the teleconference was to provide you with an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Samantha Bell, Regulatory Project Manager at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Clinical Team Leader
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: September 22, 2016, 1:00 P.M. to 2:00 P.M.

Application Number: NDA 208743
Product Name: Abaloparatide
Indication: Treatment of postmenopausal women with osteoporosis
Applicant Name: Radius Health, Inc.

Meeting Chair: Theresa Kehoe, M.D.
Meeting Recorder: Samantha Bell

FDA ATTENDEES

Division of Bone, Reproductive, and Urologic Products (DBRUP):
Hylton V. Joffe, M.D., M.M.Sc., Director
Theresa Kehoe, M.D., Clinical Team Leader
Stephen Voss, M.D., Medical Officer
Jacqueline Karp, M.D., Medical Officer
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager
Robin Duer, R.N., B.S.N., M.B.A., Associate Director for Labeling

Office of New Drugs, Office of Drug Evaluation III:
Amy Egan, M.D., M.P.H., Deputy Director

Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP):
LaiMing Lee, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology (DCP) III
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP III
Fang Li, Ph.D., Pharmacometrics Reviewer, Division of Pharmacometrics (DPM)
Jeffry Florian, Ph.D., Pharmacometrics Team Leader, DPM

OTS, Office of Biostatistics, Division of Biometrics III:
Jia Guo, Ph.D., Biometrics Reviewer
Mahboob Sobhan, Ph.D., Biometrics Team Leader

Office of Pharmaceutical Quality:
Mark Seggel, Ph.D., Application Technical Lead, Office of New Drug Products (ONDP)
Thao Vu, Regulatory Business Process Manager, ONDP

Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management:
CAPT Walter Fava, R.Ph., M.S.Ed., Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Kimberly Lehrfeld, Pharm.D., BCBS, Team Leader, Division of Risk Management

OSE, Office of Pharmacovigilance and Epidemiology:
Jie (Jenni) Li, Ph.D., MBBS, Team Leader, Division of Epidemiology

Office of Combination Products:
Bindi Nikhar, M.D., Associate Clinical Director

Center for Devices and Radiological Health (CDRH):
Robert Meyer, B.S., M.E., Reviewer, Office of Device Evaluation, General Hospital, Respiratory, Infection Control, and Dental Devices (DAGRID), General Hospital Devices Branch

Office of Scientific Investigations (OSI)
Roy Blay, Ph.D., Reviewer

EASTERN RESEARCH GROUP ATTENDEES
Peggah Khorrami, Independent Assessor

APPLICANT ATTENDEES
David Hanley, Ph.D., Executive Director, Technical Operations
Gary Hattersley, Ph.D., Chief Scientific Officer
Gregory C. Williams, Ph.D., MBA, Chief Development Officer
Martie Griffin, Head of Corporate Quality
Tristan Hu, Ph.D., Head of Biometrics
Michael Macalush, M.S., Director, Regulatory Affairs
Deepa Desai, Director, Regulatory Affairs – Advertising, Promotion and Labeling
Lorraine Fitzpatrick, M.D., Chief Medical Officer

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

Significant issues identified by the review team to date include:

1. We are continuing to evaluate the applicability of Study BA058-05-003 efficacy data to the U.S. postmenopausal osteoporosis population.

   From a statistical perspective, we found that the model-based estimation of U.S. treatment effects by leveraging information from regions outside the U.S. (your submission dated August 15, 2016) is not appropriate. The validity of your estimation model is in question because:

   a. The regression model for estimation is not validated. Model prediction performance is unknown.

   b. The predicted bone mineral density (BMD) value is consistently greater than the observed BMD value in the U.S. for each BMD parameter, which implies that the model estimation is biased.

2. The occurrence of tachycardia and palpitations in the clinical fracture study, study BA058-05-012 (your Thorough QT study) as discussed below, and Study BA058-05-001B, also discussed below, is a current review issue.

   We note based upon Figure 5.1 from Study BA058-05-012 (your Thorough QT study) Expert Cardiac Report, that the placebo-adjusted change from baseline in heart rate is approximately 15 and 20 beats per minute (bpm) at 15 minutes post-dose following a single administration of subcutaneous abaloparatide 80 and 240 mcg, respectively, compared to 0.3 bpm in the moxifloxacin group. The data from the study show that the effect of abaloparatide on heart rate is approximately 6 bpm higher at 15 minutes versus 1 hour post-dose. The pharmacokinetic data showed that mean $AUC_{0\text{-}inf}$ was 2.3-fold higher following 240 mcg, compared to 80 mcg.

   Data from phase 1 Study BA058-05-001B following 7 days of once daily administration of 80, 100, and 120 mcg subcutaneous abaloparatide further supports the dose-dependent heart rate response observed in the Thorough QT study.

3. Pharmacokinetic data from Study BA058-05-011 (renal impairment study) following a single administration of subcutaneous abaloparatide 80 mcg showed that the mean exposure increase ($AUC_{0\text{-}inf}$) was 1.7 and 2.1-fold higher in patients with moderate and severe renal impairment, respectively, compared to subjects with normal renal function. The exposure increases in patients with moderate and severe renal impairment and the potential impact on heart rate and other adverse events is a current review issue.

4. Our review of the results of your human factors (HF) validation study for your proposed abaloparatide multi-dose prefilled pen containing 30 daily doses of 80 mcg per dose

identified three areas of concern involving failure of critical use steps, which pose risk of medication error:

a. Failure to prime the pen during the initial one time set up which poses risk of delivery of a partial dose(s).

b. Priming the pen with each dose instead of only one time at the initial set up of each new device which, if not realized by the user, could lead to loss of drug and could result in omission of doses.

c. Difficulty removing the needle after injection, which has resulted in accidental needle sticks.

We find that your study results do not demonstrate that your proposed product can be used safely and effectively in the intended use scenario by the intended users. As such, we believe that the risks associated with the use of your product have not been adequately mitigated. Therefore, we recommend the following:

a. Based on the failures reported in your HF validation study and subjective feedback from your participants, your instructions for priming the abaloparatide pen lack clarity and may lead to medication errors. We recommend that you emphasize the instructions about priming the abaloparatide pen only upon initial set up by including a statement at the beginning of the Instructions for Use (IFU). For example, you may consider the following language 'Before you use a new pen for the first time, you must remove air bubbles after attaching the needle as described in Step X to receive the correct dose.'

b. Clarify the graphic and instructions for removing the needle in Step 19, as some participants reported that they were confused by the terminology, (b) (4) and did not find the diagram clear.

Given that these changes impact critical tasks, we ask that you validate the effectiveness of these changes in the IFU in a focused HF validation study that evaluates use steps that are specific to the modifications. We are requesting the study results be submitted by mid-December in order to conduct our review in this review cycle.

Guidance on human factors procedures to follow can be found in Applying Human Factors and Usability Engineering to Medical Devices, available online at:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

Guidance on Safety Considerations for Product Design to Minimize Medication Errors, available online at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development, available online at:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, available online at:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

DISCUSSION AT THE MEETING

Radius asked the FDA if the protocol for the focused HF validation study should be submitted to the FDA for review prior to conduct and if the FDA would expedite the review of the protocol. The FDA recommended Radius submit the protocol for review and agreed to expedite the review.

3.0 INFORMATION REQUESTS

At this time, outstanding information requests include:

The clinical information request (IR) sent September 16, 2016, with requested due date of October 7, 2016:

1) Clarify the methods used to calculate patient compliance with study medication in Study 003. The protocol stated that compliance would be ascertained by 3 methods: patient diaries, cartridge accountability, and site-assessment of remaining drug content of returned cartridges. The study report presents compliance estimates that appear to be based on patient diary entries of missed doses (table 14.3.5.12A). This table also includes estimates of doses delivered based on measurements of returned drug volumes in the drug dispense/return log. Submit compliance estimates based on the latter by treatment group and study site and address any possible discrepancies from the diary-based estimates.

2) The 6-month report for Study 005 includes an adverse event (AE) of intestinal adenocarcinoma (patient #1030040). The 12-month and 18-month reports (in the Safety Update) appear to have changed this AE for this patient to ovarian epithelial cancer. Clarify that this is a change in diagnosis of one neoplasm, rather than a second neoplasm.

The chemistry, manufacturing, and controls (CMC) IR sent September 19, 2016, with a requested due date of September 26, 2016.

Post meeting comment: FDA acknowledges the September 26, response to the CMC IR.

There currently are no new IRs.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Your proposed Risk Evaluation and Mitigation Strategy is under review. At this time no issues have been identified that would require escalation of your proposed REMS.

5.0 ADVISORY COMMITTEE MEETING

There are currently no plans to present this application before the Bone, Reproductive, and Urologic Drugs Advisory Committee.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The proposed date for the Late Cycle Meeting is December 20, 2016.
Initial product labeling and postmarketing commitment requests will be provided by December 9, 2016.
We intend to send the Late Cycle Background Package by December 8, 2016.

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/s/

THERESA E KEHOE
10/19/2016

From: Bell, Samantha
Sent: Friday, September 16, 2016 6:00 PM
To: Macalush, Michael (mmacalush@radiuspharm.com)
Subject: NDA 208743 Information Request

Dear Mr. Macalush:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide, NDA 208743.

We are reviewing the application and have the following comments and requests for information:

Clarify the methods used to calculate patient compliance with study medication in Study 003. The protocol stated that compliance would be ascertained by 3 methods: patient diaries, cartridge accountability, and site-assessment of remaining drug content of returned cartridges. The study report presents compliance estimates that appear to be based on patient diary entries of missed doses (table 14.3.5.12A). This table also includes estimates of doses delivered based on measurements of returned drug volumes in the drug dispense/return log. Submit compliance estimates based on the latter by treatment group and study site, and address any possible discrepancies from the diary-based estimates.

The 6-month report for Study 005 includes an adverse event (AE) of intestinal adenocarcinoma (patient #1030040). The 12-month and 18-month reports (in the Safety Update) appear to have changed this AE for this patient to ovarian epithelial cancer. Clarify that this is a change in diagnosis of one neoplasm, rather than a second neoplasm.

We are requesting a response by October 7, 2016.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
09/16/2016

Executive CAC
Date of Meeting: 9/6/2016

Committee: Karen Davis Bruno, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Tim McGovern, Ph.D., OND IO, Member
Sushanta Chakder, Ph.D., DGIEP, Alternate Member
Mukesh Summan, Ph.D., DABT, DBRUP, Pharmacology/Toxicology Supervisor
Gemma Kuijpers, Ph.D., DBRUP, Presenting Reviewer

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

NDA #: 208743
Drug Name: Abaloparatide
Sponsor: Radius Health, Inc.

Rat Carcinogenicity Study:
The Sponsor conducted a 2-year carcinogenicity study in F344 rats with doses of **0, 10, 25, 50 mcg/kg/day**. A positive control group treated **with 30 mcg/kg/day** PTH(1-34) was also included. Mortality was increased in a dose-related manner in 10, 25 and/or 50 µg/kg abaloparatide-treated males and females and 30 µg/kg PTH(1-34)-treated males. Dosing was discontinued in 10, 25 and 50 µg/kg/day abaloparatide-treated males, 30 µg/kg PTH(1-34) treated-males and 50 µg/kg abaloparatide-treated females due to high mortality rates. The 10, 25 and 50 µg/kg/day abaloparatide-treated males were sacrificed early in weeks 97, 88, and 99, respectively. The main cause of the dose-related mortality was the development of osteosarcoma. Treatment with abaloparatide resulted in increased incidences of osteosarcoma, osteoblastoma, and combined osteosarcoma or osteoblastoma, in males and females, at all doses.

Survival and tumor incidence due to abaloparatide in a 2-year rat carcinogenicity study

Group	*1*	*2*	*3*	*4*	*5*
Treatment	*Control (0µg/kg/day)*	*Low dose (10 µg/kg/day)*	*Mid dose (25 µg/kg/day)*	*High dose (50 µg/kg/day)*	*PTH1-34 (30 µg/kg/day)*
MALES (N)	(60)	(60)	(59)	(60)	(60)
Survival	18/60[b]	19/60	15/59[a]	16/60[d]	16/60[NT]
Osteosarcoma	**1**[d]	**31**[d]	**46**[d]	**52**[d]	**39**[d]
Osteoblastoma	**0**[d]	**1**	**15**[d]	**20**[d]	**10**[c]
Osteosarcoma/Osteoblastoma	**1**[d]	**31**[d]	**48**[d]	**54**[d]	**43**[d]
AUC multiple**	-	3x	14x	24x	68x
FEMALES (N)	(60)	(60)	(61)	(60)	(60)
Survival	26/60[b]	33/60	24/61	14/60[b]	25/60[NT]
Osteosarcoma	**1**[d]	**11**[b]	**22**[d]	**37**[d]	**24**[d]
Osteoblastoma	**0**[b]	**8**[b]	**7**[b]	**9**[c]	4
Osteosarcoma/Osteoblastoma	**1**[d]	**16**[d]	**27**[d]	**40**[d]	**27**[d]
AUC multiple**		4x	12x	25x	43x

[a,b,c,d,e] Statistically significant (trend test, or pairwise comparison vs control) (CDER analysis)

[a] $p \leq 0.05$, [b] $p \leq 0.01$, [c] $p \leq 0.001$, [d] $p \leq 0.0001$

[NT] Not Tested

** AUC(rat) / AUC(human) @ 80 µg/day (1546 pg·h/mL, Study BA058-5-001b)

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee agreed that the study was adequate, noting prior approval of the protocol.
- The Committee agreed that there were drug-related increases in osteosarcoma and osteoblastoma in males and females in all dose groups.
- The Committee agreed that the clinical relevance of the osteosarcoma and osteoblastoma increases is uncertain based on prior clinical experience with this drug class.

Karen Davis Bruno, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DBRUP
/MSumman, DBRUP
/GKuijpers, DBRUP
/SBell, DBRUP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
09/14/2016

KAREN L DAVIS BRUNO
09/14/2016

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

From:	Macalush, Michael
To:	Wasilik, Maria
Cc:	Desai, Deepa; Williams, Greg; Bell, Samantha
Subject:	RE: follow up to NDA 208743 Information Request
Date:	Friday, September 02, 2016 11:15:13 AM
Attachments:	02Sep16 Response to FDA 31Aug16 email request signed.pdf

Dear Ms. Wasilik,

In response to your 31 Aug 16 follow up email request, Radius is providing a response in the attached pdf file.

Please let us know if you have any further comments or questions.

Thank you and best regards, Mike

Best regards,

Michael Macalush
Michael Macalush, MS
Director, Regulatory Affairs

Radius Health, Inc.
4 Gatehall Drive
Parsippany, New Jersey 07054
Office: 973.385.1708
Mobile: (b) (6)
mmacalush@radiuspharm.com

Radius
www.radiuspharm.com

From: Wasilik, Maria [mailto:Maria.Wasilik@fda.hhs.gov]
Sent: Wednesday, August 31, 2016 4:09 PM
To: Desai, Deepa <Ddesai@radiuspharm.com>
Cc: Williams, Greg <gwilliams@radiuspharm.com>; Macalush, Michael <mmacalush@radiuspharm.com>; Bell, Samantha <Samantha.Bell@fda.hhs.gov>
Subject: follow up to NDA 208743 Information Request

Dear Ms. Desai,

We have questions regarding your response.

Provide the AUC values for male and female rats that you used to calculate the AUC multiples. What time point(s) in the 2-year rat study were these AUC values from?

Submit a response as soon as possible.

Please confirm receipt.

Sincerely,
Maria Wasilik

From: Desai, Deepa [mailto:Ddesai@radiuspharm.com]
Sent: Wednesday, August 31, 2016 1:19 PM
To: Wasilik, Maria; Bell, Samantha
Cc: Williams, Greg; Macalush, Michael
Subject: FW: NDA 208743 Information Request

Dear Ms. Wasilik and Ms. Bell,

Reference is made to your Information Request below sent via email to Michael Macalush yesterday, August 30th. I am covering for Mike during his vacation and providing Radius' response, as follows:

In response to your below question ***"Which AUC (area-under-the-curve) data did you use to calculate the AUC multiples mentioned in your proposed label (Black Box Warning and Section 13.1: Carcinogenesis, Mutagenesis, Impairment of Fertility) and on page 22 of your 'Nonclinical Overview'? The AUC multiples in these two documents appear to be different. In which studies were the rat and human AUCs that you used for the multiple calculation determined?"***

Radius acknowledges that the exposure multiples mentioned in the proposed draft PI are different from those found on page 22 of the Nonclinical Overview and reported in the Carcinogenicity report. The AUC data used to calculate the exposure multiples used in the Nonclinical Overview and the Carcinogenicity study were based on the steady state PK exposure levels following a 80 mcg dose obtained in the Phase 1b trial in healthy postmenopausal women at day 7, corresponding to an AUC =1546 hr*pg/ml (Section 2.7.2.2.2.2.2.1/Study BA058-05-001b). This represents approximately 4X, 18X and 30X the systemic exposures based on AUC for the corresponding 10, 25 and 50 µg/kg dose levels administered to rats in the 2-year carcinogenicity study. The exposure multiples mentioned in the proposed draft PI were calculated using different exposure values resulting in a calculated (b) (4) fold multiples of the exposure in humans following an 80 mcg dose. While these predicted differences in exposure do not change the conclusions or overall interpretation of the Carcinogenicity study, to resolve this discrepancy and provide consistency across the NDA, Radius will revise the draft PI to indicate 4X, (b) (4) multiples of the human exposures following an 80 µg steady state exposure to abaloparatide-SC.

Radius will also update the other NDA documents to be consistent with this change.

We believe that this fully addresses your question and will provide a formal update to the NDA within about 1 week.

Please let us know if you have any further comments or questions.

Best regards,

Deepa Desai
Deepa Desai
Director, Regulatory Affairs – Advertising, Promotion and Labeling

Radius Health, Inc.
4 Gatehall Drive
Parsippany, New Jersey 07054
Office: 973.385.1714
Mobile: (b) (6)
ddesai@radiuspharm.com

Radius
www.radiuspharm.com

Begin forwarded message:ores

From: "Wasilik, Maria" <Maria.Wasilik@fda.hhs.gov>
Date: August 30, 2016 at 10:08:37 AM EDT
To: "mmacalush@radiuspharm.com" <mmacalush@radiuspharm.com>
Cc: "Wasilik, Maria" <Maria.Wasilik@fda.hhs.gov>, "Bell, Samantha" <Samantha.Bell@fda.hhs.gov>
Subject: NDA 208743 Information Request

Dear Mr. Macalush:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide, NDA 208743.

We are reviewing the application and have the following request for information:

Which AUC (area-under-the-curve) data did you use to calculate the AUC multiples mentioned in your proposed label (Black Box Warning and Section 13.1: Carcinogenesis, Mutagenesis, Impairment of Fertility) and on page 22 of your 'Nonclinical Overview'? The AUC multiples in these two documents appear to be different. In which studies were the rat and human AUCs that you used for the multiple calculation determined?

I am covering for Samantha Bell this week. We are requesting a response as soon as possible. Please confirm receipt.

Sincerely,

Maria Wasilik, R.Ph.
Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products

Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5379
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

Phone 301-796-0567 Fax 301-796-9897

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/s/

MARIA R WASILIK
09/02/2016

From:	Desai, Deepa
To:	Wasilik, Maria
Cc:	Williams, Greg; Macalush, Michael; Bell, Samantha
Subject:	RE: follow up to NDA 208743 Information Request
Date:	Wednesday, August 31, 2016 4:30:12 PM

Dear Ms. Wasilik,

Confirming receipt of your follow-up request. We will respond as soon as possible.

Thank you and have a nice evening.

Best,

Deepa

From: Wasilik, Maria [mailto:Maria.Wasilik@fda.hhs.gov]
Sent: Wednesday, August 31, 2016 4:09 PM
To: Desai, Deepa <Ddesai@radiuspharm.com>
Cc: Williams, Greg <gwilliams@radiuspharm.com>; Macalush, Michael <mmacalush@radiuspharm.com>; Bell, Samantha <Samantha.Bell@fda.hhs.gov>
Subject: follow up to NDA 208743 Information Request

Dear Ms. Desai,

We have questions regarding your response.

Provide the AUC values for male and female rats that you used to calculate the AUC multiples. What time point(s) in the 2-year rat study were these AUC values from?

Submit a response as soon as possible.

Please confirm receipt.

Sincerely,
Maria Wasilik

From: Desai, Deepa [mailto:Ddesai@radiuspharm.com]
Sent: Wednesday, August 31, 2016 1:19 PM
To: Wasilik, Maria; Bell, Samantha
Cc: Williams, Greg; Macalush, Michael
Subject: FW: NDA 208743 Information Request

Dear Ms. Wasilik and Ms. Bell,

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In response to your below question ***"Which AUC (area-under-the-curve) data did you use to calculate the AUC multiples mentioned in your proposed label (Black Box Warning and Section 13.1: Carcinogenesis, Mutagenesis, Impairment of Fertility) and on page 22 of your 'Nonclinical Overview'? The AUC multiples in these two documents appear to be different. In which studies were the rat and human AUCs that you used for the multiple calculation determined?"***

Radius acknowledges that the exposure multiples mentioned in the proposed draft PI are different from those found on page 22 of the Nonclinical Overview and reported in the Carcinogenicity report. The AUC data used to calculate the exposure multiples used in the Nonclinical Overview and the Carcinogenicity study were based on the steady state PK exposure levels following a 80 mcg dose obtained in the Phase 1b trial in healthy postmenopausal women at day 7, corresponding to an AUC =1546 hr*pg/ml (Section 2.7.2.2.2.2.2.1/Study BA058-05-001b). This represents approximately 4X, 18X and 30X the systemic exposures based on AUC for the corresponding 10, 25 and 50 µg/kg dose levels administered to rats in the 2-year carcinogenicity study. The exposure multiples mentioned in the proposed draft PI were calculated using different exposure values resulting in a calculated (b) (4) fold multiples of the exposure in humans following an 80 mcg dose. While these predicted differences in exposure do not change the conclusions or overall interpretation of the Carcinogenicity study, to resolve this discrepancy and provide consistency across the NDA, Radius will revise the draft PI to indicate 4X, (b) (4) multiples of the human exposures following an 80 µg steady state exposure to abaloparatide-SC.

Radius will also update the other NDA documents to be consistent with this change.

We believe that this fully addresses your question and will provide a formal update to the NDA within about 1 week.

Please let us know if you have any further comments or questions.

Best regards,

Deepa Desai
Deepa Desai
Director, Regulatory Affairs – Advertising, Promotion and Labeling

Radius Health, Inc.
4 Gatehall Drive
Parsippany, New Jersey 07054
Office: 973.385.1714
Mobile: (b) (6)
ddesai@radiuspharm.com

Radius
www.radiuspharm.com

Begin forwarded message:ores

From: "Wasilik, Maria" <Maria.Wasilik@fda.hhs.gov>
Date: August 30, 2016 at 10:08:37 AM EDT
To: "mmacalush@radiuspharm.com" <mmacalush@radiuspharm.com>
Cc: "Wasilik, Maria" <Maria.Wasilik@fda.hhs.gov>, "Bell, Samantha" <Samantha.Bell@fda.hhs.gov>
Subject: NDA 208743 Information Request

Dear Mr. Macalush:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide, NDA 208743.

We are reviewing the application and have the following request for information:

Which AUC (area-under-the-curve) data did you use to calculate the AUC multiples mentioned in your proposed label (Black Box Warning and Section 13.1: Carcinogenesis, Mutagenesis, Impairment of Fertility) and on page 22 of your 'Nonclinical Overview'? The AUC multiples in these two documents appear to be different. In which studies were the rat and human AUCs that you used for the multiple calculation determined?

I am covering for Samantha Bell this week. We are requesting a response as soon as possible. Please confirm receipt.

Sincerely,

Maria Wasilik, R.Ph.
Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5379
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

Phone 301-796-0567 Fax 301-796-9897

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/s/

MARIA R WASILIK
09/01/2016

From: Macalush, Michael
To: Wasilik, Maria
Subject: Re: NDA 208743 Information Request
Date: Tuesday, August 30, 2016 10:28:23 AM

Hi Maria, Received. Thank you. We will respond as quickly as possible. Best, Mike

Sent from my iPhone

On Aug 30, 2016, at 10:08 AM, Wasilik, Maria <Maria.Wasilik@fda.hhs.gov> wrote:

> Dear Mr. Macalush:
>
> Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide, NDA 208743.
>
> We are reviewing the application and have the following request for information:
>
> Which AUC (area-under-the-curve) data did you use to calculate the AUC multiples mentioned in your proposed label (Black Box Warning and Section 13.1: Carcinogenesis, Mutagenesis, Impairment of Fertility) and on page 22 of your 'Nonclinical Overview'? The AUC multiples in these two documents appear to be different. In which studies were the rat and human AUCs that you used for the multiple calculation determined?
>
> I am covering for Samantha Bell this week. We are requesting a response as soon as possible. Please confirm receipt.
>
> Sincerely,
>
> Maria Wasilik, R.Ph.
> Regulatory Project Manager
> Division of Bone, Reproductive, and Urologic Products
> Food and Drug Administration
> Center for Drug Evaluation and Research
> White Oak Building 22, Room: 5379
> 10903 New Hampshire Avenue
> Silver Spring, Maryland 20903
>
> Phone 301-796-0567 Fax 301-796-9897

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/s/

MARIA R WASILIK
08/30/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208743

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Radius Health, Inc.
950 Winter Street
Waltham, MA 02451

ATTENTION: Michael Macalush, M.S.
Director, Regulatory Affairs

Dear Mr. Macalush:

Please refer to your New Drug Application (NDA) dated March 30, 2016, received March 30, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abaloparatide Injection, 80 mcg/ 40 microliters.

We also refer to your May 27, 2016, correspondence, received May 27, 2016, requesting review of your proposed proprietary name, (b) (4)

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

The proposed proprietary name, (b) (4) is vulnerable to name confusion and wrong drug medication errors due to its orthographic similarity and overlapping product characteristics with a pending proposed proprietary name. Therefore, the ultimate acceptability of your proposed proprietary name, (b) (4) is dependent upon which underlying application is approved first. If another product is approved prior to your product, with a name that would be confused with your proposed proprietary name of (b) (4), you will be requested to submit another name.

We acknowledge that our conclusion differs from that of the external study you submitted. However, the pending proposed proprietary name was not identified in the external study conducted by (b) (4)

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

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta M. Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-4952. For any other information regarding this application, contact Samantha Bell, Regulatory Project Manager in the Office of New Drugs, at 301-796-9687.

Sincerely,

{See appended electronic signature page}

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

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
08/23/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208743

PROPRIETARY NAME ACKNOWLEDGEMENT

Radius Health, Inc
950 Winter Street
Waltham, MA 02451

ATTENTION: Michael Macalush, M.S.
Director, Regulatory Affairs

Dear Mr. Macalush:

Please refer to your New Drug Application (NDA) dated March 30, 2016, received March 30, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abaloparatide for Injection, 80 mcg/40mcL.

We acknowledge receipt of your May 27, 2016, correspondence, received May 27, 2016, requesting a review of your proposed proprietary name, (b) (4)

The user fee goal date is August 25, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta M. Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4952. For any other information regarding this application, contact Samantha Bell, Regulatory Project Manager, in the Office of New Drugs at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Shawnetta Jackson
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

SHAWNETTA M JACKSON
06/10/2016

From: Bell, Samantha
Sent: Tuesday, April 12, 2016 12:10 PM
To: Macalush, Michael (mmacalush@radiuspharm.com)
Subject: NDA 208743 Information Request

Dear Mr. Macalush:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abaloparatide, NDA 208743.

We are reviewing the application and have the following comments and requests for information:

"In the clinsite.xpt file provided for Part III of the OSI request, you indicate that the efficacy endpoint is the percentage of patients with >= 1 incidents of new vertebral fractures.

In the Define table you indicate that TRTEFFE (Treatment Efficacy Endpoint) is the summary statistic for each primary efficacy endpoint by treatment by site. In the clinsite.xpt file that you submitted for the placebo treatment arm in Study BA058-05-003, the values for TRTEFFE appear to represent percentages of subjects at each site that met the primary efficacy endpoint. However the values for the abaloparatide and teriparatide arms at each site are all 0 (zero).

- For subjects in Study BA058-05-003 provide revised data for the abaloparatide and teriparatide arms that provides the corrected summary statistic TRTEFFE variable values.
- Similarly for subjects in Study BA058-05-005 (randomized subjects limited to those subjects in the abaloparatide and placebo treatment arms who continued on in the extension treatment with alendronate for six months), provide revised data for TRTEFFE variable values that reflect the percentage of subjects with >= 1 vertebral fracture for subjects in abaloparatide and placebo treated subjects continuing in the BA058-05-005 from baseline to interim follow-up at 24 months (18 months of treatment in BA058-05-003 and subsequent 6 month treatment with alendronate).

We are requesting a response by April 19, 2016.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
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Silver Spring, MD 20993

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/s/

SAMANTHA S BELL
04/12/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 073176

DENY -
BREAKTHROUGH THERAPY DESIGNATION

Radius Health, Inc.
Attention: Gregory C. Williams, Ph.D.
Chief Development Officer
950 Winter St.
Waltham, MA 02451

Dear Dr. Williams:

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

We also refer to your May 22, 2015, request for Breakthrough Therapy designation for the treatment of osteoporosis in postmenopausal women.

We have reviewed your request and while we have determined that the treatment of osteoporosis in postmenopausal women meets the criteria for a serious or life-threatening disease or condition, the preliminary clinical evidence you submitted does not indicate that your drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Therefore, designation as a Breakthrough Therapy cannot be granted at this time.

We have provided further rationale to address your claimed advantage of abaloparatide over teriparatide:

1. With regard to fracture efficacy, the direct comparison of abaloparatide and teriparatide in your phase 3 trial showed comparable relative risk reductions for new vertebral fractures at 86% and 80%, respectively. Furthermore, the 95% confidence intervals for relative risk reduction of new vertebral fractures with abaloparatide overlap those of the currently approved agents denosumab and zoledronic acid.
2. Your potential safety benefit claim of less hypercalcemia has unclear clinical relevance when we take into account our experience with the Forteo clinical program and Forteo's postmarketing history. In addition, hypercalcemia is not an associated risk with any of the other approved treatments for osteoporosis. Lastly, there is no evidence that abaloparatide offers other safety advantages over Forteo with regard to orthostatic hypotension, soft tissue calcification, and risk of osteosarcoma.

You may submit a new request if you obtain new clinical evidence that demonstrates a substantial improvement in the treatment of postmenopausal osteoporosis over existing therapies for abaloparatide.

For further information regarding Breakthrough Therapy designation, refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf)

For further information regarding Fast Track, refer to the guidance noted in the above paragraph.

If you have any questions, contact Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

HYLTON V JOFFE
07/16/2015

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 73176
Request Receipt Date	May 26, 2015
Product	Abaloparatide
Indication	Treatment of postmenopausal osteoporosis in women at high risk of fracture
Drug Class/Mechanism of Action	Parathyroid hormone-related peptide analog/Osteoanabolic
Sponsor	Radius, Inc.
ODE/Division	ODE III/DBRUP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	July 26, 2015

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

The proposed indication for abaloparatide is treatment of postmenopausal osteoporosis in patients at high risk of fracture

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐ YES ☒ NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

a. Is the condition serious/life-threatening[1])? ☒ YES ☐ NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?

☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

1

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Abaloparatide is under development for treatment of postmenopausal osteoporosis (PMO). The Applicant has had a Pre-NDA meeting and is nearing NDA submission. Abaloparatide is a 34 amino acid analogue of human parathyroid hormone-related peptide (PTHrP). PTHrP is secreted endogenously by osteoblasts and, like parathyroid hormone (PTH), contributes to calcium homeostasis. PTH and PTHrP share some amino acid sequence homology and bind to the same receptor; however, the receptor interaction with PTHrP elicits a distinct conformation and response compared to the receptor interaction with PTH. Teriparatide (Forteo, recombinant human PTH [1-34]) is the only other product with an anabolic mechanism of action that is approved for the treatment of PMO.

PMO is a systemic skeletal disease characterized by low bone mass and degradation of bone microarchitecture, which lead to increased fragility and risk of fracture. Sequelae of osteoporotic fractures, most notably hip fractures, are frequently characterized by significant morbidity and mortality with a significant impact on public health.

On May 8, 2014 the sponsor requested Breakthrough Therapy Designation for abaloparatide, claiming 5 clinically important benefits of abaloparatide 80 mcg/day relative to teriparatide from Phase 1 and Phase 2 study data. The sponsor ascribes these differences to the molecular characteristics distinguishing abaloparatide and teriparatide.

1. Faster increases in Hip and spine BMD
2. Greater increases in hip and spine BMD
3. Healthier bone (less cortical porosity seen in pre-clinical studies)
4. More responders to abaloparatide than to teriparatide
5. Enhanced safety (re: hypercalcemia)

On July 1, 2014 the breakthrough therapy designation was denied. The Division determined that the preliminary clinical evidence that was submitted did not indicate that abaloparatide met the required criterion of demonstrating substantial improvement over existing therapies on one or more clinically significant endpoints. The bone mineral density endpoints used to support the breakthrough therapy designation request are considered imperfect surrogates for the clinical benefit of fracture reduction. There was also no evidence that abaloparatide offered a meaningful safety advantage over Forteo with regard to hypercalcemia (Appendix).

The Sponsor now resubmits a request for breakthrough therapy designation based on the Phase 3 fracture trial data. Study BA058-05-003 (003) is an 18 month trial that enrolled approximately 2,400 women with postmenopausal osteoporosis. Subjects were enrolled and randomly assigned in a 1:1:1 ratio to receive a daily dose of either abaloparatide 80 mcg SC, placebo, or teriparatide 20 mcg SC for 18 months. This trial has been completed and the sponsor submits efficacy and safety data in support of this breakthrough therapy designation request.

This review focuses on the new data from Study 003.

7. Information related to endpoints used in the available clinical data:

The sponsor lists the following benefits of abaloparatide 80 mcg/day relative to teriparatide in support of breakthrough therapy designation (sponsor's sequential hierarchy):

1) Faster increases in hip, femoral neck and spine BMD
2) Greater increases in hip and femoral neck BMD
3) Significantly greater bone build at 8/9 BMD measures
4) Significant reduction of vertebral, clinical and nonvertebral fractures
5) Significantly fewer wrist fractures together with preservation of wrist BMD
6) More responders and greater clinical benefit for the patient population
7) Broader population demonstrates comparative efficacy among patients representative of those treated by physicians
8) Enhanced safety as reflected by reduced hypercalcemia and hypercalciuria

The sponsor provides clinical data from the completed Phase 3 fracture trial, Study 003, to support the breakthrough therapy designation request. The primary efficacy endpoint is the number of abaloparatide treated subjects showing new morphometric vertebral fractures at End-of-Treatment (18 months) when compared to placebo. The Division accepts morphometric vertebral fracture as a valid endpoint for all fracture trials for osteoporosis therapies.

Secondary endpoints evaluated using a hierarchal approach include percent change in total hip bone mineral density compared to placebo at 18 months; percent change in femoral neck bone mineral density compared to placebo at 18 months; percent change in lumbar spine bone mineral density compared to placebo at 18 months; nonvertebral fractures compared to placebo at 18 months; percent change in total hip bone mineral density compared to teriparatide at 6 months; percent change in femoral neck mineral density compared to teriparatide at 6 months, nonvertebral fractures at compared to teriparatide; and percent change in lumbar spine bone mineral density compared to teriparatide at 6 months. These endpoints are accepted by the division to support efficacy claims.

Some endpoints and analyses the sponsor is using to support this request for breakthrough therapy designation are exploratory or post-hoc analyses, including bone mineral density comparisons to placebo at 6 and 12 months (exploratory), bone mineral density comparisons other than lumbar spine, total hip and femoral neck, reduction in clinical vertebral fractures, reduction in wrist fractures, and responder analyses.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population.

Currently, there are seven molecular entities approved for treatment of osteoporosis based on fracture reduction efficacy. Table 1 lists the primary endpoint of absolute and relative risk reductions for new morphometric vertebral fractures for therapies approved for treatment of women with postmenopausal osteoporosis. Confidence intervals (CI) are provided where available.

Table 1: Absolute and Relative Risk Reductions of new morphometric vertebral fracture for drugs approved for treatment of postmenopausal osteoporosis.

	12 months		24 months		36 months	
Drug (tradename, approval)	**ARR (95% CI)**	**RRR (95% CI)**	**ARR (95% CI)**	**RRR (95% CI)**	**ARR (95% CI)**	**RRR (95% CI)**
teriparatide (Forteo, 2002)			9.3* (5.5,13.1)	65 (45,78)		
denosumab (Prolia, 2010)	1.4 (0.8,1.9)	61 (42,74)	3.5 (2.7,4.3)	71 (61,79)	4.8 (3.9,5.8)	68 (59,74)
zoledronic acid (Reclast, 2007)	2.2 (1.4,3.1)	60 (43,72)	5.5 (4.4,6.6)	71 (62,78)	7.6 (6.3,9.0)	70 (62,76)
ibandronate (Boniva, 2003)					4.9	52 (29,68)
risedronate (Actonel, 2000) North American	4.0	65	5.9	55	5.0	41
risedronate Multinational	7.7	61	13.1	59	10.9	49
raloxifene 1 (Evista, 1999) no baseline fracture					2.4	55 (29,71)
raloxifene 2 ≥ 1 baseline fracture					6.1	30 (14,44)
alendronate (Fosamax, 1995) FIT 1					7.1	47
alendronate FIT 2					2.3[#]	48
ARR = Absolute Risk Reduction; RRR = Relative Risk Reduction *Forteo trial - 19 months median exposure [#]FIT 2 trial = 48 month assessment						

Other fracture endpoints that are evaluated as secondary endpoints include nonvertebral and hip fracture. For approval, it is not required to demonstrate fracture reduction efficacy at all fracture sites. Table 2 below outlines the incidence and risk reductions for nonvertebral fracture.

Table 2: Incidence, Absolute Risk Reduction, and Relative Risk Reduction of nonvertebral fracture for drugs approved for treatment of postmenopausal osteoporosis.

	nonvertebral fracture			
Drug	Placebo fx incidence (%)	Drug fx incidence (%)	ARR (95% CI)	RRR (95% CI)
teriparatide (Forteo, 2002)	5.5	2.6	2.9	53
denosumab (Prolia, 2010)	8.0	6.5	1.5 (0.3,2.7)	20 (5,33)
zoledronic acid (Reclast, 2007)	10.7	8.0	2.7 (1.4,4.0)	25 (13,36)
ibandronate (Boniva, 2003)	8.2	9.1		
risedronate (Actonel, 2000) combine NA, MN	11	7		36
raloxifene (Evista, 1999) combined	9.3	8.8		6 (2, 11)
alendronate (Fosamax, 1995) FIT 1 (36 months)			4.3	26
alendronate FIT 2 (48 months)			3.3	22

Osteoporotic hip fractures are associated with significant morbidity and mortality. Three products are labeled for reductions in hip fracture over 3 years: Fosamax (drug 1.1%, placebo 2.2%, ARR 1.1%, RRR 51%); Reclast (drug 1.4%, placebo 2.5%, ARR 1.1%, RRR 41%); and Prolia (drug 0.7%, placebo 1.2%, ARR 0.3%, RRR (b)(4)%).

Etidronate (Didronel®) and pamidronate (Aredia®) are bisphosphonates approved for treatment of Paget's disease of bone. Etidronate is also approved for the prevention of heterotopic ossification and pamidronate is approved for the treatment of hypercalcemia of malignancy. Both drugs are approved outside the US for treatment of osteoporosis and may be used off-label for this indication.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

Currently, there are no other products whose sponsors have requested breakthrough therapy designation for treatment of postmenopausal osteoporosis.

10. Information related to the preliminary clinical evidence:

The sponsor submits the phase 3 fracture trial results in support of their request for breakthrough designation. Preliminary data from the phase 2 studies accompanied the original breakthrough therapy designation request and have been previously reviewed (Appendix).

Table 3: Abaloparatide Phase 3 trial 003

Study ID	Design	Primary Endpoint	Treatment Group (N)	Incidence of new vertebral fracture	Relative Risk Reduction
BA058-05-003	Randomized, double-blind, 3-arm, single dose, placebo and active comparator-controlled, comparative multicenter trial	Efficacy of 18 months of treatment with Abaloparatide-SC on reduction of vertebral fracture incidence compared to placebo and teriparatide	Placebo (821)	4.2%	
			Abaloparatide (824)	0.6%	86%
			Teriparatide (818)	0.8%	80%

The completed clinical trial 003 is a global, randomized, double-blind, placebo-controlled, comparative trial, with an open-label active comparator arm, in which 2,463 eligible patients were enrolled and randomly assigned in a 1:1:1 ratio to receive a daily dose of either abaloparatide 80 mcg SC, placebo, or open-label teriparatide 20 mcg SC for 18 months. The primary objective was to determine the safety and efficacy of abaloparatide when compared with teriparatide and placebo for the prevention of vertebral fractures at 18 months. Key secondary objectives included assessment of the prevention of non-vertebral fractures, change in vertical height, BMD of the lumbar spine, total hip, and femoral neck, and hypercalcemia. A descriptive comparison of the primary efficacy endpoint between abaloparatide and teriparatide groups will be provided.

The Phase 1 and 2 BMD, cortical porosity and hypercalcemia data provided in support of the sponsor's initial BTDR were reviewed previously (*References, Section 13*). In this second BTDR, the sponsor provides more BMD and hypercalcemia data from their Phase 3 trial, in addition to fracture efficacy data. As potential clinically meaningful safety and efficacy parameters, the new fracture and hypercalcemia data are reviewed.

Fracture Efficacy

The sponsor outlines the fracture data supporting their request for breakthough therapy designation, as presented in Table 4. Abaloparatide met the primary efficacy endpoint with a statistically significant 86% relative risk reduction (95% CI 61%, 95%) for new vertebral fractures as compared to the placebo group. While this could be considered an incremental improvement based on cross-study comparisons to existing therapies, the 95% confidence intervals overlap the relative risk reductions achieved with currently approved agents denosumab and zoledronic acid (Table 1). Furthermore, the teriparatide active-control arm in trial 003 provides an opportunity to compare head-to-head the efficacy and safety of abaloparotide with teriparatide. This direct comparison showed that the 86% relative risk reduction for new vertebral fractures with abaloparatide is similar to the 80% relative risk reduction seen with teriparatide.

The nonvertebral fracture relative risk reduction of 43% approximates the relative risk reduction of 53% achieved in the original Forteo trial (Table 2). It is unclear why there is such disparity in results between trial 003 (28% relative risk reduction for teriparatide) and the original Forteo trial (53% relative risk reduction). Other agents are labeled with nonvertebral fracture relative risk reductions in the range of 20 – 36%.

Clinical fractures are not defined and are not included in the original statistical analyses. The evaluation of clinical fracture does not add support to this breakthrough therapy designation request.

Table 4: Trial 003: Fracture incidence and relative risk reduction of fracture vs placebo at 18 months

	Fracture Incidence			Relative Risk Reduction (95%CI)	
Fracture site	**Abaloparatide**	**Placebo**	**Teriparatide**	**Abaloparatide**	**Teriparatide**
Vertebral	0.6%	4.2%	0.8%	86% (61,95)	80%
Non-vertebral				43% (0,68)	28%
Clinical				45% (12, 66)	

The sponsor reports a reduction in the estimated incidence rate of wrist fractures with abaloparatide compared to placebo and teriparatide, although no statistical justification or explanation of the reported results are provided.

The bone mineral density findings in trial 003 are similar to those from the Phase 2 trials, and do not materially add to the fracture efficacy data presented. The sponsor believes that early BMD increases support improved early efficacy for abaloparatide. However, as outlined in Table 1, the fracture reduction efficacy achieved with densosumab and zoledronic acid at month 12 was significant.

Hypercalcemia

In the Forteo GHAC fracture trial (the trial used to support approval of Forteo), subjects received 1000 mg calcium and 400 – 1200 IU vitamin D daily. The frequency of at least one episode of 4 – 6 hour post-dose hypercalcemia (> 10.6 mg/dL) was 2% in the placebo group and 11% in the 20 mcg teriparatide group. No deaths or serious adverse events were reported related to hypercalcemia in Forteo clinical trials. Episodes of hypercalcemia greater than 13.0 mg/mL have been reported during post approval use of Forteo with no reports of hypercalcemia deaths. For abaloparatide's phase 3 trial 003, subjects received 500-1000 mg calcium and 400 – 800 IU vitamin D daily. The sponsor reports hypercalcemia (> 10.7 mg/dL) event rates of 0.4%, 3.4% and 6.4% in the placebo, abaloparatide and teriparatide groups, respectively. Based on this head-to-head comparison with teriparatide, the hypercalcemia data do not suggest a substantial safety improvement over teriparatide. In addition, hypercalcemia is not an associated risk with any of the other approved treatments for osteoporosis. The Division believes that the hypercalcemia profile of abaloparatide does not merit breakthrough therapy designation.

As with teriparatide in preclinical development, fatal osteosarcomas were observed in abaloparatide-treated rats. Non-neoplastic changes in rat soft tissues included mineralization, and were observed at comparable frequency with abaloparatide and teriparatide-treated rats.

The overall safety profile of abaloparatide did not influence our prior recommendation to deny breakthrough therapy designation.

11. Division's recommendation and rationale (pre-MPC review):
☐ GRANT :

Provide brief summary of rationale for granting:

☒ DENY:

Provide brief summary of rationale for denial:

The sponsor has submitted preliminary clinical evidence that does not provide evidence of a substantial improvement over existing therapy for treatment of PMO. The division does not consider the incremental improvement in fracture risk reduction sufficient to merit breakthrough therapy designation. As with Forteo, abaloparatide has the same preclinical malignancy and soft tissue mineralization concerns. There appears to be a marginally improved risk of hypercalcemia with abaloparide compared to Forteo, but the clinical relevance of this finding is unclear and no other approved osteoporosis therapies carry this risk.

12. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

The Division does not foresee any further potential abaloparatide data that might qualify abaloparatide for Breakthrough Therapy Designation.

13. List references, if any:

Appendix: Briefing Document for initial BDTR submitted May 9, 2014:

Briefing Document
Breakthrough Therapy Designation
Division of Bone, Reproductive, and Urologic Products
June 24, 2014

Summary Box

1. **IND Number** 73176
2. **Company name** Radius Health, Inc.
3. **Drug name** Abaloparatide
4. **Indication** Treatment of postmenopausal osteoporosis in patients at high risk of fracture
5. **Is the drug intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition?** Yes, osteoporotic fractures, most notably hip fractures, are associated with significant morbidity and mortality.
6. **Does the preliminary clinical evidence indicate that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints?** No. it cannot be assumed that the rate and degree of BMD increases achieved with abaloparatide will convey better fracture protection. In addition, the sponsor's potential safety benefit claim of less hypercalcemia has unclear clinical relevance when we take into account our experience with the Forteo clinical program and Forteo's postmarketing use. In addition, there is no evidence that abaloparatide offers other safety advantages over Forteo.

Division: Division of Bone Reproductive and Urologic Products
Medical officer: John T. Stinson, M.D.
Clinical Team Leader: Theresa Kehoe, M.D.

1. Introduction

On May 9, 2014 Radius Health, Inc. submitted a request for Breakthrough Therapy Designation for abaloparatide for the treatment of postmenopausal women with osteoporosis at high risk of fracture under IND 073176. The Sponsor believes that the Phase 2 trial data demonstrate substantial improvement in efficacy and safety of abaloparatide compared to current therapy.

2. Description of the drug

BA058 is an analogue of parathyroid hormone-related peptide (PTHrP). PTHrP is secreted endogenously by osteoblasts and, like PTH, contributes to calcium homeostasis. While PTH and PTHrP share some amino acid sequence homology and bind to the same receptor, PTHrP differs from PTH in biologic function as a paracrine regulator in several tissues including bone and kidney. PTHrP and PTH bind to the PTHR1 receptor. However, the receptor interaction with PTHrP elicits a distinct conformation and response compared to the receptor interaction with PTH, with differential effects on bone. The sponsor is developing abaloparatide as a 34 amino acid analogue of human parathyroid hormone- related peptide (PTHrP), with molecular modifications of specific amino acids.

Currently, the sponsor is developing 2 formulations of BA058 – a subcutaneous injection, the subject of this breakthrough request, and a transdermal patch which is in early stages of development.

The sponsor claims 5 clinically important benefits of abaloparatide 80 mcg/day relative to teriparatide, which is another PTH product that is already FDA-approved for the treatment of postmenopausal osteoporosis (PMO):

A. Faster increases in Hip and spine BMD
B. Greater increases in hip and spine BMD
C. Healthier bone (less cortical porosity seen in pre-clinical studies)
D. More responders to abaloparatide than to teriparatide

E. Enhanced safety (re: hypercalcemia)

3. Description of the disease and available therapies

Postmenopausal osteoporosis (PMO) is a systemic skeletal disease characterized by low bone mass and degradation of bone microarchitecture, which lead to increased fragility and risk of fracture. Sequelae of osteoporotic fractures are frequently characterized by significant morbidity and mortality with a significant impact on public health. The most commonly applied therapeutic approach to treatment of osteoporosis is to decrease bone loss with antiresorptive agents. Bisphosphonates, estrogens, selective estrogen receptor modulators, and denosumab all reduce bone loss by interfering at some level with osteoclastic bone resorption. The other approach is through promoting bone anabolism. When administered intermittently at low doses, human parathyroid hormone (PTH) has a well-documented anabolic effect on bone, increasing bone mass. The 34 amino acid terminal fragment of PTH has the full bone anabolic activity of native PTH (1-84). Teriparatide (Forteo®) is a recombinant human PTH (1-34) that was approved as a new therapy for osteoporosis in 2002. Forteo was approved with a Post Marketing Requirement to conduct surveillance for osteosarcoma. Osteosarcoma was evident in rat studies but not in primates, and to date no conclusions may be drawn from the limited data accumulated through ongoing pharmacovigilance studies. Abaloparatide also causes osteosarcoma in rats (see Section E below).

4. Drugs being studied for the same indication and breakthrough therapy status

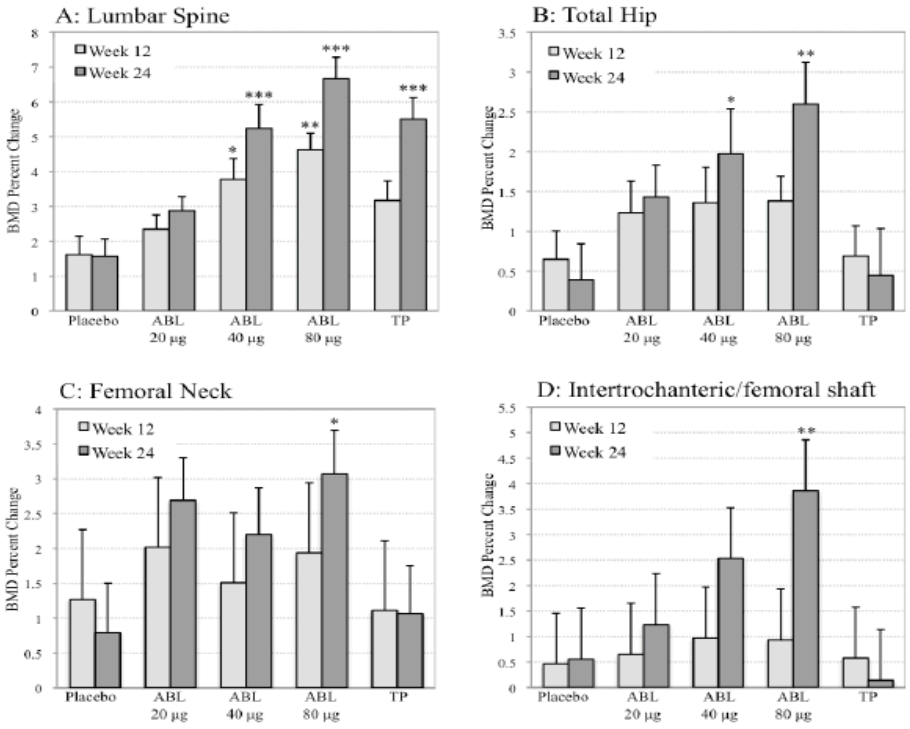
(b) (4)

5. Preliminary clinical evidence

As of December 8, 2013, 1390 subjects had been treated with at least one dose of abaloparatide, 1146 receiving subcutaneous (b) (4) in six Phase 1 and two Phase 2 studies. The sponsor references preliminary clinical data from Phase 2 trial BA058-05-02 in support of breakthrough designation. This was a multicenter randomized double-blind placebo-controlled trial of 24 weeks in 183 women with PMO who completed the study (ITT n=221). Subjects were randomized to abaloparatide 20, 40, and 80 mcg, placebo, or teriparatide 20 mcg. Endpoints included BMD of the lumbar spine, total hip and femoral neck by DXA and bone turnover markers. Forty eight subjects completed a 24 week extension study for a total duration of 48 weeks.

Results of the BMD analysis are outlined in Figure 1 below. The data indicate an earlier and more robust response to abaloparatide than teriparatide. Similar findings were seen beyond 24 weeks although these longer-term data are limited (e.g., only 20% of the ITT population completed 48 weeks of treatment). The intertrochanteric/femoral shaft region, with proportionally less cancellous bone and therefore less sensitivity to osteoporosis treatment, is not generally accepted as an anatomic site revealing of meaningful BMD data.

Figure 1: Mean (SEM)BMD percent change from baseline at Weeks 12 and 24 in A) lumbar spine, B) total hip, C) femoral neck, D) intertrochanteric/femoral shaft (ITT population, N=221)



The Phase 3 trial, BA058-05-03 is currently enrolling with approximately 2070 subjects enrolled and randomized to receive 80 mcg BA058, placebo, or active control teriparatide 20 mcg. The primary endpoint is the incidence of new vertebral fractures. In comparing fracture rates in subjects treated with abaloparatide, teriparatide and placebo, the sponsor's Phase 3 trial for abaloparatide appears to be designed and powered to demonstrate fracture efficacy.

6. Discussion

The sponsor presents five points for a claimed advantage of abaloparatide over teriparatide supporting breakthrough designation.

A, B. BMD response: The sponsor's principal position supporting Breakthrough Designation for abaloparatide is based on superior BMD response at the hip and lumbar spine compared to teriparatide in Phase 2 dose-finding study BA058-05-02. The sponsor presents BMD efficacy data that, while promising, do not merit breakthrough designation. That the relative increase in rate and degree of hip and femur BMD response in abaloparatide-treated subjects will convey better fracture protection cannot be assumed. In Forteo clinical fracture trial B3D-MC-GHAC (GHAC), greater BMD response was found at critical sites with the 40 mcg dose compared to the 20 mcg dose. At 18 months of therapy, the mean lumbar spine BMD increase was 9.7% for the 20 mcg dose and 13.7% for the 40 mcg dose. Total hip BMD increases were 2.6% for the 20 mcg dose and 3.6% for the 40 mcg dose. However, the higher dose was associated with no greater fracture efficacy (relative risk 0.35 for the 20 mcg dose versus 0.31 for the 40 mcg dose) and more adverse events, leading to marketing approval of only the 20 mcg dose of Forteo. Other agents investigated for treatment of PMO have also raised BMD without lowering fracture risk.

We recognize the robust BMD increases achieved with anabolic agents. In addition to PTH analogues, other anabolic agents are in development. (b) (4)

C. Better bone health: The sponsor claims improved bone health with abaloparatide based on the finding of no increased cortical porosity in preclinical studies. Cortical porosity remains an investigational parameter with no proven association with fracture risk. We also note that cortical porosity assessment by micro CT was not performed in the sponsor's Phase 2

studies and is not included in the Phase 3 protocols. Therefore, the claim of improved bone health based on cortical porosity cannot be adequately substantiated.

D. **More responders with abaloparatide**: In Phase 2 Trial BA058-05-02, the sponsor performed a *post hoc* assessment of the 24 week responder rate in the abaloparatide 80 mcg dose group, and the teriparatide and placebo groups. The sponsor categorized responders by BMD increases of > 0% or > 3%. Almost all patients in the abaloparatide (94%) and teriparatide groups (93%) had BMD increases of > 0% in lumbar spine. However, total hip BMD increased > 0% in 80% of subjects in the abaloparatide group and 53% of those in the teriparatide group (p=0.014). Femoral neck BMD increases > 0% were seen in 86% of abaloparatide subjects and in 58% of the teriparatide group. For subjects experiencing an increase in total hip BMD > 3%, 37% were in the abaloparatide group, while 16% and 15% were in the teriparatide and placebo groups respectively.

While the reported responder analysis in hip BMD response appears favorable for abaloparatide, it again remains to be seen that this response implies greater fracture protection than teriparatide.

E. Enhanced safety (hypercalcemia) In the Phase 2 dose-finding Trial BA058-05-02, all subjects received 400 IU vitamin D and 500 mg calcium daily. Serum calcium levels were measured pre- and post-dose (4 hours) at multiple times and were higher throughout the study in the teriparatide group. The percentage of patients with post-dose calcium levels of ≥ 10.2 mg/mL were 17% and 48% in the abaloparatide 80 mcg and teriparatide groups respectively. Clinically significant elevations of serum calcium levels (≥ 10.5 mg/mL) were seen in 18% of abaloparatide-treated patients and in 40% of those treated with teriparatide. Further details on the degree of calcium elevation are not available. Urinary increases in calcium are frequently concomitant with serum calcium increases. In Trial BA058-05-02, hypercalciuria was reported in 9% of subjects in the 80 mcg abaloparatide group and 11% of subjects in the teriparatide group.

The preliminary data indicate less risk of hypercalcemia with abaloparatide. In the Forteo GHAC fracture trial, subjects received 1000 mg calcium and 400 – 1200 IU vitamin D daily. The frequency of at least one episode of 4 – 6 hour post-dose hypercalcemia (> 10.6 mg/dL) was 2% in the placebo group and 11% in the 20 mcg teriparatide group. Episodes of hypercalcemia greater than 13.0 mg/mL have been reported during post approval use of Forteo. No deaths or serious adverse events were reported related to hypercalcemia in Forteo clinical trials, and no hypercalcemia deaths have been reported post approval.

Other safety concerns not discussed by the sponsor include clinical adverse reactions such as orthostatic hypotension. In the Forteo development program, vasodilation was noted in the nonclinical program and syncope was noted in early clinical trials. Clinical evaluation for orthostatic hypotension occurred in the subsequent fracture trial. Increases in standing heart rate without significant change in blood pressure were noted with 40 mcg teriparatide compared to placebo. In the abaloparatide program, similar vasodilation effects were noted in the nonclinical program. Clinical data on heart rate and blood pressure response to abaloparatide are not presented in this briefing package. However, in the adverse events data presented for trial BA058-05-002, an imbalance in dizziness is noted in the abaloparatide 80 mcg group (11%, vs. 4% in placebo, and 4% in teriparatide).

In addition, safety concerns arising from the nonclinical program have not been discussed by the sponsor. In the Forteo program, development of osteosarcoma with teriparatide use was noted in the rat studies. The findings seen in the Forteo program were reprised in the abaloparatide program. At similar exposure multiples to human therapeutic dosage of PTH (1-34), fatal osteosarcomas were first observed in abaloparatide-treated male rats on Day 310 and in female rats at Day 398. Osteosarcoma presented earlier in the abaloparatide studies. The tumors first appeared in Forteo-treated male rats on Day 343 and in female rats on Day 512. The earlier presentation may be because the dose of BA058 utilized (50 mcg/kg most likely) was pharmacologically more active than the 30 mcg/kg teriparatide dose used in the prior Forteo program thereby stimulating osteogenesis and causing osteoblastic tumor formation.

The sponsor's potential safety benefit claim of less hypercalcemia has unclear clinical relevance when we take into account our experience with the Forteo clinical program and Forteo's postmarketing use. In addition, there is no evidence that abaloparatide offers other safety advantages over Forteo.

7. Division's Recommendation
The Division recommends denial of the sponsor's request for breakthrough designation.

Recommendation to Sponsor
The development of abaloparatide for the treatment of PMO has provided data that, however encouraging, do not merit breakthrough designation.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

5-7-15/M. Raggio

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/

JOHN T STINSON
07/13/2015

THERESA E KEHOE
07/13/2015

HYLTON V JOFFE
07/13/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 073176

MEETING MINUTES

Radius Health, Inc.
Attention: Anne Marra
Executive Director, Regulatory Affairs and Project Management
950 Winter Street
Waltham, MA 02451

Dear Ms. Marra:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for abaloparatide (BA058).

We also refer to the meeting between representatives of your firm and the FDA on June 3, 2015. The purpose of the meeting was to discuss the Agency's responses to your CMC questions.

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

If you have any questions, call Thao Vu, Regulatory Business Process Manager at (240) 402-2690.

Sincerely,

{See appended electronic signature page}

Mark R. Seggel, Ph.D.
Acting CMC Lead
Branch V
Division of New Drug Products II/ONDP
Office of Pharmaceutical Quality
CDER/FDA

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA, CMC
Meeting Date and Time:	June 3, 2015, 2:00PM ET
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	IND 073176
Product Name:	abaloparatide (BA058)
Indication:	Treatment of post-menopausal osteoporosis
Sponsor/Applicant Name:	Radius Health, Inc.
Meeting Chair:	Mark Seggel, Ph.D.
Meeting Recorder:	Kerri-Ann Jennings, M.S., B.S.N., RN, LCDR

FDA ATTENDEES

Mark Seggel, Ph.D., Acting CMC Lead, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Xavier Ysern, Ph.D., Reviewer, Division of New Drug API, ONDP, OPQ
Donna Christner, Ph.D., Acting Chief, Branch II, Division of New Drug API, ONDP, OPQ
Danielle Harris, Pharm.D., BCPS, Team Leader, DMEPA
Deborah Myers, R.Ph, M.B.A., Safety Evaluator, DMEPA
Bindi Nikhar, M.D., Associate Clinical Director, Office of Combination Products
Theresa Kehoe, M.D., Medical Team Leader, Division of Bone, Reproductive, and Urologic Products (DBRUP), Office of New Drugs (OND)
John Stinson, M.D., Medical Officer, DBRUP, OND
Lynnda Reid, Ph.D., Pharmacology Toxicology Supervisor, DBRUP, OND
Gemma Kuijpers, Ph.D., Pharmacology and Toxicology Reviewer, DBRUP, OND
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff, DBRUP, OND
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager, DBRUP, OND
Mary Brooks, R.N., B.S.N., M.S., Senior Regulatory Review Officer/Nurse Consultant, CDRH
Kerri-Ann Jennings M.S., B.S.N., RN, LCDR, Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO), OPQ
Heather Strandberg, Pharm.D., Organizational Excellence, OPRO, OPQ

SPONSOR ATTENDEES

David Hanley, Ph.D.	RADIUS Health	Executive Director, Technical Operations
Gary Hattersley, Ph.D.	RADIUS Health	Chief Scientific Officer
Gregory C. Williams, Ph.D.	RADIUS Health	Chief Development Officer
(b) (4)		Regulatory Advisor
Michael Macalush	RADIUS Health	Director, Regulatory Affairs

BACKGROUND

Abaloparatide (BA058) is being developed for the treatment of post-menopausal osteoporosis. Radius Health, Inc. submitted a Type B meeting request to the Agency on March 5, 2015, to discuss the Agency's response to their CMC questions.

FDA sent Preliminary Comments to Radius Health, Inc. on June 2, 2015.

SPONSOR'S QUESTIONS AND AGENCY RESPONSES
(Sponsor's questions in italic text)

***Question 1**: Does the Agency agree that the Sponsor's proposed test methods and specifications for drug substance release and stability are acceptable for the abaloparatide-SC NDA submission?*

FDA Response to Question 1:

No. While the proposed drug substance specification captures most critical tests and attributes, we have the following recommendations:

- Add a test for biological activity, or provide a justification, based on characterization studies, for excluding such a test and,
- Establish acceptance criteria for each identified individual impurity.

The suitability of the acceptance criterion for each test will be determined during review of the entire NDA package.

Please note that there should be only a single drug substance (or drug product) regulatory specification that covers both release and stability. Internal acceptance criteria for tests at release can be included in the regulatory specification but should be identified as such.

Discussion:

- Radius Health, Inc. stated that they have a bioassay (test and acceptance criterion) for the drug substance and that the bioassay can be used also for the testing of the biological activity of the (b) (4) degradant. This bioassay might not be used for the drug product due to incompatibility with some components of the drug product.
- The Sponsor agreed, as part of the drug substance characterization studies, to carry out studies (b) (4)

- FDA agreed that testing for biological activity can be carried out only for the drug substance provided it is adequately justified,
- If the Sponsor considers that bioassay testing will not be part of the of release or stability specifications, it will provide a justification for its absence.
-

Question 2**:** *Does the Agency agree that the Sponsor's proposed test methods and specifications for drug product release are acceptable for the abaloparatide-SC NDA submission?*

FDA Response to Question 2:

See response to Question 1.

Discussion:

- See discussion under Question 1.

Question 3**:** *In aged samples of abaloparatide-SC finished product, the degradant* (b) (4) *has recently been identified, with a new, improved test method. Does the Agency agree with the Sponsor's proposed approach to qualify this degradation product and determine an acceptable specification level for the abaloparatide-SC NDA submission?*

FDA Response to Question 3:

No. The strategy for qualifying the (b) (4) degradant, as described on pages 18 – 25 of the Briefing Package, should include comparative data on the biological activity of the (b) (4) degradant" and its parent compound.

An acceptance criterion greater than or equal to (b) (4)% for the (b) (4) degradation product should be justified based on adequate qualification data. Qualification data may be derived from completed nonclinical and clinical studies. If nonclinical toxicity studies were conducted with test compound containing degradant at levels exceeding the acceptance criterion by adequate multiples, the data from these studies may serve to qualify the degradant. Similarly, if clinical studies were conducted with product containing degradant at levels greater than or equal to the proposed acceptance criterion of (b) (4)%, these studies may provide clinical qualification data.

Discussion:

- Radius Health understands the need to evaluate the biological activity of the [redacted] (b) (4) degradant and agreed to perform a series of ligand binding and enzyme assays.
- FDA asked Radius Health to justify the duration of the proposed 14-day rat toxicity study. FDA accepted the justification that degradant effects are likely to be identified within a 14-day time frame.
- Radius stated that relevant assessments of serum calcium and pharmacokinetics will be included in the 14-day study.
- Radius Health stated that in completed trials, patients have likely received some [redacted] (b) (4) degradant as part of the drug product formulation, although the amounts are unknown. Radius also stated that information on the amount of degradant in the completed animal studies is not available. Radius noted that product used in the nonclinical studies was formulated daily.
- It is unknown if formation of the degradant in the product would change its carcinogenic potential.
- It was agreed that the sufficiency of the planned nonclinical safety assessments will depend on the results obtained.

Question 4**:** *Except for the specifications for* [redacted] (b) (4) *discussed in question 3, does the Agency agree that the Sponsor's proposed test methods and specifications for drug product stability are acceptable for the abaloparatide-SC NDA submission?*

FDA Response to Question 4:

See response to Question 1.

We remind the Applicant that the drug product specification should be met during the proposed shelf-life of the drug product. The shelf-life includes storage time and in-use time (shelf-life of drug product = storage time (5°C) + in-use time (~ 30 days, 25°C)). It is unclear if, during the 30-day proposed in-use time, the drug product will always be at 25°, or if the drug product will be allowed to reach room temperature before injection and then be stored at 5°C after injection (excursions to room temperature).

Discussion*:*

- The sponsor accepted FDA's response, no discussion occurred.

Question 5**:** *The Sponsor proposes to submit the abaloparatide-SC NDA with validation batch release data, 6 month stability data for 3 registration stability batches, as well as supportive* [redacted] (b) (4) *month stability data from batches of the same formulation as the current, which were used in Phase 3 studies. The Sponsor additionally proposes to submit ongoing stability data during the abaloparatide-SC NDA review cycle. Does the Agency agree that this approach is acceptable?*

FDA Response to Question 5:

No. Primary stability data for at least 12 months at the proposed storage condition and 6 months at accelerated condition for 3 primary batches should be provided at the time of NDA submission. Additional stability data received within 30 calendar days after receipt of the original submission will be acceptable for review purposes. The expiration dating period will be evaluated based on the provided stability data (shelf-life of drug product = storage time (5°C) + in-use time (~ 30 days, 25°C or 5°C with brief excursion to room temperature)).

Discussion:

- Radius Health understands, but asked if providing additional information 45 days post submission would be acceptable.
- FDA stated that any updates should be submitted within 30 days.

Post-Meeting Comment: While we continue to advise that your application be complete upon submission, we would not refuse to file if you submit the 12 month stability data according to your proposal. This later submission might constitute a major amendment and may therefore extend the review clock by an additional 3 months if we deem that it cannot be reviewed in the original timeframe.

Question 6: *Does the Agency agree that the Sponsor's proposed approach to qualifying the intended commercial delivery device (UnoPen) is acceptable for the abaloparatide-SC NDA submission?*

FDA Response to Question 6:

As discussed at the May 28, 2015, Clinical PreNDA meeting, we acknowledge the recent submission of information regarding the device used in the Phase 3 fracture trial and the to-be-marketed device/combination product. We will have further comments on the adequacy of the performance characteristics of your proposed device once review of this information is complete.

We also acknowledge submission of your use-risk analysis and human factors study protocol. We will review the materials and provide comments. We recommend that you do not conduct your human factors study until we have completed our review of the proposed protocol.

Discussion:

- Radius provided a proposal (b) (4) If equivalence is not demonstrated, Radius will conduct a bioequivalence study (refer to Radius Health Inc.'s June 3 slides, # 9).
- FDA stated that their approach appears reasonable but the proposal would require further internal discussion. FDA will send a separate correspondence addressing the proposal.
- FDA suggested that preliminary *in vitro* data obtained under standardized conditions, if available, be submitted to the IND.
- FDA asked Radius Health to provide manufacturing data for the needles as part of the total injector device system.

Additional Microbiology Product Quality Comments:

Pharmaceutical development information in the NDA submission must include [redacted]

Sterilization validation information in the NDA submission must include (and is not limited to) the following:

- Product-specific [redacted] studies for the [redacted] used in the [redacted] manufacturing process.
- Complete validation [redacted] of the containers, closures, filling equipment and components that come in product contact (results from at least one run must be recent).
- Media fill simulations that include simulation of holding times (results from at least one run must be recent).
- Environmental monitoring program (alert/action levels, methods and test frequency).
- Container-closure integrity studies for the container-closure system.
- Method suitability studies for the sterility and bacterial endotoxins tests for the finished product.

ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion

ATTACHMENTS AND HANDOUTS
Radius Health, Inc.'s Slides

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/s/

THAO M VU
06/29/2015

MARK R SEGGEL
06/29/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 073176

MEETING MINUTES

Radius Health, Inc.
Attention: Anne Marra
Executive Director, Regulatory Affairs and Project Management
950 Winter St.
Waltham, MA 02451

Dear Ms. Marra:

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

We also refer to the meeting between representatives of your firm and the FDA on May 28, 2015. The purpose of the meeting was to discuss proposals for the content, analyses, and format of nonclinical and clinical data for NDA submission.

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

If you have any questions, call Samantha Bell, Regulatory Project Manager at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Clinical Team Leader
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	May 28, 2015, 2:00 P.M. to 3:00 P.M.
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	IND 073176
Product Name:	Abaloparatide
Indication:	Treatment of women with postmenopausal osteoporosis
Sponsor/Applicant Name:	Radius Health, Inc.
Meeting Chair:	Theresa Kehoe, M.D.
Meeting Recorder:	Samantha Bell

FDA ATTENDEES

Division of Bone, Reproductive, and Urologic Products (DBRUP):
Hylton V. Joffe, M.D., M.M.Sc., Director
Theresa Kehoe, M.D., Medical Team Leader
John Stinson, M.D., Medical Officer
Gemma Kuijpers, Ph.D., Pharmacology and Toxicology Reviewer
Frederic Moulin, Ph.D., Pharmacology and Toxicology Reviewer
Lynnda Reid, Ph.D., Pharmacology and Toxicology Supervisor
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager

Office of New Drugs, Office of Drug Evaluation III:
Julie Beitz, M.D., Director
Amy Egan, M.D., M.P.H., Deputy Director

Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP):
Lin Zhou, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology (DCP) III
Yow-Ming Wang, Ph.D., Clinical Pharmacology Team Leader, DCP III

OTS, Office of Biostatistics, Division of Biometrics III:
Jia Guo, Ph.D., Biometrics Reviewer

Mahboob Sobhan, Ph.D., Team Leader

Office of Pharmaceutical Quality, Office of New Drug Products:
Mark Seggel, Ph.D., CMC Lead

Office of Surveillance and Epidemiology (OSE), Immediate Office:
Shawnetta Jackson, Project Manager

OSE, Office of Medication Error Prevention and Risk Management:
CAPT Walter Fava, R.Ph., M.S.Ed., Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Deborah Myers, R.Ph., Safety Evaluator, DMEPA
Danielle Harris, Pharm.D., BCPS, Team Leader, DMEPA

OSE, Office of Pharmacovigilance and Epidemiology:
Jie (Jenni) Li, Ph.D., MBBS, Team Leader, Division of Epidemiology
Wei Liu, Ph.D., MSc, Visiting Scientist, Division of Epidemiology

Office of Combination Products:
Bindi Nikhar, M.D., Associate Clinical Director

Office of Business Informatics:
Lisa Lin, MBA, Senior Regulatory Analyst, Office of Business Informatics

Center for Devices and Radiological Health (CDRH):
CDR Mary Brooks, RN, BSN, MS, Senior Regulatory Review Officer/Nurse Consultant, Office of Device Evaluation, General Hospital, Respiratory, Infection Control, and Dental Devices (DAGRID), General Hospital Devices Branch

EASTERN RESEARCH GROUP ATTENDEES
Marc Goldstein, Independent Assessor

SPONSOR ATTENDEES
Bob Ward, CEO
David Hanley, Ph.D., Executive Director, Technical Operations
Gary Hattersley, Ph.D., Chief Scientific Officer
Gregory C. Williams, Ph.D., Chief Development Officer
(b) (4) Regulatory Advisor
Michael Macalush, Director, Regulatory Affairs
Thomas Zimmerman, M.D., VP, Medical
Tristan Hu, Ph.D., Executive Director, Biometrics

1.0 BACKGROUND

Abaloparatide (BA058) is an analogue of parathyroid hormone-related peptide (PTHrP). PTHrP is secreted endogenously by osteoblasts and, like parathyroid hormone, contributes to calcium homeostasis. Radius is developing abaloparatide for the treatment of postmenopausal women with osteoporosis. The sponsor has completed several Phase 1 studies, two Phase 2 studies (BA058-05-002, BA058-05-007), and an 18-month Phase 3 trial (BA058-05-003) with a 24-month extension (BA058-05-005). Radius would like to discuss the nonclinical and clinical development of abaloparatide to support the forthcoming NDA to be submitted in late 2015 for the treatment of osteoporosis in postmenopausal women.

FDA sent Preliminary Comments to Radius Health on May 21, 2015.

2. DISCUSSION

2.1. Nonclinical

Question 1: *Does the Agency agree that the completed non-clinical studies are adequate to support the submission, filing and review of the abaloparatide–SC NDA for the treatment of osteoporosis in postmenopausal women?*

FDA Response to Question 1:
The nonclinical studies conducted with abaloparatide appear to be adequate for NDA submission. We remind you that qualification of impurities in drug substance and drug product may be needed for the NDA.

Discussion at the Meeting:
There was no further discussion at the meeting.

2.2. Clinical

Question 2: *Does the Agency agree that the planned abaloparatide safety and efficacy databases are adequate to support the submission, filing and review of the abaloparatide-SC NDA for the treatment of osteoporosis in postmenopausal women?*

FDA Response to Question 2:
As proposed, the planned abaloparatide safety and efficacy databases appear adequate to support an NDA submission for abaloparatide. You state that the efficacy evaluation will be primarily based on the Phase 3 Study 003 data with efficacy assessments of abaloparatide versus placebo and teriparatide at 18 months, and the first 6-month data from its extension Study 005.

Confirm that all subjects enrolled in Study 005 will have completed the 6 month primary endpoint and will be included in the analyses.

All datasets in Studies BA058-05-003 and BA058-05-005 should contain the subject identification number for both studies (i.e., for each subject enrolled in Study 003, the Study 003 subject identification number should be included in the Study 005 datasets and for each subject enrolled in Study 005, the Study 005 subject identification number should be included in the Study 003 datasets.

Datasets for the Integrated Summary of Safety (ISS) and all individual clinical studies should be provided in a single version of MedDRA, preferably the most recent version.

In the NDA, provide a listing of all major and minor protocol violations and deviations.

In the NDA, provide a listing of all study discontinuations and temporary treatment suspensions in your Phase 2 and 3 studies.

Discussion at the Meeting:
Radius confirmed that all subjects enrolled in Study 005 will have completed the 6 month evaluation and will be included in the analyses.

Question 3: *Does the Agency agree that the completed and ongoing human PK, PD, Thorough QT/QTc and special population studies are adequate to support submission, filing and review of the abaloparatide–SC NDA for the treatment of osteoporosis in postmenopausal women?*

FDA Response to Question 3:
The Agency agrees that the completed and ongoing human pharmacokinetic (PK), pharmacodynamic (PD), Thorough QT/QTc and renal function studies are adequate to support submission, filing and review of the abaloparatide NDA. However, as recommended at the Type A Guidance Meeting of March 21, 2012, we request analysis of data from your Phase 3 studies to evaluate if the efficacy data differ by hepatic function status.

We request that you analyze immunogenicity data collected during the clinical development of your product to evaluate the incidence of anti-drug antibody formation and the impact of immunogenicity on PK/PD, clinical efficacy and safety.

Additional comments:
The Office of Clinical Pharmacology requests that in addition to the standard electronic Common Technical Document (eCTD submission), you provide a review aid by generating a stand-alone document summary based on questions listed in the appended "Question-based

Clinical Pharmacology Summary for NDA or BLA submission". The answers to these questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. Your answers to the questions should be annotated with links to the detailed information in the study reports and to the raw data located in SAS transport files.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 4: *Does the Agency agree with the proposed analyses for the recently completed Phase 3 study in osteoporosis (BA058-05-003) and the ongoing extension study (BA058-05-005), including the comparators and primary and secondary endpoints as defined in the amended SAP for BA058-05-003 (incorporating the review division's comments on the draft SAP) and draft SAP for BA058-05-005?*

FDA Response to Question 4:
The Agency agrees with the proposed analysis of the primary and secondary endpoints of both studies as defined in the amended Statistical Analysis Plan (SAP) for Study 003 and the draft SAP for Study 005. We remind you that data documenting the comparative incidence of new morphometric vertebral fractures by 24 months are essential for submission and review. The Agency agrees with performing analysis of the primary endpoint in the modified Intent to Treat (mITT) population, unless the number of subjects in the mITT population differs significantly from that of the Intent to Treat (ITT) population, which would be a review issue.

Discussion at the Meeting:
Regarding the "data documenting the comparative incidence of new morphometric vertebral fractures by 24 months," Radius proposed to submit the datasets from their spine X-ray provider (b) (4), as well as the Charter for Independent Imaging Assessment and the X-ray Data Transfer Specification as appendices to the Case Study Reports (CSRs) of Studies 003 and 005 in the NDA. The Agency reiterated the need for 24 month data and the expectation that both tabulation and analysis datasets will be included in the NDA. The Agency asked Radius to confirm that an interim study report to discuss the 6 month efficacy and safety data would be included in the NDA. Radius confirmed that complete datasets and an interim study report would be submitted with the NDA.

Question 5: *The abaloparatide-SC NDA will include a single large, global, multicenter, comparative pivotal trial (n=2460 treated patients) of the dose studied in the Phase 3 trial and for which approval will be sought (i.e., 80 mcg daily subcutaneous injection), with patient safety and fracture outcomes linked to patient treatment durations of 18 and 24 months. By comparison, the other clinical trials conducted in this development program*

varied significantly in study design, study population (i.e., healthy volunteers vs patients), treatment dose/duration, dosage form (SC and TD), and study endpoints. To avoid diluting and/or obscuring the safety and efficacy data associated with the proposed dose (i.e., 80 mcg) and treatment duration (i.e., 18 months) in the pivotal trial, the Sponsor proposes to submit individual summaries of all clinical trials completed at the time of submission without pooled safety or efficacy analyses. Does the Agency concur with this approach?

FDA Response to Question 5:

We agree that individual clinical trial reports should be included for all clinical trials completed at the time of submission.

The Integrated Summary of Effectiveness (ISE) should include summaries from studies BA058-05-003 and BA058-05-005 as well as any supporting studies that inform the dose chosen for the Phase 3 trial.

The Integrated Summary of Safety (ISS) should focus on the pooled safety data from all Phase 2 and 3 abaloparatide studies. However, an analysis of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs, should also be included.

We request submission of case report forms and a detailed discussion of all subjects who died, experienced serious adverse events, or dropped out of a study because of an adverse event.

We agree that data from studies of the (b) (4) are not required with an NDA submission for the subcutaneous formulation of abaloparatide.

Discussion at the Meeting:

(b) (4)

(b) (4)

Radius clarified that summaries of all efficacy information on abaloparatide 80 µg will be included in the eCTD Section 2.7.3 (Summary of Clinical Efficacy [SCE]) and that they do not plan to provide an ISE in the eCTD Module 5.3.5.3. Radius explained that the ISE will include summaries of efficacy from Phase 3 Studies BA058-05-003 and BA058-05-005 as well as a justification of the dose selection supported by data from Phase 2 Study BA058-05-002. The SCE will essentially be based on the individual study results from the 3 studies, where the 005 study results contain the analyses based on the pooled data from Study 003 and Study 005. For the proposed submission, the ISE, if provided, would essentially contain the same information as the SCE and therefore would not be included.

The Agency referred to the "*Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document"*, which explains that there is a difference between the summary and overview documents contained in Module 2 and the ISE/ISS. The ISE and ISS are not summaries, but rather detailed integrated analyses of all relevant data from the clinical study reports. Therefore, a detailed ISE is required.

Radius agreed to pool safety data from the Phase 2 and 3 abaloparatide studies in the ISS. Radius proposed that the pooled data will include information from all treatment groups from the Phase 3 Study 003, all treatment groups from the Phase 2 Study 002 and only the placebo and abaloparatide 80 µg groups from the Phase 2 Study 007. Radius explained that the ISS will be based on all safety data from Study 003, all safety data from Study 002 and safety data from only those patients who received placebo or abaloparatide 80 µg from Study 007. The Agency agreed and reminded the sponsor to include a unique identification number for every subject.

***Additional Comments*:**
FDA encourages sponsors to submit a Pharmacovigilance (PV) Plan developed to detect new safety risks and to further evaluate identified safety risks with abaloparatide following market approval. Information on PV Plans has been included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005) and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the PV plan is available, please include it in the NDA application in the appropriate module so that it can be reviewed accordingly.

Discussion at the Meeting:
Radius acknowledged the Agency's comments.

2.3. Biometrics

Question 6: *The Sponsor proposes to submit a mixture of legacy and standardized datasets in the NDA. The datasets for legacy Phase 1 and 2 studies (most completed prior to 2010) and the Phase 3 studies (initiated in 2010) did not follow the CDASH standard and will conform to the standards defined in the Study Data Specification (SDS) v 2.0. The datasets for the three recently conducted (2014) Phase 1 studies will conform to CDSIC standards, specifically SDTM for case report form tabulation data and ADaM for analysis data. The Sponsor also proposes to provide SDTM domain datasets as well as the ADaM ADSL analysis datasets for the pivotal 003 and 005 studies to assist the Agency's review of the efficacy and safety data. Does the Agency agree that this approach is acceptable?*

FDA Response to Question 6:
Yes, your approach is acceptable. Please refer to the *Study Data Standards Resources* website for guidance and detailed information regarding to standardized study data submission.

Discussion at the Meeting:
In responding to the pooled safety analyses using all Radius Phase 2 and 3 abaloparatide studies, the sponsor proposed to submit the pooled safety analysis datasets that will conform to the standards defined in the Study Data Specifications (SDS) v 2.0. Radius explained the legacy Phase 2 studies and the Phase 3 studies were not captured in CDISC data structures. The resulting pooled analysis datasets will follow the standards defined in the Study Data Specifications (SDS) v 2.0 for legacy data, and the structure of these pooled analysis datasets will follow the same structure that was used for Study 003 analysis data provided in support of safety analyses.

Radius proposed:

1. Pooled analysis datasets conforming to the standards defined in the Study Data Specifications (SDS) v 2.0;
2. Data definition file in define.pdf format.
3. The following coding dictionaries:
    - MedDRA v 17.1;
    - WHODrug v September 1, 2014

This proposed submission will involve the up-coding of Adverse Events in Study 002 from MedDRA v 11.1 and in Study 007 from MedDRA v 15.1 to the version stated above. It will also involve the up-coding of concomitant medications in Study 002 from WHODrug v September 1, 2008 and in Study 007 from WHODrug v December 1, 2011 to the version stated above. Details of the impact of these up-coding activities will be documented in the Notes to Reviewer file included with the data definition file accompanying these pooled ISS analysis datasets.

The Agency agreed with the proposal and asked Radius to place legacy data in the legacy folder, and sdtm datasets in the sdtm folder, and explain in the study data reviewer guide so that the reviewer can easily retrieve data for review.

Post-Meeting Comment:
Consider the following additional general guidance in preparing your submission. These topics are also covered in the latest guidance (Study Data Technical Conformance Guide (2.1) and related guidance - Study Data Standards Resources).

The Study Data Technical Conformance Guide (2.1) defines, clarifies, and supersedes certain content of the previous guidance containing information/specifications on standardized data. (Study Data Specifications documents (Versions 1.0 - 2.0) and CDER Study Data Common Issues Documents (Versions 1.0 -1.1)).

Where the Study Data Technical Conformance Guide does not explicitly re-define, restate, clarify, or otherwise alter the information provided in previous guidance, sponsors should adhere to the previous guidance. This primarily relates to "legacy" data information, as the Study Data Technical Conformance Guide focuses on "standardized" data.

The Study Data Technical Conformance Guide does include a section on Data Validation and Traceability, which describes the Agency's current thinking on validation of standardized study data and the traceability of study data within and across the components of the submission (8. Data Validation and Traceability). This section also includes a specific sub-section on the conversion of legacy study data to standardized study data (8.3.2 Legacy Study Data Conversion to Standardized Study Data). The Agency prefers standardized study data, but also recognizes the need to transition to standardized data submissions and to support various methodologies in the transition, to include support for the concurrent submission of legacy and standardized study data within the same submission.

While the Study Data Technical Conformance Guide is specifically written to implement the electronic submission requirements of section 745A(a) of the FD&C Act with respect to standardized study data contained in certain investigational new drug applications (INDs), new drug applications (NDAs); abbreviated new drug applications (ANDAs); and certain biologics license applications (BLAs) that are submitted to the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER), the Agency does expect sponsors to adhere to previous applicable guidance where the Study Data Technical Conformance Guide does not explicitly supersede, and/or provide specific information and/or specification related to study data submission. For example, the Study Data Technical Conformance Guide does not provide information and/or specification for legacy study data submission, except to the extent described in the paragraph above.

Additional Comments:
We have the following comments on sections of the application that are not included in your background package. These sections are necessary for review of your application and should be submitted and complete at the time of NDA submission:

Risk Management:

We have identified the serious risk of osteosarcoma associated with the use of abaloparatide. At a minimum, the Prescribing Information for abaloparatide will include a boxed warning and Medication Guide to address the risk of osteosarcoma. Your NDA submission must include a risk management plan with appropriate rationale for any proposed risk mitigation to address this risk in the post-marketing setting.

Discussion at the Meeting:
Radius acknowledged the Agency's comments.

Other Drug and Device Issues:

- The specific drug formulation and delivery system (device/pen injector) used for each study included in your development program is not clear. Submit a table that outlines the drug formulation and the specific device/pen injector (including cartridge size) used for each study in your development program. We recommend that you also provide this table prior to the Pre-NDA meeting.

- We acknowledge the recent submission of information regarding the device used in the phase 3 fracture trial and the to-be-marketed device/combination product. We will have further comments on the adequacy of the performance characteristics of your proposed device once review of this information is complete.

- We note that the to-be-marketed drug-device combination product is different than the drug-device combination product used in your Phase 3 fracture trial. It will be necessary to bridge between the phase 3 drug-device product and the to-be-marketed drug-device combination product. Conduct a PK comparability study with the combination product (drug delivered via BD pen injector) used in the Phase 3 study and the to-be-marketed combination product (drug delivered using the Unopen injector) to compare systemic exposure and demonstrate bioequivalence between the two using bioequivalence criteria.

- Site of injection: As stated in the Phase 3 protocol, "All injections are to be given in the periumbilical region, rotating the exact site of injection each day. If it is deemed medically necessary by the investigator for an injection to be administered at a site other than the abdomen, the alternate site of injection is to be recorded and the reason for the change documented in the medical chart." We request that you provide a summary of site of injections used by patients in the studies where the to-be-marketed formulation was tested. The summary will provide clinical experience on sites of injection to inform labeling.

  Discussion at the Meeting:
  Radius provided the requested table that outlines the drug formulation and the specific device/pen injector (including cartridge size) used for each study. Radius confirmed that "Formulation 2" referenced in the provided table is the to-be-marketed formulation.

Radius explained that the to-be-marketed abaloparatide SC Drug Product (DP) is presented as a (b) (4) mL multi-dose glass cartridge containing sterile (b) (4) solution, which is assembled into a pen-injector. The pen has no contact with the DP. For the intended commercial product, the closed cartridge is irreversibly integrated into the disposable pen injector for self-administration using the UnoPen, manufactured by Ypsomed. Although the pen was not developed to be a separately marketed device, Radius stated that it has been developed in accordance with the ISO standards for medical devices. The pen used in clinical studies was an experimental drug delivery system, manufactured by Becton-Dickson. Radius stated that the pen used in the clinical studies is equivalent to the currently marketed BD Pen II® that is approved in Europe under CE marking (b) (4) (b) (4) were modified for use with abaloparatide. While the intended commercial delivery device (abaloparatide UnoPen) has not been used in clinical studies, Radius stated that it delivers abaloparatide solution to the same subcutaneous site (periumbilical region) and its use is based on the same operating principles as the BD pen. Radius stated that the abaloparatide UnoPen has identical injection depth, identical needle dimensions, as well as comparable injection duration forces for operation and dose reproducibility as the BD pen used in clinical studies (data to be provided in the NDA). Based on this information, Radius believes that the bioequivalence (BE) of subcutaneously delivered abaloparatide solution from these injector pens is self-evident, (b) (4)

The Agency explained the need to provide an adequate bridge between the to-be-marketed combination product and the combination product used in the clinical fracture study. The Agency acknowledged the device-related data submitted recently, and stated that at this time, we cannot agree that (b) (4) as the review of information is ongoing. The Agency recommended the sponsor provide data regarding possible device-related dispersion forces, sheering of medication, and comparative performance data between the BD pen and the UnoPen. The Agency also explained why the submission of PK data prior to NDA submission is helpful as the design of pen devices often changes post-approval. The sponsor acknowledged the Agency's concerns, but stated that their concern is the time to provide data from a PK study. The Agency stated it was not acceptable to conduct and submit data from a PK study during review of the NDA. Radius will discuss a schedule for providing additional data needed to support an adequate bridge, and will prepare a proposal for discussion at the CMC Pre-NDA meeting scheduled for June 3, 2015.

Combination Product:
Your proposed abaloparatide drug product that is to be injected using the Abaloparatide Unopen is a drug-device combination product and as such is subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at: *https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products*.

Human Factors:

We acknowledge submission of your use-risk analysis and human factors study protocol. We will review the materials and provide comment. We recommend that you do not conduct your human factors study until we have completed our review of the proposed protocol.

Discussion at the Meeting:
The Agency stated the review of this submission is ongoing.

Other Meeting Discussion:
Radius confirmed that all subjects in Study 005 will have completed the 6 month visit. Radius confirmed the number of subjects for which histomorphometry data will be available is 105. Radius will provide an in depth discussion of calcification from renal CT scans in the study report.

The Agency is still reviewing the immunogenicity assessment plan provided in the amendment submission dated March 31, 2014.

Radius presented "potential for rolling NDA submission with possible compassionate use access during the review cycle". The Agency explained that the criteria for expanded access/compassionate use that must be met include "no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat that stage of disease or condition in the relevant patient population." Requests for rolling submission and review may be made for drugs that have been designated as either Fast Track or Breakthrough Therapy. The Agency acknowledged the sponsor's recent request for Breakthrough Therapy designation and recommended that any further discussion regarding rolling review occur following the Agency's decision on the Breakthrough Therapy request.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The sponsor acknowledged the preliminary comments regarding a complete application during the meeting. The Agency stated it was not acceptable to conduct a PK study, supporting an adequate bridge between the to-be-marketed combination product and the combination product used in the clinical fracture study, during review of the NDA.

  The Agency communicated to the sponsor that the NDA application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was communicated in the preliminary comments and the sponsor acknowledge the Agency's comments.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. The sponsor stated they intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, the Agency notes that a chemistry pre-submission meeting is scheduled for June 3, 2015. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number

b. Principal investigator
c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

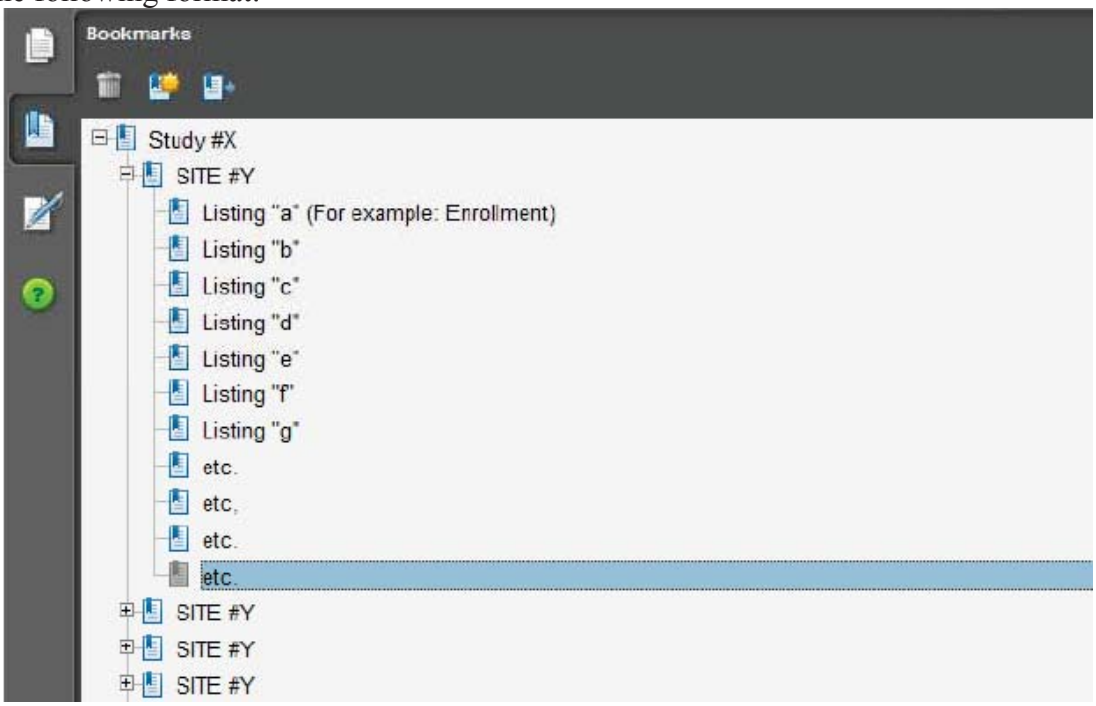
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)

c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection

Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

(b) (4) Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Further discussion regarding the need to provide an adequate bridge between the to-be-marketed combination product and the combination product used in the clinical fracture study may be needed. Radius will discuss a schedule for providing additional data needed support an adequate bridge internally and present a proposal for discussion at the CMC Pre-NDA meeting scheduled for June 3, 2015.

Review and comments for the submission of the use-risk analysis and human factors study protocol and recent submission of information regarding the device used in the phase 3 fracture trial and the to-be-marketed device/combination product is pending.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	June 27, 2015

6.0 ATTACHMENTS AND HANDOUTS

Radius Slides for Nonclin Clin PreNDA Meeting 28 May 2015

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

/s/

THERESA E KEHOE
06/22/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 73176

MEETING PRELIMINARY COMMENTS

Radius Health, Inc.
Attention: Anne Marra
Executive Director Regulatory Affairs and Project Management
950 Winter Street
Waltham, MA 02451

Dear Ms. Marra:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Abaloparatide (BA058).

We also refer to your March 5, 2015, correspondence, received March 6, 2015, requesting a meeting to discuss the Agency's responses to your CMC questions.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

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

If you have any questions, call me at (301) 796-2919.

Sincerely,

{See appended electronic signature page}

Kerri-Ann Jennings, MS, BSN, RN
LCDR, USPHS, Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-NDA, CMC
Meeting Date and Time:	June 3, 2015, 2:00PM ET
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	IND 73176
Product Name:	Abaloparatide (BA058)
Indication:	Treatment of post-menopausal osteoporosis
Sponsor/Applicant Name:	Radius Health, Inc.

FDA ATTENDEES (tentative)
Mark Seggel, Ph.D., Acting CMC Lead, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Xavier Ysern, Ph.D., Reviewer, Division of New Drug API, ONDP, OPQ
Donna Christner, Ph.D., Acting Chief, Branch II, Division of New Drug API, ONDP, OPQ
Danielle Harris, Pharm.D., BCPS, Team Leader, DMEPA
Bindi Nikhar, M.D., Reviewer, Office of Combination Products
Theresa Kehoe, M.D., Medical Team Leader, Division of Bone, Reproductive, and Urologic Products (DBRUP)
John Stinson, M.D., Medical Officer, DBRUP
Gemma Kuijpers, Ph.D., Pharmacology and Toxicology Reviewer, DBRUP
Hylton V. Joffe, M.D., M.M.Sc., Director, DBRUP
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff, DBRUP
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager, DBRUP
Kerri-Ann Jennings MS, BSN, RN, LCDR, USPHS, Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO), OPQ

SPONSOR ATTENDEES

David Hanley, PhD	RADIUS Health	Executive Director, Technical Operations
Gary Hattersley, PhD	RADIUS Health	Chief Scientific Officer
Gregory C. Williams, PhD	RADIUS Health	Chief Development Officer
(b) (4)		Regulatory Advisor
Michael Macalush	RADIUS Health	Director, Regulatory Affairs

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 3, 2015, 2:00PM ET, 10903 New Hampshire Avenue, White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903 between Radius Health, Inc. and CDER Office of Pharmaceutical Quality. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

Abaloparatide (BA058) is being developed for the treatment of post-menopausal osteoporosis. Radius Health, Inc. submitted a Type B meeting request to the Agency on March 6, 2015, to discuss the Agency's response to their CMC questions.

The Agency granted the meeting and Preliminary Comments are as provided below.

SPONSOR'S QUESTIONS AND AGENCY RESPONSES
(Agency responses in italics)

***Question 1*:** Does the Sponsor's proposed test methods and specifications for drug substance release and stability are acceptable for the abaloparatide-SC NDA submission?

FDA Response to Question 1:

No. While the proposed drug substance specification captures most critical tests and attributes, we have the following recommendations:

- *Add a test for biological activity, or provide a justification, based on characterization studies, for excluding such a test and,*
- *Establish acceptance criteria for each identified individual impurity.*

The suitability of the acceptance criterion for each test will be determined during review of the entire NDA package.

Please note that there should be only a single drug substance (or drug product) regulatory specification that covers both release and stability. Internal acceptance criteria for tests at release can be included in the regulatory specification but should be identified as such.

***Question 2*:** Does the Agency agree that the Sponsor's proposed test methods and specifications for drug product release are acceptable for the abaloparatide-SC NDA submission?

FDA Response to Question 2:

See response to Question 1.

***Question 3*:** In aged samples of abaloparatide-SC finished product, the degradant (b) (4) has recently been identified, with a new, improved test method. Does the Agency agree with the Sponsor's proposed approach to qualify this degradation product and determine an acceptable specification level for the abaloparatide-SC NDA submission?

FDA Response to Question 3:

No. The strategy for qualifying the (b) (4) degradant, as described on pages 18 – 25 of the Briefing Package, should include comparative data on the biological activity of the (b) (4) degradant" and its parent compound.

An acceptance criterion greater than or equal to (b) (4)% for the (b) (4) degradation product should be justified based on adequate qualification data. Qualification data may be derived from completed nonclinical and clinical studies. If nonclinical toxicity studies were conducted with test compound containing degradant at levels exceeding the acceptance criterion by adequate multiples, the data from these studies may serve to qualify the degradant. Similarly, if clinical studies were conducted with product containing degradant at levels greater than or equal to the proposed acceptance criterion of (b) (4)%, these studies may provide clinical qualification data.

***Question 4*:** Except for the specifications for (b) (4) discussed in question 3, does the Agency agree that the Sponsor's proposed test methods and specifications for drug product stability are acceptable for the abaloparatide-SC NDA submission?

FDA Response to Question 4:

See response to Question 1.

We remind the Applicant that the drug product specification should be met during the proposed shelf-life of the drug product. The shelf-life includes storage time and in-use time (shelf-life of drug product = storage time (5°C) + in-use time (~ 30 days, 25°C)). It is unclear if, during the

30-day proposed in-use time, the drug product will always be at 25°, or if the drug product will be allowed to reach room temperature before injection and then be stored at 5°C after injection (excursions to room temperature).

Question 5: The Sponsor proposes to submit the abaloparatide-SC NDA with validation batch release data, 6 month stability data for 3 registration stability batches, as well as supportive (b) (4) month stability data from batches of the same formulation as the current, which were used in Phase 3 studies. The Sponsor additionally proposes to submit ongoing stability data during the abaloparatide-SC NDA review cycle. Does the Agency agree that this approach is acceptable?

FDA Response to Question 5:

No. Primary stability data for at least 12 months at the proposed storage condition and 6 months at accelerated condition for 3 primary batches should be provided at the time of NDA submission. Additional stability data received within 30 calendar days after receipt of the original submission will be acceptable for review purposes. The expiration dating period will be evaluated based on the provided stability data (shelf-life of drug product = storage time (5°C) + in-use time (~ 30 days, 25°C or 5°C with brief excursion to room temperature)).

Question 6: Does the Agency agree that the Sponsor's proposed approach to qualifying the intended commercial delivery device (UnoPen) is acceptable for the abaloparatide-SC NDA submission?

FDA Response to Question 6:

As discussed at the May 28, 2015, Clinical PreNDA meeting, we acknowledge the recent submission of information regarding the device used in the phase 3 fracture trial and the to-be-marketed device/combination product. We will have further comments on the adequacy of the performance characteristics of your proposed device once review of this information is complete.

We also acknowledge submission of your use-risk analysis and human factors study protocol. We will review the materials and provide comments. We recommend that you do not conduct your human factors study until we have completed our review of the proposed protocol.

Additional Microbiology Product Quality Comments:

Pharmaceutical development information in the NDA submission must include (b) (4)

Sterilization validation information in the NDA submission must include (and is not limited to) the following:

- *Product-specific* (b) (4) *studies for the* (b) (4) *used in the* (b) (4) *manufacturing process.*

- *Complete validation of* [redacted] (b) (4) *of the containers, closures, filling equipment and components that come in product contact (results from at least one run must be recent).*

- *Media fill simulations that include simulation of holding times (results from at least one run must be recent).*

- *Environmental monitoring program (alert/action levels, methods and test frequency).*

- *Container-closure integrity studies for the container-closure system.*

- *Method suitability studies for the sterility and bacterial endotoxins tests for the finished product.*

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

/s/

KERRI-ANN JENNINGS
06/02/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 073176

MEETING PRELIMINARY COMMENTS

Radius Health, Inc.
Attention: Anne Marra
Executive Director, Regulatory Affairs and Project Management
950 Winter St.
Waltham, MA 02451

Dear Ms. Marra:

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

We also refer to your March 31, 2015, correspondence, requesting a Pre-NDA meeting to discuss proposals for the content, analyses, and format of nonclinical and clinical data for NDA submission.

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, call me at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Samantha Bell, B.S., B.A., R.A.C.
Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	May 28, 2015, 2:00 P.M. to 3:00 P.M.
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	IND 073176
Product Name:	Abaloparatide
Indication:	Treatment of women with postmenopausal osteoporosis
Sponsor/Applicant Name:	Radius Health, Inc.

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 28, 2015, 2:00 P.M. to 3:00 P.M. between Radius Health and the FDA. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact me if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Abaloparatide (BA058) is an analogue of parathyroid hormone-related peptide (PTHrP). PTHrP is secreted endogenously by osteoblasts and, like parathyroid hormone, contributes to calcium homeostasis. Radius is developing abaloparatide for the treatment of postmenopausal women with osteoporosis. The sponsor has completed several Phase 1 studies, two Phase 2 studies (BA058-05-002, BA058-05-007), and an 18-month Phase 3 trial (BA058-05-003) with 24-month extension (BA058-05-005). Radius would like to discuss the nonclinical and clinical development of abaloparatide to support the forthcoming NDA to be submitted in late 2015 for the treatment of osteoporosis in postmenopausal women.

2.0 DISCUSSION

2.1. Nonclinical

Question 1: *Does the Agency agree that the completed non-clinical studies are adequate to support the submission, filing and review of the abaloparatide–SC NDA for the treatment of osteoporosis in postmenopausal women?*

FDA Response to Question 1:
The nonclinical studies conducted with abaloparatide appear to be adequate for NDA submission. We remind you that qualification of impurities in drug substance and drug product may be needed for the NDA.

2.2. Clinical

Question 2: *Does the Agency agree that the planned abaloparatide safety and efficacy databases are adequate to support the submission, filing and review of the abaloparatide-SC NDA for the treatment of osteoporosis in postmenopausal women?*

FDA Response to Question 2:
As proposed, the planned abaloparatide safety and efficacy databases appear adequate to support an NDA submission for abaloparatide. You state that the efficacy evaluation will be primarily based on the Phase 3 Study 003 data with efficacy assessments of abaloparatide versus placebo and teriparatide at 18 months, and the first 6-month data from its extension Study 005.

Confirm that all subjects enrolled in Study 005 will have completed the 6 month primary endpoint and will be included in the analyses.

All datasets in Studies BA058-05-003 and BA058-05-005 should contain the subject identification number for both studies (i.e., for each subject enrolled in Study 003, the Study 003 subject identification number should be included in the Study 005 datasets and for each subject enrolled in Study 005, the Study 005 subject identification number should be included in the Study 003 datasets.

Datasets for the Integrated Summary of Safety (ISS) and all individual clinical studies should be provided in a single version of MedDRA, preferably the most recent version.

In the NDA, provide a listing of all major and minor protocol violations and deviations.

In the NDA, provide a listing of all study discontinuations and temporary treatment suspensions in your Phase 2 and 3 studies.

Question 3: *Does the Agency agree that the completed and ongoing human PK, PD, Thorough QT/QTc and special population studies are adequate to support submission, filing and review of the abaloparatide–SC NDA for the treatment of osteoporosis in postmenopausal women?*

FDA Response to Question 3:
The Agency agrees that the completed and ongoing human pharmacokinetic (PK), pharmacodynamic (PD), Thorough QT/QTc and renal function studies are adequate to support submission, filing and review of the abaloparatide NDA. However, as recommended at the Type A Guidance Meeting of March 21, 2012, we request analysis of data from your Phase 3 studies to evaluate if the efficacy data differ by hepatic function status.

We request that you analyze immunogenicity data collected during the clinical development of your product to evaluate the incidence of anti-drug antibody formation and the impact of immunogenicity on PK/PD, clinical efficacy and safety.

Additional comments:
The Office of Clinical Pharmacology requests that in addition to the standard electronic Common Technical Document (eCTD submission), you provide a review aid by generating a stand-alone document summary based on questions listed in the appended "Question-based Clinical Pharmacology Summary for NDA or BLA submission". The answers to these questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. Your answers to the questions should be annotated with links to the detailed information in the study reports and to the raw data located in SAS transport files.

Question 4: *Does the Agency agree with the proposed analyses for the recently completed Phase 3 study in osteoporosis (BA058-05-003) and the ongoing extension study (BA058-05-005), including the comparators and primary and secondary endpoints as defined in the amended SAP for BA058-05-003 (incorporating the review division's comments on the draft SAP) and draft SAP for BA058-05-005?*

FDA Response to Question 4:
The Agency agrees with the proposed analysis of the primary and secondary endpoints of both studies as defined in the amended Statistical Analysis Plan (SAP) for Study 003 and the draft SAP for Study 005. We remind you that data documenting the comparative incidence of new morphometric vertebral fractures by 24 months are essential for submission and review. The Agency agrees with performing analysis of the primary endpoint in the modified Intent to Treat (mITT) population, unless the number of subjects in the mITT population differs

significantly from that of the Intent to Treat (ITT) population, which would be a review issue.

Question 5: *The abaloparatide-SC NDA will include a single large, global, multicenter, comparative pivotal trial (n=2460 treated patients) of the dose studied in the Phase 3 trial and for which approval will be sought (i.e., 80 mcg daily subcutaneous injection), with patient safety and fracture outcomes linked to patient treatment durations of 18 and 24 months. By comparison, the other clinical trials conducted in this development program varied significantly in study design, study population (i.e., healthy volunteers vs patients), treatment dose/duration, dosage form (SC and TD), and study endpoints. To avoid diluting and/or obscuring the safety and efficacy data associated with the proposed dose (i.e., 80 mcg) and treatment duration (i.e., 18 months) in the pivotal trial, the Sponsor proposes to submit individual summaries of all clinical trials completed at the time of submission without pooled safety or efficacy analyses. Does the Agency concur with this approach?*

FDA Response to Question 5:
We agree that individual clinical trial reports should be included for all clinical trials completed at the time of submission.

The Integrated Summary of Effectiveness (ISE) should include summaries from studies BA058-05-003 and BA058-05-005 as well as any supporting studies that inform the dose chosen for the Phase 3 trial.

The Integrated Summary of Safety (ISS) should focus on the pooled safety data from all Phase 2 and 3 abaloparatide studies. However, an analysis of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs, should also be included.

We request submission of case report forms and a detailed discussion of all subjects who died, experienced serious adverse events, or dropped out of a study because of an adverse event.

We agree that data from studies (b) (4) are not required with an NDA submission for the subcutaneous formulation of abaloparatide.

***Additional Comments*:**
FDA encourages sponsors to submit a Pharmacovigilance (PV) Plan developed to detect new safety risks and to further evaluate identified safety risks with abaloparatide following market approval. Information on PV Plans has been included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005) and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the PV plan is available,

please include it in the NDA application in the appropriate module so that it can be reviewed accordingly.

2.3. Biometrics

Question 6: *The Sponsor proposes to submit a mixture of legacy and standardized datasets in the NDA. The datasets for legacy Phase 1 and 2 studies (most completed prior to 2010) and the Phase 3 studies (initiated in 2010) did not follow the CDASH standard and will conform to the standards defined in the Study Data Specification (SDS) v 2.0. The datasets for the three recently conducted (2014) Phase 1 studies will conform to CDSIC standards, specifically SDTM for case report form tabulation data and ADaM for analysis data. The Sponsor also proposes to provide SDTM domain datasets as well as the ADaM ADSL analysis datasets for the pivotal 003 and 005 studies to assist the Agency's review of the efficacy and safety data. Does the Agency agree that this approach is acceptable?*

FDA Response to Question 6:

Yes, your approach is acceptable. Please refer to the *Study Data Standards Resources* website for guidance and detailed information regarding to standardized study data submission.

Additional Comments:
We have the following comments on sections of the application that are not included in your background package. These sections are necessary for review of your application and should be submitted and complete at the time of NDA submission:

Risk Management:

We have identified the serious risk of osteosarcoma associated with the use of abaloparatide. At a minimum, the Prescribing Information for abaloparatide will include a boxed warning and Medication Guide to address the risk of osteosarcoma. Your NDA submission must include a risk management plan with appropriate rationale for any proposed risk mitigation to address this risk in the post-marketing setting.

Other Drug and Device Issues:

- The specific drug formulation and delivery system (device/pen injector) used for each study included in your development program is not clear. Submit a table that outlines the drug formulation and the specific device/pen injector (including cartridge size) used for each study in your development program. We recommend that you also provide this table prior to the Pre-NDA meeting.

- We acknowledge the recent submission of information regarding the device used in the phase 3 fracture trial and the to-be-marketed device/combination product. We will have further comments on the adequacy of the performance characteristics of your proposed device once review of this information is complete.

- We note that the to-be-marketed drug-device combination product is different than the drug-device combination product used in your Phase 3 fracture trial. It will be necessary to bridge between the phase 3 drug-device product and the to-be-marketed drug-device combination product. Conduct a PK comparability study with the combination product (drug delivered via BD pen injector) used in the Phase 3 study and the to-be-marketed combination product (drug delivered using the Unopen injector) to compare systemic exposure and demonstrate bioequivalence between the two using bioequivalence criteria.

- Site of injection: As stated in the Phase 3 protocol, "All injections are to be given in the periumbilical region, rotating the exact site of injection each day. If it is deemed medically necessary by the investigator for an injection to be administered at a site other than the abdomen, the alternate site of injection is to be recorded and the reason for the change documented in the medical chart." We request that you provide a summary of site of injections used by patients in the studies where the to-be-marketed formulation was tested. The summary will provide clinical experience on sites of injection to inform labeling.

Combination Product:
Your proposed abaloparatide drug product that is to be injected using the Abaloparatide Unopen is a drug-device combination product and as such is subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at: *https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products*.

Human Factors:
We acknowledge submission of your use-risk analysis and human factors study protocol. We will review the materials and provide comment. We recommend that you do not conduct your human factors study until we have completed our review of the proposed protocol.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 16, 2015, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to

begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

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

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

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

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

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:

a. Site number
b. Principal investigator
c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

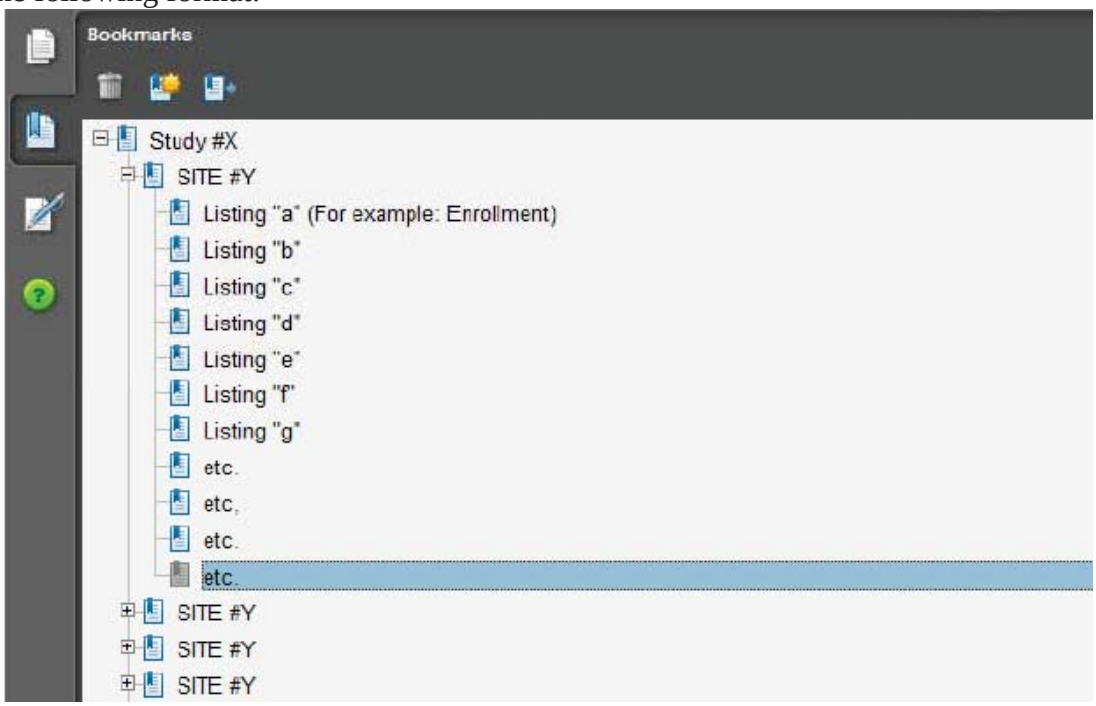
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated

b. Subject listing for treatment assignment (randomization)
c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to

voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

(b) (4) **Pre-NDA Request Item**[1]	**STF File Tag**	**Used For**	**Allowable File Formats**
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

CLINICAL PHARMACOLOGY SUMMARY

1. Goal

In addition to summarizing the relevant findings the goal of the Clinical Pharmacology Summary is to focus sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions a generic questionnaire is provided that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Summary generated by sponsors is a **stand-alone word document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies*)* and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple dose, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology, dose-ranging, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal t1/2 and AUC.

2.4 Exposure-Response

2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship. Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-effectiveness relationship. Provide point estimate as well as a measure of the inter-subject variability for continuous and categorical endpoints. Indicate

proportion of responders, if applicable.
Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, Cmax or Cmin is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Of major interest are safety endpoints determining the therapeutic range. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, Cmax or Cmin is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) Cmax and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc-interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the exposure-response relationship for both efficacy and safety of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [Cmax, tmax, AUC, Cmax,ss, Cmin,ss, Cmax,ss/Cmin,ss, tmax,ss, AUC0-τ, CL/F, V/F and t1/2 (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, Cmax, Cmin, CL/F and t1/2 of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute bioavailability of drug of parent drug and relative bioavailability, lag time, tmax, tmax,ss, Cmax, Cmax,ss and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 What are the characteristics of drug metabolism?

2.5.7 What are the characteristics of drug elimination in urine?

2.5.8 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) Cmax and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.9 How do the PK parameters change with time following chronic dosing?

Indicate whether the mean ratio of AUC0-τ at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, Cmax, clearance, volume of distribution and t1/2 for pairs studied: elderly vs.young, male vs.female, normal body weight vs. obese, race/ethnicity x vs. race/ethnicity y, mild vs. severe target disease

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (dose or interval) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Body Weight

2.6.2.3 Elderly

2.6.2.4 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.5 Race/Ethnicity

2.6.2.6 Renal Impairment

2.6.2.7 Hepatic Impairment

2.6.2.8 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?

Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

2.7.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.2 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report the 90% confidence intervals about the geometric mean ratio for AUC and Cmax for the drug of interest in the presence and absence of each of the co-administered drugs. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report 90% confidence intervals about the geometric mean ratio for AUC and Cmax of each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.3 Does the label specify co-administration of another drug?

2.7.4 What other co-medications are likely to be administered to the target population?

2.7.5 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

2.8.1 Was the manufacturing process changed during the development program? (Include a table listing all the products used throughout the clinical development programs.)

2.8.2 Was the proposed to-be-marketed formulation comparable to the formulation used in the pivotal clinical trials with respect to pharmacokinetics and/or pharmacodynamics?

2.9 Analytical Section

2.9.1 What bioanalytical methods are used to assess therapeutic protein concentrations?

Briefly describe the methods and summarize the assay performance. Please provide tables for each assay to address the below questions

2.9.1.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.1.2 What are the lower and upper limits of quantitation?

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.1.3 What are the accuracy, precision, and selectivity at these limits?

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.1.4 What is the sample stability under conditions used in the study?

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at ≤ –20° C.

2.9.1.5 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

2.9.2 What bioanalytical methods are used to assess the pharmacodynamic markers?

Briefly describe the methods and summarize the assay performance.

2.9.3 What bioanalytical methods are used to assess the immunogenicity?

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference (including drug interference) and matrix, etc.

2.9.3.1 What is the performance of the binding anti-product antibody assay(s)?

2.9.3.2 What is the performance of the neutralizing assay(s)?

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/s/

SAMANTHA S BELL
05/21/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 073176

DENY -
BREAKTHROUGH THERAPY DESIGNATION

Radius Health, Inc.
Attention: Gregory C. Williams, Ph.D.
Chief Development Officer
201 Broadway, 6th Floor
Cambridge, MA 02139

Dear Dr. Williams:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for abaloparatide (BA058).

We also refer to your May 8, 2014, request for Breakthrough Therapy designation for treatment of postmenopausal osteoporosis.

We have reviewed your request and while we have determined that treatment of postmenopausal osteoporosis meets the criteria for a serious or life-threatening disease or condition, the preliminary clinical evidence you submitted does not indicate that abaloparatide may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Therefore, designation for abaloparatide as a Breakthrough Therapy cannot be granted at this time.

Bone mineral density is an imperfect surrogate endpoint for fracture risk reduction. For example, 40 mcg of teriparatide does not lead to substantial improvement in fracture efficacy beyond that seen with the marketed 20 mcg Forteo dose, despite greater increases in bone mineral density. Therefore, it cannot be assumed that the rate and degree of bone mineral density increases achieved with abaloparatide will substantially reduce fractures compared to Forteo. In addition, the available data do not support a substantial improvement with regard to the risk of hypercalcemia compared to Forteo when we take into account our assessment of the Forteo clinical program and Forteo's postmarketing experience. There is also no evidence that abaloparatide offers other substantial safety advantages over Forteo.

You may submit a new request if you obtain new clinical evidence that demonstrates a substantial improvement in treatment of postmenopausal osteoporosis over existing therapies for abaloparatide.

For further information regarding Breakthrough Therapy designation, refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf)

For further information regarding Fast Track, refer to the guidance noted in the above paragraph.

If you have any questions, contact Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

HYLTON V JOFFE
07/02/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 073176

Radius Health, Inc.
Attention: Louis St. L. O'Dea, M.D., M.B., B.Ch., B.A.O., F.R.C.P.(C)
Senior Vice President and Chief Medical Officer
300 Technology Square, 5th Floor
Cambridge, MA 02139

Dear Dr. O'Dea:

Please refer to your Investigational New Drug Application (Pre-IND) submitted for BA058, an analog of parathyroid hormone (PTH)-related protein.

We also refer to the meeting between representatives of your firm and the FDA on January 21, 2010. The purpose of the meeting was to discuss the objectives and design of your phase 3 clinical program and to discuss the results of your completed phase 1 and 2 studies. The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Clinical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2 (EOP2)
Meeting Date and Time:	January 21, 2010, 1:30 P.M. – 3:00 P.M.
Meeting Location:	Food and Drug Administration Center for Drug Evaluation and Research 10903 New Hampshire Avenue Building 22, Conference Room 1421 Silver Spring, MD 20903
Application Number:	IND 073176
Product Name:	BA058, an analog of parathyroid hormone (PTH)-related protein
Indication:	Treatment of postmenopausal women with osteoporosis who are at high risk of fracture
Sponsor/Applicant Name:	Radius Health, Inc.
Meeting Chair:	Theresa Kehoe, M.D.
Meeting Recorder:	Nenita Crisostomo, R.N.

FDA ATTENDEES

Scott Monroe, M.D. – Director, Division of Reproductive and Urologic Products (DRUP)
Theresa Kehoe, M.D. – Clinical Team Leader, DRUP
Vaishali Popat, M.D. – Medical Officer, DRUP
Marcea Whitaker, M.D. – Medical Officer, DRUP
Lynnda Reid, Ph.D. – Supervisor, Pharmacology/Toxicology, DRUP
Gemma Kuijpers, Ph.D. – Pharmacologist, DRUP
Hae-Young Ahn, Ph.D. – Deputy Director, Division of Clinical Pharmacology III (DCP3) @ DRUP
Jee Eun Lee, Ph.D. – Clinical Pharmacology Reviewer, DCP3 @ DRUP
Mahboob Sobhan, Ph.D. – Biostatistics Team Leader, Division of Biostatistics II (DBII)
Nenita Crisostomo, R.N. – Regulatory Health Project Manager, DRUP

RADIUS HEALTH, INC.

Richard Lyttle, Ph.D. – President and Chief Executive Officer, Radius
Louis O'Dea, M.D. – Chief Medical Officer, Radius
Gary Hattersley, Ph.D. – Vice President Research, Radius
Jonathan Guerriero, M.B.A. – Director of Programs, Radius
(b) (4) – Consultant to Radius in Early Clinical Development
(b) (4) – Consultant to Radius in Quality and Manufacturing
(b) (4) – Consultant to Radius in Regulatory Affairs
(b) (4) Consultant to Radius in Preclinical Safety
(b) (4) – Consultant to Radius in Radiology
Kelly Sullivan, Ph.D. – Senior Regulatory and Safety Associate, Radius
Ms Kathleen McKay – Senior Project Manager, Radius

BACKGROUND

This investigational new drug (IND) application was submitted on December 9, 2005, under the sponsorship of Nuvios, Inc, now changed to Radius Health, Inc. BA058 is a 34-amino acid synthetic analog of human PTH-related peptide (hPTHrP) being developed by Radius Health, Inc. for the treatment of postmenopausal osteoporosis. The sponsor's hypothesis is that BA058 will achieve a bone anabolic effect with less bone resorption and a lower rate of hypercalcemia than PTH and its analogs. Radius believes that preclinical *in vitro* and *in vivo* pharmacology studies and preliminary data from the clinical development program support this hypothesis. BA058 has been studied in three Phase 1 studies and dose-finding Phase 2 study with treatment up to 12 months. Forteo® (teriparatide) was included in the Phase 2 study as a reference drug. BA058 was reported to have greater bone mineral density (BMD) efficacy at a number of anatomical sites, particularly at the hip, than teriparatide while being less likely to induce hypercalcemia.

This EOP2 meeting was requested by the Sponsor to discuss their Phase 3 clinical program and to discuss the results of their completed Phase 1 and 2 studies. The Sponsor's specific objectives of the meeting were:

1. To reach agreement on the adequacy of the preclinical package to be submitted in support of BA058 registration
2. To reach agreement on the adequacy of the completed Phase 1 and 2 clinical studies to move forward into Phase 3, and as a basis for selection of BA058 80 µg for Phase 3 development and registration
3. To reach agreement on the adequacy of the design of the Phase 3 program to achieve registration of BA058 in the proposed indication, treatment of postmenopausal women with osteoporosis who are at high risk for fractures

SPONSOR'S QUESTIONS AND THE DIVISION'S COMMENTS

Preliminary comments were provided to the sponsor on January 20, 2010, in response to questions posed in the December 18, 2009, Meeting Information Package. The sponsor's questions presented in the Meeting Information Package are presented below in *italics,* followed by the Division's responses in normal text. Additional discussion and comments made at the meeting are presented in **bold** text.

Chemistry, Manufacturing, and Controls

QUESTION 1: *Based upon the characterization and specifications developed for BA058, both drug substance and drug product, does the Agency concur with the suitability of the RADIUS CMC program for Phase 3 and commercial product?*

FDA RESPONSE: Overall, the information appears to be adequate, with the following additional comments:

1. Drug Substance
    a. The specifications appear to be adequate for the Phase 3 study, however, the acceptance criteria should be set for the (b) (4) Content, Specific Optical Rotation, and Residual Solvents.

b. Full review will be performed on the specifications and acceptance criteria for the commercial product at the time of the new drug application (NDA) review to determine adequate controls for the commercial product.

c. Full chemistry, manufacturing, and controls (CMC) information should be provided on the drug substances manufactured by (b) (4) Lonza, either in the application or in a Drug Master File with the appropriate Letter of Authorization. This should include full characterization (for example, confirmation of primary sequence and secondary/tertiary structure) for drug substance provided by both suppliers. In addition, the application should contain a comparison of the two drug substances.

2. Drug Product

a. Ensure that the drug product complies with all requirements of USP<1>.

b. Content Uniformity and Visible Particles should comply with relevant USP chapters, or information should be provided to show that the European Pharmacopeia methods are equivalent or better than the USP methods.

c. Provide information on the injection system for evaluation by Center for Devices and Radiological Health (CDRH). Include information on tests performed to ensure that the correct dose is accurately delivered over the entire volume of the cartridge.

d. The stability data gathered to date using the (b) (4) rubber crimp caps can be used as supportive. The primary stability studies should be performed in your proposed container closure system.

Additional Discussion During the Meeting: The Sponsor agreed to all of the above recommendations.

Preclinical

QUESTION 2: *Based upon the totality of the preclinical assessments conducted and the results of the planned studies are acceptable, will the preclinical program be adequate to support the registration of BA058 in the proposed indication?*

FDA RESPONSE:

1. The preclinical program appears to be adequate. However, the results of all studies including ongoing or planned carcinogenicity and bone quality studies need to be reviewed to evaluate whether the results support registration.
2. We recommend that you submit the protocols of the rat and monkey bone quality studies for review by the Division.
3. Reproductive toxicity studies will be needed to support indications in men or premenopausal women.
4. Qualification of impurities in drug substance and drug product may be needed for the NDA.
5. Soft tissue mineralizations were observed in the absence of hypercalcemia in rats and monkeys. Concomitantly, no bone effect was noted in the 39-week monkey study. This raises concern about the safety of your product (see Clinical Response to Question 3).

Additional Discussions During the Meeting: **The Sponsor stated that the apparent lack of hypercalcemia was due to the 24-hour post dose sampling time. Increased serum calcium was observed 3 hours, but not 24 hours, after dosing at all doses in rat and monkey toxicity studies. The hypercalcemia and tissue mineralizations in monkeys may, in part, be related to the high dietary calcium levels. Kidney mineralization in monkeys was accompanied by a dose-dependent change in renal function. However, renal parameters were not affected in the Phase 2 clinical study. The sponsor argued that the apparent lack of a bone effect in the 39-week monkey study was probably due to insensitivity of the histological evaluation method.**

QUESTION 3: *Based upon the outcome of the Phase 1 clinical studies and the results of the Phase 2 clinical study following patients up to 12 months, does the Agency have any concerns about their completeness to support the described Phase 3 development plan in support of BA058 product registration?*

FDA RESPONSE:

Clinical Pharmacology:

1. A "thorough QT/QTc study" conducted in healthy volunteers is recommended. These assessments should be based on "*Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/ucm073161.pdf)." We recommend that you submit a protocol to the Division to be reviewed by the QT Interdisciplinary Review Team (QTIRT) prior to initiating the study.

   Additional Discussion during the Meeting: The Sponsor stated that QT prolongation had been assessed in clinical trials and no significant QT prolongation had been observed. The Division stated that because an active control, such as moxifloxacin, was not used, the sensitivity of the QT measurements was in question and it would be difficult to interpret the data. The Division stated that there would be a follow-up consult with the QTIRT regarding the QT assessment.

2. Because the formulation used for the dose-proportionality study was different from the formulation used in pivotal clinical trials, we recommend that you conduct a dose-proportionality study. It will be beneficial to manage dose adjustment based on any covariate in the future.

3. We recommend that the pharmacokinetics (PK) of BA058 in patients with impaired renal function be studied. The initial PK study could be a single-dose study with end stage renal disease patients not yet on dialysis where the PK parameters between patients with renal disease and subjects with normal renal function are compared.

   Additional Discussion during the Meeting: The sponsor stated that the effect of renal impairment on the PK of BA058 would be assessed in a subgroup of patients with moderate renal impairment whose creatinine clearance would be about 35 mL/min. The Division stated that severe impairment should be defined as creatinine clearance of less than 30 mL/min and questioned how the sponsor would access the PK in patients with severe renal impairment. The Sponsor stated that BA058 (b) (4) **than postmenopausal osteoporosis. The currently proposed inclusion criterion of including patients with**

serum creatinine ≤1.5 allows for assessment of population PK in subjects with normal to moderate renal impairment. The Division stated that it would be essential to include a sufficient number of patients in each level of renal function group to ensure adequate representation of patients with various levels of renal function. The Division also expressed a concern that in the Phase 3 study all subjects in a given treatment arm will receive the same dose and those with reduced renal function may be at risk due to higher exposure.

4. Clarify the effect of chronic dosing with BA058 on serum calcium levels during the first 24-hours post-dose in the Phase 2 trial.

Clinical:

1. As outlined in the Information Request letter of February 17, 2007, the Division recommended that the 3-month Phase 2 dose-finding study be extended to 12 months or a second Phase 2 trial of 12 months duration be conducted.

   In your Phase 2 study BA058-05-02, the primary endpoint was change in bone mineral density at 24 weeks. Of the total 222 subjects enrolled, 55 subjects were studied for the requested 48 weeks with only seven of these subjects receiving the 80 mcg dose. While the efficacy results appear consistent from Week 24 to Week 48, the adverse event rates and changes in blood pressure appear to be dose-related. Overall, the small number of subjects with Week 48 data makes interpretation of efficacy and safety difficult. Therefore, due to small number of patients, the Phase 2 data do not appear to provide sufficient support for advancing the 80 mcg dose alone into Phase 3. For this reason, we strongly encourage you to study at least 2 doses in the Phase 3 trial.

   Additional Discussion During the Meeting: The sponsor argued that:
   1) Safety evaluations in the Phase 2 trial showed that there was no difference between the 40 mcg and 80 mcg dose in terms of effect of BA058 on diastolic and systolic supine blood pressure, serum calcium, or hypercalcemia. The Division stated that in this Phase 2 trial, no difference in the blood pressure was seen in the Forteo® arm as well; however, orthostatic hypotension is a known safety concern for Forteo®, and is included in the full prescribing information for it. Therefore, this negative data does not rule out the possibility of a safety concern with BA058.

   2) Efficacy was greater for 80 mcg dose compared to 40 mcg dose. Specifically, spine BMD data shows approximately 20-25% greater efficacy compared to Forteo®. Similarly, the hip BMD data shows 25% greater efficacy at 80 mcg dose. The Division stated that, ultimately, it is the Sponsor's decision and risk to proceed with their Phase 3 program as currently planned. At this time, there is no assurance that the selected 80 mcg dose is both safe and effective. Therefore, the Division strongly encouraged the Sponsor to study two doses in their Phase 3 program.

2. We are highly concerned about the nonclinical findings of tissue mineralization in absence of hypercalcemia seen in the 39-week monkey study. Pending review of the finalized Phase 2 study report, additional safety data may be required.

   Additional Discussion During the Meeting: To address the Division's concern about tissue mineralization, the Sponsor proposed to perform renal function monitoring in the Phase 3 study. The Division advised that the issue of renal function should be fully addressed with supportive documents, to include all available data and

literature. The Division stated that the Sponsor should submit a proposal to adequately address tissue mineralization. The proposal should include a discussion of the sensitivity and specificity of the modalities chosen to address tissue mineralization and renal function. The Sponsor added that they will submit a full study report of the Phase 2 trial before proceeding to Phase 3, which will include data on serum calcium levels as well as renal function.

QUESTION 4: *Does the Agency have any comments or concerns about the adequacy of the Phase 3 study design to support the registration of BA058 for treatment of postmenopausal women with osteoporosis who are at a high risk for fracture?*

FDA RESPONSE:

Clinical Pharmacology:

1. Dose-response relationships were observed in the Phase 2 study. Although 80 mcg showed the strongest biomarker response, it is still unclear if 80 mcg would be the optimal dose with fracture data as well. Thus, two doses between 40 mcg and 80 mcg should be examined in the Phase 3 clinical trials.

   Additional Discussion During the Meeting: The Sponsor stated that there would be little benefit obtained from the 40 mcg dose because the 80 mcg dose showed a pronounced effect in the Phase 2 study. The Division stated that although the BMD and biomarker responses with 40 mcg seemed to be lower than those with 80 mcg, this is not necessarily the case for the ultimate clinical outcome, fracture incidence. The Sponsor may jeopardize the opportunity for selecting an optimal dose by excluding 40 mcg which showed considerable biomarker responses.

   The Sponsor stated there was no increase in adverse events with increased dose of BA058 or Forteo®. Although there was a slight increase in serum calcium levels at 4-hour post-dose, generally, there was no significant difference in serum calcium levels between the pre- and post-dose time points for both the 40 mcg and the 80 mcg doses.

2. For reliable estimates of PK parameters in the population PK analysis, obtaining informative samples is necessary. We recommend that you collect PK samples at 0.5, 2, and 4 hour postdose on Day 1 in addition to the PK samples already planned in the protocol.

   Additional Discussion during the Meeting: The Sponsor acknowledged the Agency's proposal and agreed.

3. Because dedicated studies for special populations, such as geriatric or obese patients, are not planned, it is important to have enough subjects in each subgroup of designated covariates, such as age or weight, for relevant covariate assessment in the population PK analysis. We will have more comments when the full protocol for the population PK analysis is submitted.

   Additional Discussion During the Meeting: The Sponsor stated that there would be enough subjects in each subgroup of designated covariates. With respect to PK sampling scheme, the Sponsor stated that 100% of patients, except for Forteo® treatment group, will be included in blood sampling for PK assessment.

4. Clarify if a validated bioanalytical assay to measure plasma BA058 concentrations has been developed.
5. Immunogenicity may alter the PK and the effect of the drug. Include the immunogenicity assessment plan in the protocol.

Clinical

Regarding the study design:

1. Due to the lack of adequate blinding for the Forteo® product, the blind will only be maintained between BA058 and placebo but not with regard to Forteo®. This may introduce bias which will be taken into account when considering what comparative data, if any, will be included in the full prescribing information.

   Additional Discussion During the Meeting: The Division stated that for inclusion in the product label, comparative fracture efficacy data is necessary. Bone mineral density comparative efficacy data is not sufficient. Inclusion of comparative BMD data in the product label will ultimately be a review issue.

   The Sponsor confirmed that the study will include US sites.

2. As previously outlined, we strongly recommend that you study at least two doses in the Phase 3 clinical trial. As both efficacy and safety must be considered, a dose lower than 80 mcg may offer a more acceptable risk-benefit profile.
3. The protocol should include a clear algorithm for management of calcium and vitamin D supplementation as well as study drug management in the event of hypercalcemia and hypercalciuria.
4. The Target Product Profile (TPP) outlines a dose adjustment to 40 mcg in the event of hypercalcemia. (b) (4)

   Additional Discussion During the Meeting: The Sponsor stated that they will (b) (4) **. The Division clarified that a dose reduction algorithm could be used in the clinical trial. However, if a significant number of the study population required such a dose adjustment, this would impact the efficacy determination of the 80 mcg dose.** (b) (4)

Regarding the study population:

1. We agree with your proposed study population (postmenopausal women with severe osteoporosis). We also recognize that, because of ethical concerns, it may not be possible to enroll such a population in a placebo-controlled study. Should this be the case, it is acceptable to consider a double-blind, active-controlled trial with either Forteo® or alendronate as the active comparator.

Regarding the endpoints:

1. The primary endpoint is acceptable.

2. The secondary endpoints should include comparison of all BMD results between BA058 and placebo. Bone mineral density assessment should include the mid 1/3 radius (highly cortical bone) in at least a subset of patients.

3. We recommend a standardized approach for collecting and reporting race and ethnicity information in clinical trials. Please refer to the *Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials.*

Regarding safety:

1. Propose appropriate clinical monitoring for the Phase 3 trial to address tissue mineralization in the absence of hypercalcemia seen in the nonclinical program.

2. Cardiovascular safety of BA058 is a potential issue. The potential of BA058 to prolong the total depolarization and repolarization time interval (QT) may need to be addressed with a thorough QT study.

   <u>Additional Discussion During the Meeting:</u> The Division referred to the Phase 1 trial study report which included one subject receiving the 80 mcg dose who developed QTc prolongation (of 39 seconds) and experienced syncope, hypotension, and dizziness. The Division examines adverse events closely and this event could present a potential "red flag". The Sponsor stated that they will rely on a QT company to do the QT assessments. Because the QT requirements have evolved, the Division stated that the sponsor should submit available data from any studies. The Division will seek input from the QTIRT to evaluate the data.

3. Serum calcium should be monitored with adequate frequency and at optimal time points after dosing. The 80 mcg dose may be associated with hypercalcemia-related safety issues.

4. You propose to use (b) (4) for hypercalcemia management. We recommend the use of corrected (for albumin) calcium, (b) (4) depending on serum albumin levels.

<u>Biostatistics</u>

1. We remind that Forteo® BMD must be superior to placebo prior to testing the non-inferiority hypothesis. Any claim for secondary endpoints would require adjustment for multiplicity (multiple hypotheses).

2. A detailed statistical analysis plan must be submitted for our review. We recommend Kaplan-Meier estimate of fracture incidence in addition to crude incidence rate. Point estimates (differences in incidence) of absolute and relative risk reduction (hazard ratio) and the corresponding 95% confidence intervals must also be calculated. The statistical analysis plan must also indicate how missing data will be handled.

   <u>Additional Discussion During the Meeting</u>: The Division will work with the Sponsor to establish non-inferiority margin if the Sponsor chooses to pursue an active control trial with alendronate as an active comparator.

ATTACHMENTS:

1. Radius Plan to Discuss Responses
2. Radius Slide presentation

ACTION ITEMS: Meeting minutes will be provided to the sponsor within 30 days.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-73176	GI-1	RADIUS HEALTH INC	BA058 INJECTION & FOR INJECTION

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

/s/

THERESA E KEHOE
02/19/2010

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208743

LATE-CYCLE MEETING MINUTES

Radius Health, Inc.
Attention: Deepa Desai, M.S.
Director, Regulatory Affairs
950 Winter Street
Waltham, MA 02451

Dear Ms. Desai:

Please refer to your New Drug Application (NDA) dated March 30, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for abaloparatide.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on December 20, 2016.

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

If you have any questions, call Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Clinical Team Leader
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: December 20, 2016, 11:00 A.M. to 12:30 P.M.
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: NDA 208743
Product Name: Abaloparatide
Applicant Name: Radius Health, Inc.

Meeting Chair: Theresa Kehoe, M.D.
Meeting Recorder: Samantha Bell

FDA ATTENDEES

Division of Bone, Reproductive, and Urologic Products (DBRUP):
Christine Nguyen, M.D., Deputy Director for Safety
Theresa Kehoe, M.D., Clinical Team Leader
Stephen Voss, M.D., Medical Officer
Mukesh Summan, Ph.D., DABT, Pharmacology and Toxicology Supervisor
Gemma Kuijpers, Ph.D., Pharmacology and Toxicology Reviewer
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager
Robin Duer, R.N., B.S.N., M.B.A., Associate Director for Labeling

Office of New Drugs, Office of Drug Evaluation III:
Julie Beitz, M.D., Director
Victor Crentsil, M.D., Associate Director for Regulatory Science

Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP):
LaiMing Lee, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology (DCP) III
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP III
Fang Li, Ph.D., Pharmacometrics Reviewer, Division of Pharmacometrics (DPM)

OTS, Office of Biostatistics, Division of Biometrics III:
Jia Guo, Ph.D., Biometrics Reviewer
Sonia Castillo, Ph.D., (Acting) Biometrics Team Leader

Office of Pharmaceutical Quality:
Mark Seggel, Ph.D., Application Technical Lead, Office of New Drug Products (ONDP)
Thao Vu, Regulatory Business Process Manager, ONDP

Office of Surveillance and Epidemiology (OSE), Immediate Office:
Shawnetta Jackson, Project Manager

OSE, Office of Medication Error Prevention and Risk Management:
CAPT Walter Fava, R.Ph., M.S.Ed., Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Lolita White, Pharm.D, Acting Team Lead, DMEPA
Quynh Nhu Nguyen, M.S., Associate Director for Human Factors, DMEPA
Jacqueline Sheppard, Pharm.D., Risk Management Specialist, Division of Risk Management (DRISK)
Jamie Wilkins Parker, Pharm.D., Acting Deputy Director, DRISK

OSE, Office of Pharmacovigilance and Epidemiology:
Jie (Jenni) Li, Ph.D., MBBS, Team Leader, Division of Epidemiology
Neha Gada, PharmD, Team Leader, Division of Pharmacovigilance
Samantha Cotter, Pharm.D., BCPS, FISMP, Safety Evaluator
Wei Liu, Ph.D., Reviewer, Division of Epidemiology

Office of Combination Products:
Patricia Love, M.D., M.B.A., Deputy Director

Center for Devices and Radiological Health (CDRH):
Robert Meyer, B.S., M.E., Reviewer, Office of Device Evaluation, General Hospital, Respiratory, Infection Control, and Dental Devices (DAGRID), General Hospital Devices Branch

EASTERN RESEARCH GROUP ATTENDEE
Peggah Khorrami, Independent Assessor

APPLICANT ATTENDEES
Gregory C. Williams, Ph.D., MBA, Chief Development Officer
Gary Hattersley, Ph.D., Chief Scientific Officer
David Snow, Chief Commercial Officer
Lorraine Fitzpatrick, M.D., Chief Medical Officer
Bruce Mitlak, M.D., Vice President, Clinical Development
Tristan Hu, Ph.D., Executive Director, Statistics and Data Management
David Hanley, Ph.D., Executive Director, Technical Operations
Christine Dabrowski, Ph.D, Executive Director, Pharmacovigilance
Deepa Desai, M.S., Director, Regulatory Affairs
(b) (4) Regulatory Consultant

1.0 BACKGROUND

NDA 208743 was submitted on March 30, 2016, for abaloparatide.

Proposed indication: Treatment of postmenopausal women with osteoporosis

PDUFA goal date: March 30, 2017

FDA issued a Background Package in preparation for this meeting on December 8, 2016.

2.0 DISCUSSION

1. Introductory Comments

- Welcome, Introductions, Ground rules, Objectives of the meeting
- This meeting addresses the substantive review issues noted during the primary review of your New Drug Application and will not address a final regulatory decision for the application
- The intent is to share information and to promote a collaborative and successful discussion of the substantive review issues that have been identified
- We may discuss additional information that may be needed to address the identified issues, whether it will be reviewed in the current review cycle, and, if so, whether the submission would constitute a major amendment and trigger an extension of the PDUFA goal date. However, it may not be possible to reach final agreement on the review of additional information or the possibility of an extension of the PDUFA goal date at this meeting
- We may not be prepared to discuss some of the recent information submitted in response to our information requests

Discussion:
The Agency confirmed it does not intend to issue any Discipline Review letters for this application.

2. Discussion of Substantive Review Issues

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

a. Chemistry, Manufacturing, and Controls (CMC)
b. Device
c. Clinical and Statistical
d. Division of Medication Error Prevention and Analysis (DMEPA)

Discussion:

a. Chemistry, Manufacturing, and Controls (CMC)

There was no further discussion.

b. Device
The FDA stated that the dose accuracy matter is a clinical review issue important to assessing the reliability of the fracture efficacy data. Radius stated that the dose accuracy data conform to International Organization for Standardization standards. Radius will submit the justification as requested by the FDA in the meeting background package.

c. Clinical and Statistical
There was no further discussion.

d. Division of Medication Error Prevention and Analysis (DMEPA)
The FDA acknowledged receipt of the recently submitted Human Factors (HF) validation data and revised Instructions for Use (IFU). Although the review is ongoing, FDA expressed concerns regarding device priming errors and needle stick injuries identified in the review thus far:

- One of the subject's misinterpreted the (b) (4) in the revised IFU instructions to mean (b) (4). This subject skipped the priming steps; there were other subjects who re-primed the pen.
- Difficulty with removing the needle from the pen resulted in a needlestick injury; the IFU may need improvement regarding instructions on removing needles and understanding the term (b) (4)

Radius stated that the subjects who failed the use tasks in this study were not trained. Radius intends to provide formal training for each patient, although details of training are not yet available. The Agency acknowledges that Radius intends to train each user; however, we do not expect that training occurs or is consistently provided to every single user. As such, we have concerns with the Sponsor's proposed training.

In addition, Radius expressed that it has conducted extensive Human Factors studies, 9 formative and 2 summative. However, Radius is amenable to receiving comments from FDA to improve the IFU. FDA advised Radius that if the IFU requires additional revisions to address failures on the steps discussed above, another HF validation study may be needed.

3. Additional Applicant Data

Discussion:
The FDA acknowledged Radius's November 22, 2016, submission in response to the Mid-Cycle Communication.

4. Information Requests

Discussion:
The FDA noted the outstanding Information Request regarding dose accuracy.

5. Risk Evaluation Management Strategies REMS or Other Risk Management Actions

    a. Enhanced Pharmacovigilance for osteosarcoma

    We request that you submit a protocol for review regarding enhanced pharmacovigilance of osteosarcoma and include a targeted questionnaire. Submit this protocol and targeted questionnaire by December 30, 2016.

    Include the following elements in your protocol:

    - Submission of reports suggestive of osteosarcoma to FDA's Adverse Event Reporting System (FAERS) as expedited 15-day reports, regardless of expectedness of the event
    - Review by a medically qualified person as single case reports and as part of the aggregate data analysis for cases of osteosarcoma
    - Perform targeted surveillance with the use of a guided collection form to obtain salient additional clinical information related to osteosarcoma
    - Submit interval and cumulative analyses annually for 15 years from the date of approval. Reports may originate from, but are not limited to, spontaneous reports from healthcare providers and patients, post-marketing surveillance, surveillance of the FAERS database, and literature sources.
    - Assess, summarize, and identify potential risk factors for osteosarcoma for all post-marketing data sources. Present a summary of the assessments and analyses annually in the periodic adverse drug experience report (PADER).
    - Include the MedDRA search strategy for retrieving cases of osteosarcoma

Discussion:
Regarding REMS, the FDA clarified that the risk mitigation approach for the potential osteosarcoma risk in human has changed; this safety risk could be addressed through labeling mechanisms.

Radius did not have any questions regarding the Enhanced Pharmacovigilance for osteosarcoma and intends to submit the requested protocol and targeted questionnaire by December 30, 2016.

6. Postmarketing Requirements/Postmarketing Commitments

    No Postmarketing Requirements or Commitments have been identified at this time.

Discussion:
There was no further discussion.

7. Major labeling issues

Discussion:
The following sections of the Prescribing Information were discussed:

a. Boxed Warning (BW)
Radius sought clarification about FDA's calculation of exposure in animals and rationale for inclusion of the limited duration of use in the BW. Radius will submit to FDA a summary of their calculations of exposure multiples (rat versus human) for the Agency's comparison to its calculations. The FDA explained that recommendation to limit the cumulative use of abaloparatide and/or parathyroid (PTH) analogs to 2 years or less in a patient's lifetime is to mitigate the risk of osteosarcoma. The inclusion of such risk mitigation information in the BW is consistent with current labeling standards of labeling for a Boxed Warning.

Radius proposed (b) (4) The FDA did not concur, as there are no data to support such recommendation in labeling.

b. Indication
Radius requested that the osteoporosis statement in the Indication (b) (4) as discussed at the November 2015 Osteoporosis Drug Development Workshop. The FDA stated that it has not reached final decisions on this matter, and until such decision is made, the language concerning high risk for fracture remains relevant. (b) (4) FDA maintained that the inclusion of such criteria is important to appropriately identify the target population.

c. Section 14, Trial 003
There was a discussion about why (b) (4) (b) (4) (b) (4) The FDA stated that Radius could submit their justification for inclusion of data they consider important with the revised labeling. With regard to presentation of the secondary fracture and BMD data, the FDA advised that the data should be presented using tables or Kaplan Meier curves, but not both. Radius will revise the data presented in Tables 3 and 4 using text and Kaplan Meier curves.

d. Section 14, Trial 005
There was a discussion about where and how is best to present data from trial 005. The FDA stated that cumulative results and separate presentations would not be helpful. The

FDA agreed that Radius could propose incorporation of the Study 003 and 005 data using Kaplan Meier curves.

e. Section 12.1, Mechanism of Action
Radius intends to propose some additional language. The FDA cautioned against adding language that may appear to make a claim.

f. Section 16.2, Storage and Handling
Radius proposed text consistent with the FDA revisions to the carton and container labeling. The FDA will review the revised labeling for consistency.

8. Review Plans

The team will continue to finalize reviews.

Discussion:
There was no further discussion.

9. Wrap-up and Action Items

Discussion:
There was no further discussion.

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

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

/s/

THERESA E KEHOE
01/17/2017

From:	Bell, Samantha
To:	Desai, Deepa (Ddesai@radiuspharm.com)
Subject:	NDA 208743 Updated Late Cycle Meeting Background Package
Date:	Friday, December 16, 2016 6:23:00 PM
Attachments:	NDA 208743 Updated Late-Cycle Meeting Background Package.pdf

Dear Ms. Desai,

We updated the attached NDA 208743 Late Cycle Meeting Background Package with additional REMS related text in bold for the December 20 Late Cycle Meeting.

Sincerely,

Samantha Bell

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	December 20**,** 2016, 11:00 A.M. to 12:30 P.M.
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	NDA 208743
Product Name:	Abaloparatide
Indication:	Treatment of postmenopausal women with osteoporosis
Applicant Name:	Radius Health, Inc.

FDA ATTENDEES (tentative)

Division of Bone, Reproductive, and Urologic Products (DBRUP):
Christine Nguyen, M.D., Deputy Director for Safety
Theresa Kehoe, M.D., Clinical Team Leader
Stephen Voss, M.D., Medical Officer
Jacqueline Karp, M.D., Medical Officer
Mukesh Summan, Ph.D., DABT, Pharmacology and Toxicology Supervisor
Gemma Kuijpers, Ph.D., Pharmacology and Toxicology Reviewer
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager
Robin Duer, R.N., B.S.N., M.B.A., Associate Director for Labeling

Office of New Drugs, Office of Drug Evaluation III:
Amy Egan, M.D., M.P.H., Deputy Director
Julie Beitz, M.D., Director

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LaiMing Lee, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology (DCP) III
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Fang Li, Ph.D., Pharmacometrics Reviewer, Division of Pharmacometrics (DPM)
Jeffry Florian, Ph.D., Pharmacometrics Team Leader, DPM

OTS, Office of Biostatistics, Division of Biometrics III:
Jia Guo, Ph.D., Biometrics Reviewer
Sonia Castillo, Ph.D., (Acting) Biometrics Team Leader

Office of Pharmaceutical Quality:
Mark Seggel, Ph.D., Application Technical Lead, Office of New Drug Products (ONDP)
Thao Vu, Regulatory Business Process Manager, ONDP
Hamid Shafiei, Ph.D., Reviewer, ONDP
Krishnakali Ghosh, Ph.D., Reviewer, Office of Process and Facilities (OPF), Division of Inspectional Assessment
Yeissa Chabrier-Rosello, Ph.D., OPF, Division of Microbiology Assessment

Office of Surveillance and Epidemiology (OSE), Immediate Office:
Shawnetta Jackson, Project Manager

OSE, Office of Medication Error Prevention and Risk Management:
CAPT Walter Fava, R.Ph., M.S.Ed., Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Lolita White, Pharm.D, Acting Team Lead, DMEPA
Leah Hart, Pharm.D., (Acting) Team Leader, Division of Risk Management
Jacqueline Sheppard, Pharm.D., Risk Management Specialist, Division of Risk Management

OSE, Office of Pharmacovigilance and Epidemiology:
Jie (Jenni) Li, Ph.D., MBBS, Team Leader, Division of Epidemiology
Neha Gada, PharmD, Team Leader, Division of Pharmacovigilance
Samantha Cotter, Pharm.D., BCPS, FISMP, Safety Evaluator
Monique Falconer, M.D., M.S., Medical Officer, Division of Epidemiology
Peter Waldron, M.D., Medical Officer, Division of Pharmacovigilance

Office of Combination Products:
Patricia Love, M.D., M.B.A., Deputy Director

Center for Devices and Radiological Health (CDRH):
Robert Meyer, B.S., M.E., Reviewer, Office of Device Evaluation, General Hospital, Respiratory, Infection Control, and Dental Devices (DAGRID), General Hospital Devices Branch

Office of Scientific Investigations (OSI)
Roy Blay, Ph.D., Reviewer

Office of Strategic Programs
Azada Hafiz, Operations Research Analyst, Office of Program and Strategic Analysis

EASTERN RESEARCH GROUP ATTENDEES
Peggah Khorrami, Independent Assessor

APPLICANT ATTENDEES
David Hanley, Ph.D., Executive Director, Technical Operations
Gary Hattersley, Ph.D., Chief Scientific Officer

Gregory C. Williams, Ph.D., MBA, Chief Development Officer
Martie Griffin, Head of Corporate Quality
Tristan Hu, Ph.D., Head of Biometrics
Michael Macalush, M.S., Director, Regulatory Affairs
Deepa Desai, Director, Regulatory Affairs – Advertising, Promotion and Labeling
Lorraine Fitzpatrick, M.D., Chief Medical Officer

INTRODUCTION

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

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BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

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device, all information requested on November 22, 2016, should be promptly submitted.

2. We note that you propose an acceptance criterion for the dose accuracy test of 0.04 mL +/- (b) (4) mL for the Ypsomed UnoPen. This is equivalent to +/- (b) (4) Justify why this would not impact the safety or efficacy of the product. We recognize that the single-dose comparative bioavailability data demonstrated bioequivalence. However, these findings may not convey what happens over the duration of use of the multi-use pen device. Part of your justification should include the dose accuracy testing for the Becton Dickinson II pen device used in the clinical fracture trial.

Clinical and Statistical Issues

1. We acknowledge your November 22, 2106, clinical information submission. This information is currently under review.

Division of Medication Error Prevention and Analysis (DMEPA) Issues

1. We acknowledge your intent to conduct a revised Human Factors validation protocol for abaloparatide after revisions to the product's Instructions for Use. Our recommendations regarding the protocol were conveyed in a regulatory letter dated November 8, 2016.

Inspectional Issues

1. The Drug and Device Good Manufacturing Practice (GMP) status of the facilities is under review. Clinical site inspections are ongoing and the status is under review.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

We note the safety concern of osteosarcoma identified in rat studies. Osteosarcoma remains an important potential risk that requires further evaluation. As noted in the Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (March 2005), the quality of the reports is critical for appropriate evaluation of the relationship between the product and adverse events. The FDA recommends that sponsors make a reasonable attempt to obtain complete information for case assessments during initial contacts and subsequent follow-up, especially for serious events, and encourages sponsors to use trained health care practitioners to query reporters. Computer-assisted interview technology, targeted questionnaires, or other methods developed to target events of special interest can help focus the line of questioning.

Based on appropriate scientific data, FDA has determined that enhanced pharmacovigilance may aid to provide additional data to assess the potential risk of osteosarcoma associated with abaloparatide exposure. The goal of enhanced pharmacovigilance is to capture additional descriptive data to further assess cases of osteosarcoma reported with abaloparatide and note risk factors, diagnostic imaging, and other relevant clinical data. We have determined a targeted questionnaire for all spontaneous adverse event reports or reports obtained from other post-marketing surveillance sources suggestive of osteosarcoma is necessary to characterize osteosarcoma. We request that you submit a protocol for review regarding enhanced pharmacovigilance of osteosarcoma and include a targeted questionnaire. Submit this protocol and targeted questionnaire by December 30, 2016.

Include the following elements in your protocol:

- Submit interval and cumulative analyses annually for 15 years from the date of approval.

At this time, based on the information currently available, we do not believe that a REMS will be necessary to ensure the benefits of the drug outweigh the risks.

MAJOR LABELING ISSUES

Refer to the FDA edits to the proposed labeling to be communicated on December 9, 2016. The following are the major labeling issues identified:

1. Many of the FDA edits to the product labeling are to conform with current regulations and labeling practices.

2. Boxed Warning

[redacted] FDA will continue to recommend restriction of the duration of use for abaloparatide and PTH analogs such as teriparatide. This information has been added to the Boxed Warning and other appropriate sections of the labeling.

3. Warnings and Precautions – the following Warnings and Precautions have been added, based on the clinical data and known effects of PTH analogs:
   a. Hypercalciuria
   b. Orthostatic Hypotension

4. Section 6: [redacted]

5. Section 12.1, Mechanism of Action:
   Abaloparatide is a PTHrP(1-34) analog which [redacted] the PTH1 receptor (PTH1R). [redacted] is relevant for the osteoporosis treatment indication.

   The Sponsor's in vitro data showed that, compared to PTH1-34, abaloparatide has similar affinity for the RG conformation but lower affinity for the R0 conformation of the PTH1R. In addition, the residual cAMP response appears to be more transient with abaloparatide than with PTH1-34. However, the relevance of this residual response and the nature of the relationship between cellular cAMP changes and tissue level consequences of PTH1R activation have not been clearly established.

   Data from animal pharmacology studies, Phase 2 Study BA058-05-002 and Phase 3 Study BA058-05-003 showed that abaloparatide increases both bone formation and resorption, albeit to a lesser degree than teriparatide. Also, animal histomorphometry data suggested increases in bone formation and resorption at peri- and/or endosteal bone surfaces.

   Based on our above comments, the conclusion that abaloparatide has [redacted] (proposed in Section 12.1) is not justified and should not be included in the labeling.

6. Section 13.2
   The detailed animal bone pharmacology data have been revised and moved to Section 13.2 of the label.

7. Section 14: Analysis of the primary efficacy endpoint [redacted] (b) (4) was not prespecified. [redacted] (b) (4) The efficacy data presentations have been edited to focus on the prespecified outcomes and to be consistent with the data presentations in the labeling of other osteoporosis therapies.

LCM AGENDA

1. Introductory Comments – 5 minutes (FDA)

    - Welcome, Introductions, Ground rules, Objectives of the meeting
    - This meeting addresses the substantive review issues noted during the primary review of your New Drug Application and will not address a final regulatory decision for the application
    - The intent is to share information and to promote a collaborative and successful discussion of the substantive review issues that have been identified
    - We may discuss additional information that may be needed to address the identified issues, whether it will be reviewed in the current review cycle, and, if so, whether the submission would constitute a major amendment and trigger an extension of the PDUFA goal date. However, it may not be possible to reach final agreement on the review of additional information or the possibility of an extension of the PDUFA goal date at this meeting
    - We may not be prepared to discuss some of the recent information submitted in response to our information requests

2. Discussion of Substantive Review Issues – 15 minutes

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

    Please refer to the brief memorandum section above for FDA's assessment of each issue

    a. Chemistry, Manufacturing, and Controls (CMC)
    b. Device
    c. Clinical and Statistical
    d. Division of Medication Error Prevention and Analysis (DMEPA)

3. Additional Applicant Data – 5 minutes (Applicant)

4. Information Requests – 5 minutes

5. REMS or Other Risk Management Actions – 10 minutes

    a. Enhanced Pharmacovigilance for osteosarcoma

        We request that you submit a protocol for review regarding enhanced pharmacovigilance of osteosarcoma and include a targeted questionnaire. Submit this protocol and targeted questionnaire by December 30, 2016.

Include the following elements in your protocol:

(b) (4)

- Submit interval and cumulative analyses annually for 15 years from the date of approval. (b) (4)

(b) (4)

b. REMS
Not required

6. Postmarketing Requirements/Postmarketing Commitments

   No Postmarketing Requirements or Commitments have been identified at this time

7. Major labeling issues – 30 minutes

8. Review Plans – 5 minutes

   The team will continue to finalize reviews.

9. Wrap-up and Action Items – 15 minutes

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
12/16/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208743

LATE CYCLE MEETING
BACKGROUND PACKAGE

Radius Health, Inc.
Attention: Deepa Desai, M.S.
Director, Regulatory Affairs
950 Winter Street
Waltham, MA 02451

Dear Ms. Desai:

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

We also refer to the Late-Cycle Meeting (LCM) scheduled for December 20, 2016.

Attached is our background package, including our agenda, for this meeting.

Please email a list of your attendees to samantha.bell@fda.hhs.gov at least one week prior to the meeting.

If you have any questions, call Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: December 20**,** 2016, 11:00 A.M. to 12:30 P.M.
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: NDA 208743
Product Name: Abaloparatide
Indication: Treatment of postmenopausal women with osteoporosis
Applicant Name: Radius Health, Inc.

FDA ATTENDEES (tentative)

Division of Bone, Reproductive, and Urologic Products (DBRUP):
Christine Nguyen, M.D., Deputy Director for Safety
Theresa Kehoe, M.D., Clinical Team Leader
Stephen Voss, M.D., Medical Officer
Jacqueline Karp, M.D., Medical Officer
Mukesh Summan, Ph.D., DABT, Pharmacology and Toxicology Supervisor
Gemma Kuijpers, Ph.D., Pharmacology and Toxicology Reviewer
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager
Robin Duer, R.N., B.S.N., M.B.A., Associate Director for Labeling

Office of New Drugs, Office of Drug Evaluation III:
Amy Egan, M.D., M.P.H., Deputy Director
Julie Beitz, M.D., Director

Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP):
LaiMing Lee, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology (DCP) III
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP III
Fang Li, Ph.D., Pharmacometrics Reviewer, Division of Pharmacometrics (DPM)
Jeffry Florian, Ph.D., Pharmacometrics Team Leader, DPM

OTS, Office of Biostatistics, Division of Biometrics III:
Jia Guo, Ph.D., Biometrics Reviewer
Sonia Castillo, Ph.D., (Acting) Biometrics Team Leader

Office of Pharmaceutical Quality:
Mark Seggel, Ph.D., Application Technical Lead, Office of New Drug Products (ONDP)
Thao Vu, Regulatory Business Process Manager, ONDP
Hamid Shafiei, Ph.D., Reviewer, ONDP
Krishnakali Ghosh, Ph.D., Reviewer, Office of Process and Facilities (OPF), Division of Inspectional Assessment
Yeissa Chabrier-Rosello, Ph.D., OPF, Division of Microbiology Assessment

Office of Surveillance and Epidemiology (OSE), Immediate Office:
Shawnetta Jackson, Project Manager

OSE, Office of Medication Error Prevention and Risk Management:
CAPT Walter Fava, R.Ph., M.S.Ed., Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Lolita White, Pharm.D, Acting Team Lead, DMEPA
Leah Hart, Pharm.D., (Acting) Team Leader, Division of Risk Management
Jacqueline Sheppard, Pharm.D., Risk Management Specialist, Division of Risk Management

OSE, Office of Pharmacovigilance and Epidemiology:
Jie (Jenni) Li, Ph.D., MBBS, Team Leader, Division of Epidemiology
Neha Gada, PharmD, Team Leader, Division of Pharmacovigilance
Samantha Cotter, Pharm.D., BCPS, FISMP, Safety Evaluator
Monique Falconer, M.D., M.S., Medical Officer, Division of Epidemiology
Peter Waldron, M.D., Medical Officer, Division of Pharmacovigilance

Office of Combination Products:
Patricia Love, M.D., M.B.A., Deputy Director

Center for Devices and Radiological Health (CDRH):
Robert Meyer, B.S., M.E., Reviewer, Office of Device Evaluation, General Hospital, Respiratory, Infection Control, and Dental Devices (DAGRID), General Hospital Devices Branch

Office of Scientific Investigations (OSI)
Roy Blay, Ph.D., Reviewer

Office of Strategic Programs
Azada Hafiz, Operations Research Analyst, Office of Program and Strategic Analysis

EASTERN RESEARCH GROUP ATTENDEES
Peggah Khorrami, Independent Assessor

APPLICANT ATTENDEES
David Hanley, Ph.D., Executive Director, Technical Operations
Gary Hattersley, Ph.D., Chief Scientific Officer
Gregory C. Williams, Ph.D., MBA, Chief Development Officer
Martie Griffin, Head of Corporate Quality
Tristan Hu, Ph.D., Head of Biometrics
Michael Macalush, M.S., Director, Regulatory Affairs
Deepa Desai, Director, Regulatory Affairs – Advertising, Promotion and Labeling
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- Review by a medically qualified person as single case reports and as part of the aggregate data analysis for cases of osteosarcoma.

- Perform targeted surveillance with the use of a guided collection form to obtain salient additional clinical information related to osteosarcoma.

- Submit interval and cumulative analyses annually for 15 years from the date of approval. Reports may originate from, but are not limited to, spontaneous reports from healthcare providers and patients, post-marketing surveillance, surveillance of the FDA FAERS database, and literature sources.

- Assess, summarize, and identify potential risk factors for osteosarcoma for all post-marketing data sources. A summary of the assessments and analyses shall be presented annually in the periodic adverse drug experience report (PADER).

- Include the MedDRA search strategy for retrieving cases of osteosarcoma

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8. Review Plans – 5 minutes

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

/s/

HYLTON V JOFFE
12/08/2016