

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217639Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

IND 124748

MEETING MINUTES

Radius Pharmaceuticals, Inc.
Attention: Carol S. Marchione
550 E. Swedesford Road, 3rd Floor
Wayne, PA 19087

Dear Ms. Marchione:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for elacestrant (RAD1901).

We also refer to the telecon between representatives of your firm and the FDA on February 2, 2022. The purpose of the meeting was to discuss clinical, biopharmaceutics, clinical pharmacology, and regulatory items prior to the submission of your planned NDA for elacestrant.

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

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

If you have any questions, call Sherry Hou, Regulatory Project Manager,
at 240-402-1813

Sincerely,

{See appended electronic signature page}

Sherry Hou, PharmD
Regulatory Project Manager
Oncology 1 Group
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

See appended electronic signature page}

Christy Osgood, MD
Clinical Team Lead
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: February 2, 2022, from 2:00 – 3:00 PM EST
Meeting Location: Teleconference

Application Number: IND 124748
Product Name: elacestrant (RAD1901)

Indication: Treatment of postmenopausal women, and men, with
(b) (4) -positive, human epidermal growth
factor receptor 2 -negative (HER-), advanced or metastatic
breast cancer who have progressed following at least 1 line
of endocrine therapy, (b) (4)

Sponsor Name: Radius Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Christy Osgood, MD
Meeting Recorder: Jeannette Dinin, MS

FDA ATTENDEES

Laleh Amiri-Kordestani, MD, Director, DO1
Christy Osgood, MD, Clinical Team Leader, DO1
Preeti Narayan, MD, Clinical Reviewer, DO1
Melanie Royce, MD, Clinical Reviewer, DO1
Danielle Krol, MD, Clinical Reviewer, DO1
Asma Dilawari, MD, Clinical Reviewer, DO1
Mirat Shah, MD, Clinical Reviewer, DO1
Mallorie Fiero, PhD, Biostatistics Team Leader, OTS/OB/DBV
Ting-Yu Chen, PhD, Biostatistics Reviewer, OTS/OB/DBV
Jianjin Xu, PhD, Biostatistics Reviewer, OTS/OB/DBV
Tiffany Ricks, PhD, Pharmacology Toxicology Supervisor, DHOT
Wimolnut Manheng, PhD, Pharmacology Toxicology Reviewer, DHOT
Salaheldin Hamed, PhD, Acting Clinical Pharmacology Team Leader,
OTS/OCP/DCPI
George Shen, PhD, Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Qi Zhang, PhD, Biopharmaceutics Assessor, OPQ/ONDP/DB/BB1

Mei Ou, PhD, Biopharmaceutics Team Leader, OPQ/ONDP/DB/BB1
Xing Wang, PhD, Senior Pharmaceutical Quality Assessor, OPQ/ONDP/DNDPI
Soumen Roy, PhD, Scientific Reviewer, MPCB/DMGP/OHT7/CDRH
Pamela Balcazar, MS, Health Scientist, OCE
Jeannette Dinin, MS, Regulatory Project Manager, DRO – OD
Felicia M. Diggs, RN, BSN, MSN, Regulatory Project Manager, DRO – OD
Sherry Hou, PharmD, Regulatory Project Manager, DRO – OD

SPONSOR ATTENDEES

Radius

Betsy Crisman, Project and Alliance Management

(b) (4)

Carol Marchione, Regulatory Affairs Lead

(b) (4)

Frank Perabo, MD, PhD, Medical Lead

Chhaya Shah, Chief Business Officer

Representatives from Menarini-Stemline

Madhu Anant, PhD, SVP Regulatory Affairs and Pharmacovigilance, Menarini-Stemline

Elcin Barker Ergun, BSc, MBA, CEO, Menarini Group

Ivan Burstein, MD, CEO, Stemline

Kris Grzegorzewski, MD, SVP Clinical Development & Medical Affairs, Menarini-Stemline

Nassir Habboubi, MD, Chief Medical Officer, Menarini-Stemline

Giulia Tonini, PhD, Global Biostatistical Science Manager, Menarini-Stemline

Invited Clinical Experts

(b) (4)

1.0 BACKGROUND

Radius Pharmaceuticals, Inc. (Radius) requested a Type B pre-NDA meeting to obtain feedback from the FDA on the planned NDA submission for elacestrant (RAD1901) targeted for second quarter 2022 for the following proposed indication:

Elacestrant is indicated for the treatment of postmenopausal women, and men, with (b) (4)-positive, human epidermal growth factor receptor 2 -negative (HER-), advanced or metastatic breast cancer who have progressed following at least 1 line of endocrine therapy, (b) (4)

Elacestrant is an orally bioavailable selective estrogen receptor degrader (SERD). A content and format pre-NDA WRO only meeting occurred in July of 2021. The proposed NDA submission will be based on data from the phase 3 RAD1901-308 study. Results from studies RAD1901-005 and RAD1901-106 will be submitted as supportive data. RAD1901-005 is a dose escalation study in metastatic breast cancer (mBC) and RAD1901-106 is a pharmacodynamic study; both studies were described in the prior meeting minutes. The Sponsor requested Real Time Oncology Review (RTOR) for the NDA submission which was declined by the FDA.

Study RAD1901-308

Study RAD1901-308 is an ongoing phase 3, randomized (1:1) study comparing elacestrant 400 mg oral daily vs. either fulvestrant or an aromatase inhibitor (AI; anastrozole, letrozole, or exemestane) in 478 men and postmenopausal women with ER-positive/HER2-negative metastatic breast cancer (mBC). The primary endpoints are progression free survival (PFS) by independent review committee (IRC) in patients with tumors with *ESR1-mut* and PFS in the intent to treat (ITT) population. Key secondary endpoints include overall survival (OS) in the *ESR1-mut* and OS in the ITT population. The study enrolled patients with ER-positive, HER2-negative advanced or metastatic breast cancer who must have previously received at least 1 and no more than 2 lines of endocrine therapy (either as monotherapy or in combination with CDK 4/6 inhibitor or PI3K inhibitor) in the metastatic setting, progressed during or within 28 days of prior treatment with a CDK 4/6 inhibitor in combination with either fulvestrant or an AI, and ECOG 0-1.

The trial met the prespecified primary endpoint in both the *ESR1-mut* population as well as the ITT population. The median PFS in the ITT population was 2.79 months in the elacestrant arm and 1.91 months in the control arm with a hazard ratio (HR) of 0.70 (95% CI: 0.55, 0.88) $p=0.0018$. In the *ESR1-mut* population the median PFS was 3.78 months in the elacestrant arm and 1.87 months in the control arm with HR 0.55 (95% CI: 0.39, 0.77) $p=0.0005$. At the time of final PFS analysis, a prespecified interim OS was performed and was not statistically significant for either the ITT or *ESR1-mut* populations. The median OS was not reached in either arm; however, both HR were less than 1 favoring elacestrant [ITT HR=0.751 (95% CI:0.542, 1.038); *ESR1-mut* HR=0.592 95% CI:0.361,0.958]. The final OS analysis is currently projected for late 2022 to early 2023 when 50% of subjects are expected to have experienced an OS event. An alpha level of 0.0499 will be used for the final analysis.

Treatment emergent adverse events (TEAEs) regardless of attribution were reported in 92% of patients receiving elacestrant vs. 86% on the control arm. Grade 3-4 TEAEs were 27% in the elacestrant arm vs. 21% in the control arm. Deaths were reported as 1.7% on the elacestrant arm vs. 2.6% on the control arm. The most common treatment related TEAEs $\geq 1\%$ reported for elacestrant were nausea, vomiting, diarrhea, dyspepsia, constipation, anemia, and lymphocyte count decreased. Treatment

related eye disorders (eye irritation and blurred vision) were reported in 0.8% of patients on elacestrant. Safety results are reported to be similar overall in the *ESR1-mut* population.

The FDA sent Preliminary Comments to Radius Pharmaceuticals, Inc. on January 20, 2022.

2.0 DISCUSSION

Question 1: Does the Agency agree that the efficacy and safety results from the elacestrant study (Study RAD1901-308) are adequate to support elacestrant for the following proposed indication?

FDA Response to Question 1: The observed median PFS benefit for the ITT population is only 0.88 months which is shorter than the imaging interval of 8 weeks and will be a review issue. A risk benefit assessment will be made for the proposed indication as well as for all the prespecified subgroups during the review and will be part of the overall risk benefit assessment for elacestrant and to ensure results are not driven by a particular subgroup. Please provide topline PFS and OS results, including Kaplan-Meier Curves, for the ESR1 not mutated group prior to our scheduled meeting on February 2, 2022.

The acceptability of the proposed indication and whether the efficacy and safety results represent an overall favorable risk benefit assessment will be a review issue.

Sponsor's Response to Question 1: For clarity, we have divided our response into subsections as presented below.

1.1) Evaluation of FDA's Observation of Magnitude of the PFS Benefit

Please clarify the Agency's perspective regarding, "The observed median PFS benefit for the ITT population is only 0.88 months which is shorter than the imaging interval of 8 weeks and will be a review issue." We would like to point out that the observed median benefit comes from differences in treatment group level medians, whereas the imaging interval is at the patient-level. As such, the median PFS is a summary statistic based on a single point (i.e., 50th percentile) of the distribution of PFS and does not consider the entire distribution. We suggest that the inspection of quantiles and summaries at specific time points, namely the pre-specified PFS points in the protocol agreed with FDA that can provide a fuller picture of the between group differences. In addition, we suggest consideration of the hazard ratio, which summarizes the average clinical benefit throughout the entire study, does not rely on a single point of the distribution curves and accounts for the stratification used at the time of randomization.

Meeting Discussion: The FDA acknowledged the delayed separation of the PFS curves and stated that the FDA would evaluate the entire distribution of PFS curves statistically (e.g., HR, log-rank test) and may perform additional exploratory analyses to support the primary endpoint. In addition, the FDA generally evaluates median PFS, as well as other landmark time points, to aid in interpretation of clinical meaningfulness. In general, the FDA does not include landmark time points in labeling.

Sponsor's Response to Question 1: For clarity, we have divided our response into subsections as presented below.

1.2) Data for Subjects in the ESR1 Non-Detected (nd) - PFS and OS Table and Figures and Safety Comparisons

All the tables and figures associated with this response are provided in the Appendix.

Meeting Discussion: The FDA thanked Radius for providing the requested data. The FDA acknowledged that PFS in the ESR1 Non-Detected group was not a pre specified endpoint; however, the FDA does still evaluate subgroups for consistency of effect as well as to ensure there is not a population with an unfavorable risk benefit assessment.

Sponsor's Response to Question 1: For clarity, we have divided our response into subsections as presented below.

1.3) Sponsor's Evaluation of the Benefit of Elacestrant for the Subjects in the ESR1 nd Group

In the All subjects group, the analysis of the primary endpoint, PFS, shows statistically significant and clinically meaningful improvement in subjects in the elacestrant group compared to the SOC group ($p=0.0018$, stratified log-rank test), with an HR of 0.70 (95% CI: 0.552 - 0.880) favoring subjects on elacestrant over subjects treated with SOC. The median PFS is 2.79 months for elacestrant and 1.91 months for SOC group. A forest plot of PFS of All subjects comparing the elacestrant and SOC groups shows this benefit is consistent across the prespecified subgroups, with most subgroups showing statistical significance for elacestrant versus SOC.

The ESR1 mutation group shows statistically significant improvement on PFS in the elacestrant subjects group compared to the SOC group ($p = 0.0005$, stratified log-rank test) with an HR of 0.55 95% CI: 0.38 - 0.77. The median PFS is 3.78 months in the elacestrant group versus 1.87 months in the SOC group, a clinically meaningful difference of 1.91 months. The forest plot of PFS of the ESR1 mutation group comparing the elacestrant and SOC groups shows a consistent pattern of benefit across

the prespecified subgroups with a statistically significant treatment difference among most subgroups.

The analysis of ESR1 nd group shows the difference between elacestrant and SOC is not statistically different at $\alpha=0.05$ ($p=.31$, stratified log-rank test) with an HR of 0.86 (95% CI: 0.62 - 1.19). The median PFS is 1.94 months in the elacestrant group versus 1.97 months in the SOC group; note that, the study, however, was not powered to show a difference in the ESR1-nd patients.

Results of descriptive analyses of the ESR1-nd analyses are not sufficient to rule out a difference in the ESR1-nd group. Inspection of the Kaplan Meier curve suggests the PFS pattern in this group of patients is consistent with the pattern observed in the All and the ESR1-mut patients: An early drop in PFS followed by a sustained separation of the curves favoring elacestrant, plus the maximum follow-up for elacestrant exceeds that for SOC. It is also noted that the 75th percentile for PFS is greater for elacestrant than SOC (7.29 vs 5.55).

OS, the key secondary endpoint, was analyzed at the time of the final PFS analysis (i.e., interim analysis for OS) and will be analyzed again when 50% of the subjects have died. The interim analysis of OS was not statistically significant when the analysis was adjusted for the interim look of OS (All, $p = 0.0821$, stratified log-rank test; ESR1-mut, $p = 0.0325$, stratified log-rank test; ESR1-mut-nd, $p = 0.6913$, stratified log rank test); the p-values were compared with 0.0001. The estimates of the HRs are <1 and, therefore, favor subjects randomized to elacestrant compared to those randomized to SOC (All, 0.751; ESR1-mut, 0.592; ESR1-mut-nd, 0.915). The final OS analysis using an alpha level of 0.0499 is currently projected for late 2022 to early 2023. At the time of the OS interim analysis, there were 149 OS events. Based on a conditional power determination, the expected power for the final OS analysis is 65.6% for the ALL patient population and 90.4% for the ESR1-mut patient population. In addition, conditional simulations yielded similar results 68.8% for the ALL patient population and 90.7% for ESR1-mut patient population; details of the simulations can be found in the Back-up Slides from the meeting presentation.

Meeting Discussion: The FDA acknowledged Radius's response and stated that review of the efficacy and safety of elacestrant for the ESR1 mutation not detected population will be a review issue.

Sponsor's Response to Question 1: For clarity, we have divided our response into subsections as presented below.

1.4) Sponsor's Evaluation of the Safety of Elacestrant

The main difference of treatment-related TEAEs between the treatment groups in All subjects is primarily driven by TEAEs of gastrointestinal disorders (elacestrant, 43.0%; SOC, 12.7%) and metabolism and nutritional disorders (elacestrant, 8.0%; SOC, 3.1%).

In the subjects with the ESR1 mutation, a higher percentage of elacestrant-treated subjects reported at least 1 TEAE or experienced a treatment-related TEAE during the study compared to subjects treated with SOC. This difference in the overall percentage of TEAEs between the treatment groups in subjects with the ESR1 mutation is primarily driven by TEAEs of gastrointestinal disorders (elacestrant: 40.9%; SOC: 17.0%) and metabolism and nutritional disorders (elacestrant: 10.4%; SOC: 2.8%), which were mostly Grade 1 and 2.

In the subjects with the ESR1 nd, similarly a higher percentage of elacestrant-treated subjects reported at least 1 TEAE or experienced a treatment-related TEAE during the study compared to subjects treated with SOC. This difference in the overall percentage of TEAEs between the treatment groups in subjects with the ESR1 nd is predominantly driven by TEAEs of gastrointestinal disorders (elacestrant, 45.1%; SOC, 8.9%), which were mostly Grade 1 and 2.

Overall, the percentages of subjects in both treatment groups who reported a CTCAE Grade 3 or Grade 4 treatment-related TEAE are comparable. In all subjects a numerically larger percentage of elacestrant-treated subjects reported at least 1 TEAE or experienced a treatment-related TEAE during the study compared to subjects treated with SOC (elacestrant: 7.2%, SOC: 3.1%). TEAEs leading to treatment discontinuations were 3.4% in elacestrant arm vs 0.9% in SOC.

The incidence of SAEs is 12% for the elacestrant group and 11% for the SOC group. These percentages are similar among All, ESR1-mut and ESR1-nd subjects.

The safety and tolerability profile among the three elacestrant populations are comparable.

Meeting Discussion: The FDA acknowledged Radius response about the TEAE adverse event and reminded Radius that an NDA submission should include all AEs regardless of attribution in addition to any treatment-related AEs. Draft labeling should also include the incidence of all AEs, not just those believed to be treatment related.

The FDA stated that given the increased GI toxicity of elacestrant which may result in decreased compliance, Radius should submit information about compliance of elacestrant.

Post Meeting Comment: Draft labeling should include the incidence of all adverse reactions that occurred in >5% of patients in either arm regardless of assessed causality.

Sponsor's Response to Question 1: For clarity, we have divided our response into subsections as presented below.

1.5) Overall Risk Benefit Profile of Elacestrant

The statistical and clinically meaningful improvement in PFS is shown for the primary pre-specified hypotheses in All patients and in patients with ESR1 mutation. In addition, the safety profile in All subjects, subjects with ESR1 mutation or ESR1-nd are generally comparable with a similar prevalence in treatment-related TEAE between groups. The majority of TEAEs of gastrointestinal disorders were of Grade 1 or 2, and can be appropriately managed by standard clinical practice, and did not lead to higher rates of discontinuation from study drug across groups.

Elacestrant demonstrates a well-established benefit/risk profile over SOC for the prespecified subgroups.

Meeting Discussion: Radius stated that if their event driven final OS analysis occurs during the review cycle it will be provided to the FDA. Radius will submit top level percentage of deaths in each treatment arm at the 120-day safety update.

Question 2: Following the database lock for Study RAD1901-308, it was identified that the ESR1 mutation status for subject (b) (6) should have been 'ESR1 not detected.' Due to an IRT/EDC error, this patient was initially included in the ESR1 mutation subgroup. For the primary and key secondary efficacy analyses, Radius proposes to retain the ESR1 status of the subject 'as-randomized' and conduct a sensitivity analysis excluding this patient for both endpoints. Does the Agency concur?

FDA Response to Question 2: Yes, your analysis plan for subject (b) (6) is acceptable. Please make sure to include flags for this patient in the datasets you submit.

Sponsor's Response to Question 2: The Sponsor has no additional comments.

Meeting Discussion: No discussion took place.

Question 3: Based on the positive bioequivalence data demonstrating equivalence between the clinical and proposed commercial drug product batches, the Sponsor is agreeing to a dissolution specification of $Q = \frac{(b)}{(4)}\%$ at 30 minutes for elacestrant dihydrochloride tablet products. Does the Agency concur with this request?

FDA Response to Question 3: The adequacy of the proposed dissolution acceptance criterion will be determined during the NDA review based on the totality of the provided dissolution data. In addition, before assessing the proposed dissolution acceptance criterion, the proposed dissolution method needs to be evaluated and approved by us. If you prefer that before your NDA submission, we provide a recommendation on the adequacy of the dissolution method, submit a dissolution method development report with complete information/data as described in the pre-NDA meeting minutes dated August 12, 2021, under an Amendment to your IND. In the cover letter of the amendment, include a statement that feedback from the Division of Biopharmaceutics is requested and notify the OPQ Regulatory Business Project Manager of the amendment submission for timely review. Note that in general it takes 3 months to provide feedback.

Sponsor Response to Question 3: Due to the timing to obtain Agency feedback, the Sponsor will provide all of the required information in the NDA.

Meeting Discussion: No discussion took place.

Question 4: Does the Agency concur that based upon the Study RAD1901-308 results, elacestrant provides significant improvement over the SOC for the treatment of postmenopausal women, and men, with (b) (4) positive, HER2-, advanced or metastatic breast cancer who have progressed following at least 1 line of endocrine therapy, (b) (4) therefore, the forthcoming NDA would be eligible for a Priority Review designation?

FDA Response to Question 4: A decision about priority review will be made at the time of filing.

Sponsor's Response to Question 4: The Sponsor has no additional comments.

Meeting Discussion: No discussion took place.

Question 5: Based on the application of the salt policy, in the Pre-NDA CMC Meeting Minutes, the Agency requested a discussion at a Type B meeting regarding the dosing instructions in the labeling due to dose reductions by 86 mg increments in correlation to the 345 mg tablet. To provide clarity to the prescriber, does the Agency agree with the proposed text in the Dose Administration section of labeling?

FDA Response to Question 5: Yes. However, we may request additional information or make edits during review of the NDA.

Sponsor's Response to Question 5: The Sponsor has no additional comments.

Meeting Discussion: No discussion took place.

Question 6: The elacestrant NDA will include a cross-reference letter to Guardant Health Inc.'s supplemental pre-Market Application for their companion diagnostic, 360 CDX (PMA P200010B/005) concurrently with the Radius submission of the elacestrant NDA. No other information regarding the companion diagnostic will be incorporated into the NDA, with the exception of the text in the prescribing information. Does the Agency find this proposal acceptable?

FDA Response to Question 6: Yes, we agree that the NDA should include a letter of authorization allowing CDER to cross-reference the PMA supplement submission from Guardant Health, Inc. for the Guardant360 CDx test. The PMA supplement submission should also include a letter of authorization to allow CDRH to cross-reference the NDA submission.

Sponsor's Response to Question 6: The Sponsor has no additional comments.

Meeting Discussion: No discussion took place.

Question 7: Guardant and Radius are planning to submit their registration applications concurrently to Center for Devices and Radiological Health (CDRH) and CDER, respectively. Are there any specific interactions required by the sponsors to request the Centers to coordinate the reviews in the effort to support simultaneous action?

FDA Response to Question 7: In general, it is expected that the diagnostic Sponsor should submit the PMA supplement to CDRH within 30 days of the corresponding NDA submission. However, the diagnostic Sponsor may also consider submitting a modular PMA submission where the PMA analytical module can be submitted ahead of time to allow CDRH adequate time to review the analytical performance studies prior to submission of the clinical module and the full PMA. A PMA shell should be submitted by the Sponsor for acceptance by CDRH if the diagnostic Sponsor chooses to follow the modular PMA route.

Refer to the following guidance document for additional details,
<https://www.fda.gov/media/73513/download>.

Sponsor's Response to Question 7: The Sponsor has no additional comments.

Meeting Discussion: No discussion took place.

Question 8: Does the Agency agree with the proposal for the 4-month Safety Update submission?

FDA Response to Question 8: No. The safety update should include an updated SCS, ISS and datasets, not a notification letter regardless of whether a significant safety event was noted.

Sponsor's Response to Question 8: The Sponsor will submit the safety update in accordance with the Agency's requirements.

Meeting Discussion: No discussion took place.

Question 9: Does the Agency agree with the proposal for submission of documentation to the NDA for all investigators who participated in Study RAD1901-308, regardless if they were submitted under the IND or not?

FDA Response to Question 9: Yes, this is acceptable. As noted, you should clearly note which specific investigators were not submitted to the IND.

Sponsor's Response to Question 9: The Sponsor has no additional comments.

Meeting Discussion: No discussion took place.

Question 10: The sponsor is requesting to submit an Assessment Aid to facilitate the review of the NDA. Does the Agency concur?

FDA Response to Question 10: Yes. The Assessment Aid should include all multidisciplinary information needed for review of the new molecular entity. Data and analysis should be what is most relevant to the intended indication. The Assessment Aid should be submitted at the time of NDA submission or at latest within 30 days of submission. An Assessment Aid should include statistical section(s) describing sample size calculation, interim analyses, control of Type-I error rate, pre-specified statistical analysis methods, and other statistical aspects. Also, subgroup analysis results for the primary endpoint(s) should be included in the Assessment Aid. In general, results from exploratory endpoint analyses should be kept to a minimum in the Assessment Aid.

The FDA Regulatory Project Manager will send a template for the Assessment Aid with instructions.

Sponsor's Response to Question 10: The Sponsor appreciates the Agency's feedback. Upon review of the requirements, compilation of the Assessment Aid would delay the submission of the NDA so we decided not to submit.

Meeting Discussion: The FDA acknowledged the Sponsor's response but did note that an Assessment Aid does help facilitate the FDA's review.

Question 11: Does the Agency agree that the full waiver for all pediatric studies granted to Radius for elacestrant treatment for metastatic breast cancer fulfill PREA requirements?

FDA Response to Question 11: Yes, we agree that a request for waiver of a pediatric assessment of elacestrant in (b) (4) HER2- breast cancer across all age

groups is appropriate since studies would be impossible or highly impracticable given the prevalence of the disease in children. In addition, since the molecular target of elacestrant is on the FDA's Non-relevant Target List leading to Waivers, the amended PREA requirements by FDARA can be similarly waived.

Sponsor's Response to Question 11: The Sponsor has no additional comments.

Meeting Discussion: No discussion took place.

Additional Clinical/Statistical Comments:

1. Please confirm that the proposed NDA will contain a define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of IRC determined PFS (or investigator assessed PFS) event or censoring and variables for subgroup analyses, etc. Variables used for sensitivity analysis of the SAP should be included as well.

Sponsor Response: The Sponsor confirms that the NDA will contain the define file and requested variables.

Meeting Discussion: No discussion took place.

2. Please include in your submission: (a) SAS programs that produced all efficacy results reported in the CSR Section Efficacy Evaluation, (b) all raw as well as derived variables in .xpt format, (c) SAS programs by which the derived variables were produced from the raw variables, and (d) results of any interim analysis if ever performed.

Sponsor's Response: The Sponsor confirms that the NDA will contain the requested information.

Meeting Discussion: No discussion took place.

3. The NDA should include all AEs reported in both arms regardless of attribution in datasets and in all documentation including draft labeling as assessment of treatment related AEs vary between investigators.

Sponsor's Response: The Sponsor confirms that the NDA will contain the requested information.

Meeting Discussion: No discussion took place.

Additional CDRH Comments:

1. In the device submission the following information should be included in the Device Master File (DMF) submitted to CDRH: Patient ID (based on Intent-To-Treat drug primary efficacy population), Guardant360 CDx result, variant allele frequency (VAF) (if known), tissue clinical trial assay result and VAF (if known), and treatment response.
2. Based on the information provided in the meeting materials, it appears that patients were randomized based on ESR1 mutational status from a plasma-based test (IUO/Guardant 360 CDx) performed during the screening period. In prior communication with the diagnostic Sponsor via pre-submission, CDRH requested information on whether the trial protocol includes collecting tissue samples from metastatic sites concurrently with the blood collection. This information was requested as the assessment of ESR1 resistance mutation status in both sample types will shed light on the concordance between the mutations between tissue and plasma and the shedding rate in the resistance setting. This information should be submitted in the device application.

Sponsor's Response: The Sponsor will provide this request to the Sponsor of the sPMA.

Meeting Discussion: No discussion took place.

Additional Clinical Pharmacology Comments:

1. The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with the FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format" (available at: <https://www.fda.gov/media/74346/download>). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.
2. Address the following questions in the Summary of Clinical Pharmacology:
 - a. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
 - b. What are the exposure-response relationships for efficacy, safety and biomarkers?

- c. What is the effect of elacestrant on the QT/QTc interval?
 - d. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
 - e. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
 - f. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?
- 3. Apply the following advice in preparing the clinical pharmacology sections of the original submission:
 - a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
 - b. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean $\pm$ standard deviation) and median with minimum and maximum values as appropriate.
 - c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
 - i. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - ii. Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.
 - d. Submit the following for the population pharmacokinetic analysis reports:
 - i. Standard model diagnostic plots.

- ii. Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.
- iii. Model parameter names and units in tables.
- iv. Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.

- e. Submit the following information and data to support the population pharmacokinetic analysis:
 - SAS transport files (*.xpt) for all datasets used for model development and validation.
 - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- f. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population. Refer to Guidance for Industry for [population PK](#), [exposure-response relationships](#), and [pharmacometric data and models submission guidelines](#).
- g. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.

- U.S. Food and Drug Administration**
Silver Spring, MD 20993
www.fda.gov

- ii. Serious adverse events.
 - iii. Episodes of ventricular tachycardia or fibrillation.
 - iv. Episodes of syncope.
 - v. Episodes of seizure.
 - vi. Adverse events resulting in the subject discontinuing from the study.
- k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com).
- l. A completed Highlights of Clinical Pharmacology Table.
5. Advancing in this field – and possibly reducing the burden of conducting QT studies –depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at <http://cardiac-safety.org/ecg-database/>.

Sponsor's Response: The Sponsor acknowledges receipt of these comments and will address the applicable items in the NDA.

Meeting Discussion: No discussion took place.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

new active ingredients (which includes new salts and new fixed combinations), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that the FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with the FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) 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 iPSP 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 iPSP, including an iPSP 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*.

For the latest version of the molecular target list, please refer to [FDA.gov](https://www.fda.gov).²

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

FDARA REQUIREMENTS

The Sponsors planning to submit original applications on or after August 18, 2020, or the Sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the Sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review Division with the cover letter clearly stating, "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package to be submitted at the same time as the meeting request. The Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.³

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 Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ websites, which include:

- 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.

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

- 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.
- The FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information, please visit FDA.gov.⁶

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.⁷

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from the FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the

⁶ <http://www.fda.gov/ectd>

⁷ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

message. To receive email communications from the FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with the FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁸ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁹. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.¹⁰

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate the FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review Division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs,

⁸ <https://www.fda.gov/media/84223/download>

⁹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

¹⁰ <https://www.fda.gov/media/85061/download>

including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR¹¹: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid¹²

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The power point presentation and appendix have that were used for this meeting discussion are attached.

58 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

¹¹ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

¹² <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERRY C HOU
02/10/2022 11:05:46 AM

CHRISTY L OSGOOD
02/10/2022 11:15:00 AM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 124748

MEETING MINUTES

Radius Pharmaceuticals, Inc.
Attention: Deepa Desai, MS
Director Regulatory Affairs
950 Winter Street
Waltham, MA 02451

Dear Ms. Desai:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RAD1901.

We also refer to the meeting between representatives of your firm and the FDA on June 15, 2018. The purpose of the meeting was to seek the Agency's feedback on a single, randomized comparative trial to support registration of elacestrant for the proposed indication of the treatment of metastatic breast cancer.

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 Sherry Hou, PharmD, Regulatory Project Manager, at (240) 402-1813.

Sincerely,

{See appended electronic signature page}

{See appended electronic signature page}

Sherry Hou, PharmD
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Laleh Amiri-Kordestani, MD
Acting Supervisory Associate Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
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: End-of-Phase 2

Meeting Date and Time: June 15, 2018; 2:30 – 3:30 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Application Number: IND 124748
Product Name: RAD1901

Indication: Treatment of metastatic breast cancer
Sponsor/Applicant Name: Radius Pharmaceuticals, Inc.

Meeting Chair: Laleh Amiri-Kordestani, MD
Meeting Recorder: Sherry Hou, PharmD

FDA ATTENDEES

Julia Beaver, MD, Director, Division of Oncology Products 1 (DOP1)
Laleh Amiri-Kordestani, MD, Associate Director (Acting), DOP1
Lynn Howie, MD, Clinical Reviewer, DOP1
Stella Karuri, PhD, Biometrics Reviewer, DBV
Sherry Hou, PharmD, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Gary Hattersley, PhD, Sr. VP, Chief Scientific Officer
Alison O'Neill, MD, VP, Clinical Development, Oncology
Lenore von Krusenstiern, MD, Sr. Medical Director, Oncology
Bruce Mitlak, MD, VP, Clinical Development
Hai Jiang, PhD, Sr. Director, Biostatistics
Deepa Desai, MS, Director, Regulatory Affairs
Cynthia Dinella, PharmD, Consultant to Radius, Regulatory Affairs
Aditya Bardia, MD, MPH, Key Opinion Leader (Clinical)

1.0 BACKGROUND

The sponsor requests a Type B meeting to discuss their response to the Agency's feedback from the February 15, 2018 meeting where the proposed Phase 2 clinical trial design was discussed. Based on this meeting, the sponsor would like to seek feedback on a proposed single randomized

comparative trial with progression free survival (PFS) as the primary endpoint to demonstrate the safety and efficacy of elacestrant (RAD1901) in the proposed population for registration. The sponsor is seeking feedback regarding this proposed trial including the target patient population, comparators, primary endpoint, secondary endpoints, and planned statistical analyses to determine if this trial may support registration and approval in the proposed target population.

The proposed indication for Elacestrant (RAD1901) is for (b) (4) estrogen receptor positive (ER+) and human epidermal growth factor receptor 2 negative (HER2) advanced or metastatic breast cancer (b) (4)

Elacestrant (RAD1901) is a selective estrogen receptor degrader (SERD) that selectively binds to estrogen receptor alpha (ER α). In Phase 1 studies, this agent has demonstrated safety and clinical activity in women with ER+, HER2- metastatic breast cancer who have progressed following treatment with multiple endocrine and targeted agents including fulvestrant, CDK4/6 inhibitors, and mTOR inhibitors. This agent is being developed as an oral agent with once daily dosing.

Regulatory Background:

- June 26, 2017: The sponsor met with the Agency for an EOP1 meeting where Radius obtained Agency feedback regarding their proposed single arm trial and overall development program
- October 2017: FDA granted Fast Track designation for the investigation of elacestrant for (b) (4) estrogen receptor positive (ER+) and human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer (b) (4)
- November 29, 2017: The sponsor met with the Agency for a Type B CMC meeting where the Agency provided feedback on the proposed overall strategy and approaches for the drug substance and drug product specifications and registration stability program, as well as batch sizes for registration and validation
- February 15, 2018: EOP1 meeting follow-up to discuss the protocol and SAP of a proposed single arm trial for registration. At this meeting, there was discussion of a possible randomized, comparative trial and the sponsor is now seeking feedback for this proposal

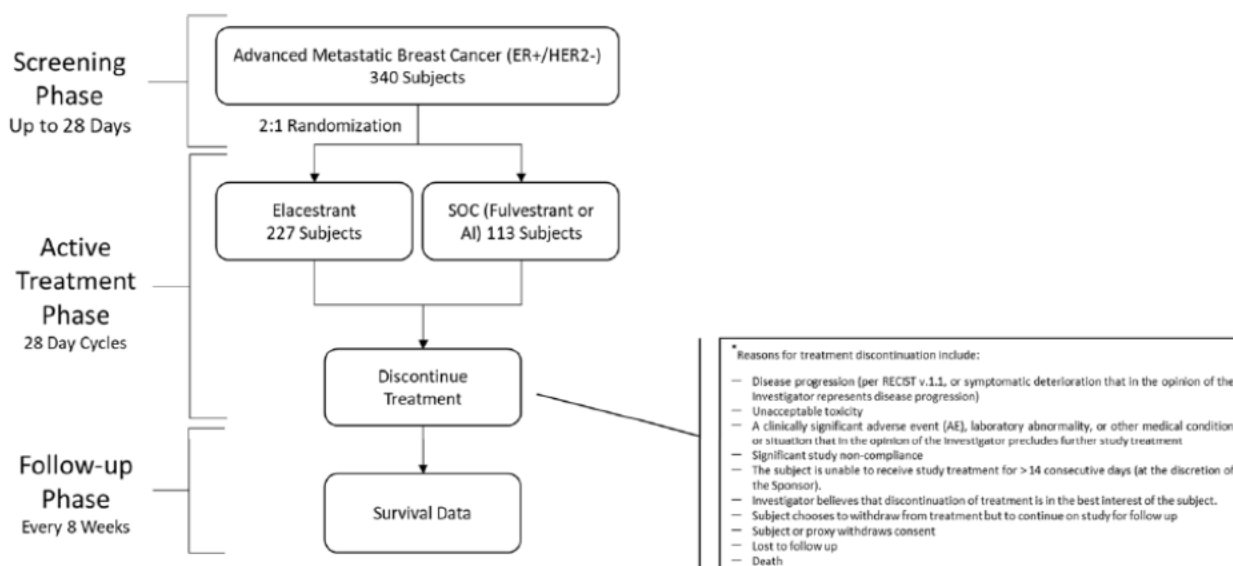
The sponsor is proposing to conduct a single randomized controlled trial to evaluate elacestrant monotherapy as compared to standard of care hormonal therapy options which would include either fulvestrant or an AI (b) (4) with ER+ and HER2- advanced or metastatic breast cancer who have relapsed or progressed following (b) (4)

(b) (4)

Combined preliminary results from the two ongoing Phase 1/1b clinical trials in women with pretreated ER+/HER2- metastatic breast cancer, elacestrant has demonstrated acceptable safety, tolerability, and antitumor activity as monotherapy. Based on confirmed responses using RECIST criteria, the ORR is 20-27%, CBR is 29-47% and there is evidence of prolonged disease stabilization with a median DoR of 17-22 weeks and a median estimated PFS of 5.4-5.6 months in the patient groups with data mature enough for estimation.

The proposed Phase 3 study is an international, multicenter, randomized, open-label, event-driven clinical trial evaluating the safety and efficacy of elacestrant to the SOC options of either fulvestrant or AI (b) (4) with advanced or metastatic ER+ HER2- breast cancer whose disease has relapsed or progressed on (b) (4) prior endocrine therapies and prior CDK 4/6 inhibitor therapy. Approximately 340 subjects will be randomized in a 2:1 ratio in to either elacestrant or SOC endocrine therapy of physician's choice (fulvestrant, anastrozole, letrozole, or exemestane). Eligible patients will be randomized stratified based on prior treatment with fulvestrant vs. no prior treatment with fulvestrant, and presence of visceral metastases vs. other.

The primary endpoint of the study is IRC assessed PFS defined as the time from randomization to the date of objective disease progression per RECIST v 1.1 as assessed by blinded IRC or death from any cause. Secondary endpoints include local investigator assessed PFS, IRC assessed ORR in those patients with measurable disease, IRC assessed DoR, locally assessed ORR and DoR, OS, IRC and local investigator assessment of CBR, safety and tolerability, PK, and patient reported outcomes including the EQ-5D-5L, the EORTC QLQ-C30 and PRO-CTCAE.



To have a power of 85% to detect a hazard ratio of 0.667 at the one-sided Type I error rate of 0.025, the study requires approximately 245 PFS events in the two treatment groups. It is estimated that 340 patients will be randomized in a 2:1 ratio to result in this number of events. The test of PFS will use a group sequential method according to the pre-specified O'Brien-Fleming-type alpha spending function for two looks to preserve the overall one-sided Type I error of 0.025. Assuming a median PFS of 4.0 months for the SOC arms, the treatment effect represents an increase in the median PFS of approximately 2.0 months (from 4.0 to 6.0 months for the elacestrant arm).

Key Inclusion/Exclusion Criteria are as follows:

Inclusion

- Histologically or cytologically confirmed locally advanced disease not amenable to curative resection or radiation therapy or metastatic disease not amenable to curative therapy.
- Appropriate candidates for hormonal monotherapy with measurable disease or non-measurable bone-only disease.

(b) (4)

- Documented ER positive tumor $\geq 1\%$ staining by IHC with or without progesterone receptor positivity.
- Documentation of HER2-negative tumor as IHC 0 or 1+ or negative in situ hybridization (ISH) results.

(b) (4)

- Subjects must have received prior treatment with a CDK 4/6 inhibitor in combination with either fulvestrant or an AI.
- Subjects may have received no more than one line of chemotherapy in the advanced or metastatic setting. Chemotherapy administered for less than one cycle will not be counted as a prior line of therapy.
- ECOG ≤ 1 .
- Resolution of all toxic effects of prior therapies or surgical procedures to Grade ≤ 1 except alopecia and peripheral neuropathy.
- Adequate organ function as defined as:
 - a. ANC $\geq 1000/\mu\text{L}$

- b. Platelet count $\geq 75,000/\mu\text{L}$
- c. Hemoglobin ≥ 9.0 g/dL
- d. Calculated serum creatinine clearance of ≥ 30 mL/min calculated by the Cockcroft-Gault formula
- e. ALT $\leq 3 \times$ ULN
- f. AST $\leq 3 \times$ ULN
- g. Total bilirubin $\leq$ ULN or total bilirubin $\leq 1.5 \times$ ULN with a direct bilirubin $\leq$ ULN of the laboratory in subjects with documented Gilbert's Syndrome
- h. Serum chemistries within the normal range of the laboratory
- i. INR $\leq 1.5 \times$ ULN. Subjects on anticoagulation may be allowed to participate with stable INR for at least one month prior to first dose of study drug.

Exclusion

- 1. Prior treatment with elacestrant or other investigational selective estrogen receptor degrader (SERD) or ER antagonist
- 2. Prior anticancer or investigational drug treatment within the following windows:
 - a. Fulvestrant treatment < 28 days prior to first dose of study drug
 - b. Any endocrine therapy < 14 days before the first dose of study drug
 - c. Chemotherapy < 21 days before the first dose of study drug
 - d. Any investigational anticancer therapy < 28 days or five half-lives (whichever is shorter) before the first dose of study drug.
- 3. Symptomatic visceral disease, untreated or progressive CNS metastases, or symptomatic pulmonary lymphangitic spread. Patients with previously treated CNS metastases are eligible provided they have completed radiotherapy at least 28 days prior to the first dose of study drug, are clinically stable, and require no steroid therapy. If anticonvulsants are required, subjects must be stable on a non-enzyme inducing anticonvulsant regimen.

(b) (4)



The Schedule of Assessments is as follows:

Table 6: Schedule of Events

Procedures/Assessments	Screening ^a	Active Treatment Period			End of Treatment (EOT) ^b	Post-Treatment (PTx)	
		Cycle 1 ^c		Subsequent Cycles ^c			
Study Day (assessment window in days)	Day -28 to -1	Day 1 ^d	Day 15 ^d (± 2 days)	Day 1 ^d (± 3 days)	(+ 14 days; within 14 days of last dose of study drug)	PTx Safety Follow-up Day 30 ^e (± 3 days)	PTx Follow-up every 8 week ^f (± 7 days)
Demography/Informed consent (IC) ^g	X						
Inclusion /Exclusion criteria	X						
Medical/Surgical history/Current medical conditions	X						
Breast cancer diagnosis, ER, PGR, HER2 status ^h	X						
Prior anti-cancer therapy ⁱ	X						
Randomization ^j		X					
Patient Reported Outcomes ^k EQ-5D-5L EORTC QLQ-C30 PRO-CTCAE	X	X	X	X	X	X ^b	
Height	X						
Weight	X	X		X	X		
Physical examination ^l	X	X		X	X		
Vital signs ^m	X	X	X	X	X		

Procedures/Assessments	Screening ^a	Active Treatment Period			End of Treatment (EOT) ^b	Post-Treatment (PTx)	
		Cycle 1 ^c		Subsequent Cycles ^c			
Study Day (assessment window in days)	Day -28 to -1	Day 1 ^d	Day 15 ^d (± 2 days)	Day 1 ^d (± 3 days)	(+ 14 days; within 14 days of last dose of study drug)	PTx Safety Follow-up Day 30 ^e (± 3 days)	PTx Follow-up every 8 week ^f (± 7 days)
ECOG performance status	X	X		X	X		
12-Lead ECG ^g	X	X	X	X	X		
Estradiol and FSH testing	X						
Urinalysis ^h	X						
Hematology ⁱ	X	X	X	X	X		
Biochemistry ^j	X	X	X	X	X		
Special biochemistry ^k	X				X		
Coagulation ^l	X	X	X	X	X		
CT/MRI of chest, abdomen, pelvis, clinically indicated sites of disease, bone lesions; Color photographs of superficial disease ^m	X	←-----→ Performed every 8 weeks (± 7 days) from the date of randomization)			X		X
Radionuclide bone scan, whole body MRI ⁿ	X	←-----→ Performed every 24 weeks (± 7 days) from the date of randomization			X		X
BMD scan (lumbar spine, total hip, and femoral neck) ^o	X				X		
Blood sample for PK ^w		X	X	Cycle 2 only			

Procedures/Assessments	Screening ^a	Active Treatment Period			End of Treatment (EOT) ^b	Post-Treatment (PTx)	
		Cycle 1 ^c		Subsequent Cycles ^e			
Study Day (assessment window in days)	Day -28 to -1	Day 1 ^d	Day 15 ^d (± 2 days)	Day 1 ^d (± 3 days)	(+ 14 days; within 14 days of last dose of study drug)	PTx Safety Follow-up Day 30 ^f (± 3 days)	PTx Follow-up every 8 week ^f (± 7 days)
Blood sample for ctDNA ^s	X		X	Cycle 3 and every other cycle while on study drug (Cycle 5, 7, 9, etc.)	X		
Collection of tumor biopsy ^v	X		X ^z				
Archival tumor sample ^v	X						
Elaeestrant Arm ^{aa}		←-----→ Once Daily					
SOC-Aromatase inhibitor Arm ^{bb}		←-----→ Once Daily					
SOC-Fulvestrant Arm ^{cc}		C1D1, C1D15, and Day 1 of every subsequent cycle					
Drug Compliance ^{dd}		←-----→					
Adverse events ^{ee}		←-----→					
Prior/Concomitant medications/treatments ^{ff}		←-----→					
Survival follow-up for subjects who discontinue treatment							X

FDA sent Preliminary Comments to Radius Pharmaceuticals, Inc. on June 1, 2018.

2. DISCUSSION

Question 1: Does the Agency agree with the proposed target patient population, (b) (4) advanced or metastatic ER+/HER2- breast cancer who have relapsed or progressed following (b) (4) is an appropriate option?

FDA Response to Question 1: We are concerned with the feasibility of the trial, (b) (4)

Sponsor's June 13, 2018 Response: Radius acknowledges FDA's concern and appreciates the recommendation to consider (b) (4) patients. Therefore, consistent with your recommendation, we propose a patient population who has progressed on endocrine based therapy + CDK 4/6 inhibitor, given in either the first or second line, with a comparator arm of endocrine monotherapies. For clarity, this would alter the target patient population definition

above to “ (b) (4) advanced or metastatic ER+/HER2- breast cancer who have relapsed or progressed following one or two prior lines of hormonal therapy, which must have included treatment with a CDK4/6 inhibitor in combination with either fulvestrant or an AI, and for whom hormonal monotherapy is an appropriate option.”

In the current treatment landscape of advanced/metastatic ER+ breast cancer endocrine based therapy plus CDK4/6 inhibitors are increasingly used in either the first or second line and Radius desires to include patients who may have been treated with this combination in either line. Early data with elacestrant supports monotherapy activity in the post-CDK4/6 inhibitor setting, and the choice of endocrine monotherapies in the comparator arm (fulvestrant or aromatase inhibitor) permits Investigators to tailor the choice of comparator agent according to a patient's prior treatment history. Radius believes this reflects the current treatment landscape for many ER+ patients who wish to delay chemotherapy, and particularly with inclusion of less heavily pre-treated patients, would be a feasible and informative trial.

Can FDA please comment on the above proposed patient population.

Meeting Discussion: FDA agrees with the sponsor's proposed patient population (b) (4)

Question 2: Does the Agency agree with the other inclusion and exclusion criteria as provided in the protocol?

FDA Response to Question 2: (b) (4) **We suggest modifying your definition of postmenopausal to that of those patients ≥ 60 years of age, or those < 60 with absence of menses for > 12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression with an FSH and estradiol in the postmenopausal range, or if < 60 and taking tamoxifen or toremifene that FSH and plasma estradiol are in postmenopausal ranges. See also FDA Response to Question 1.**

Sponsor's June 13, 2018 Response: Radius agrees to modify the inclusion criteria (b) (4) and agrees to modify the definition of postmenopausal status in accordance with the guidance provided by FDA. No further discussion needed.

Meeting Discussion: None.

Question 3: Does the agency agree (b) (4)

FDA Response to Question 3: No, see FDA Response to Question 1.

Sponsor's June 13, 2018 Response: Please see Radius's response to Question 1.

Meeting Discussion: FDA agrees with the sponsor's proposed comparators given the revisions in the proposed patient population.

Question 4: Does the Agency agree that PFS based on the blinded central Imaging Review Committee (IRC) assessment is an appropriate primary endpoint for this comparative trial?

FDA Response to Question 4: Yes, PFS based on IRC as a primary endpoint is appropriate. However, OS should be a key secondary endpoint with alpha allocated. Please note that demonstration of no detriment in OS will be critical.

Sponsor's June 13, 2018 Response: Radius accepts the FDAs comment and will update the statistical analysis plan (SAP) and protocol accordingly. Please also see Radius response to Question 6d.

Meeting Discussion: None.

Question 5: Does the Agency agree with the proposed secondary endpoints, which include the following:

- PFS based on local investigator assessment;
- Objective Response Rate (ORR) based on blinded central IRC assessment;
- Duration of Response (DoR) based on blinded central IRC assessment;
- ORR based on local investigator assessment;
- DoR based on local investigator assessment;
- Overall survival (OS);
- Clinical Benefit Rate (CBR) based on blinded central IRC assessment;
- CBR based on local investigator assessment

FDA Response to Question 5: Yes, see FDA Response to Question 4 above.

Sponsor's June 13, 2018 Response: Radius accepts the FDAs comment and has no further questions.

Meeting Discussion: None.

Question 6:

For the statistical analysis plan,

- a) Does the Agency agree with the proposed event-driven sample size, the power calculation, and the 2:1 randomized treatment allocation ratio?

FDA Response to Question 6a: The event-driven sample size, power calculations and 2:1 treatment allocation appear acceptable. However, see FDA Response to Question 1.

Sponsor's June 13, 2018 Response: Radius accepts the FDAs comment on the event-driven sample size, power calculations and 2:1 treatment allocation.

Meeting Discussion: None.

b) Does the Agency agree [REDACTED] (b) (4)

FDA Response to Question 6b: We do not recommend [REDACTED] (b) (4)

Sponsor's June 13, 2018 Response: Radius accepts the FDA's comment and will remove the [REDACTED] (b) (4)

Meeting Discussion: The sponsor clarified, they no longer intend [REDACTED] (b) (4)
[REDACTED] FDA agreed with the sponsor's proposal to test sequentially PFS in the ESR1 mutant population, then PFS in all patients. The sponsor plans to submit a protocol and SAP for review. FDA recommended the sponsor to meet with CDRH via a pre-submission meeting in order to discuss the potential for companion/complementary diagnostic.

c) Does the Agency agree with the proposed statistical methods for analyzing the primary efficacy endpoint, including its derivation, censoring rules for missing data and sensitivity analyses?

FDA Response to Question 6c: We recommend that you also perform a sensitivity analysis to assess the impact of initiation of non-protocol antineoplastic therapies before disease progression.

Sponsor's June 13, 2018 Response: Radius accepts the FDA's comment and will update the SAP to add the sensitivity analysis. Radius has no further question.

Meeting Discussion: None.

d) Does the Agency agree with the proposed statistical methods for analyzing the secondary efficacy endpoints and proposed safety analyses?

FDA Response to Question 6d: The study should have a detailed statistical plan (including number of deaths needed for the final analysis, power, type I error rate, improvement targeted) for overall survival.

Please note that if you intend to make any efficacy claims based on secondary endpoints after the primary endpoint shows significance, overall type I error rate must be adjusted for multiple secondary endpoints. Please also note that the inclusion of secondary endpoints in the label will be a review issue based on whether the data are clinically relevant.

Sponsor's June 13, 2018 Response: Radius accepts the FDAs comments and will update the Protocol and SAP accordingly.

Meeting Discussion: None.

e) Does the Agency have any other comments to the SAP?

FDA Response to Question 6e: You have proposed a radiographic assessment interval of 8-week. This is insufficient considering the small magnitude of effect you have targeted.

Sponsor's June 13, 2018 Response: Based on the revised patient population, Radius believes that an 8-week interval for radiological assessment is adequate. Please see Radius Response to Question 1.

Meeting Discussion: The Agency agrees that an 8-week radiologic assessment interval for the newly proposed patient population is appropriate.

Question 7: Does the Agency agree that, (b) (4)
can be used as the basis for regulatory approval?

FDA Response to Question 7: No, see FDA Response to Question 6b.

Sponsor's June 13, 2018 Response: Radius has no further comment. Please see our response to Question 6b.

Meeting Discussion: None.

Question 8: Does the Agency agree with the proposed safety monitoring, including the use of an IDMC?

FDA Response to Question 8: Yes, we agree with your proposed safety monitoring.

Sponsor's June 13, 2018 Response: Radius has no further comment.

Meeting Discussion: None.

Question 9: Does the Agency have any other comments on the proposed randomized comparative trial protocol?

FDA Response to Question 9: No.

Sponsor's June 13, 2018 Response: Radius has no further comment.

Meeting Discussion: None.

Question 10: Does the Agency agree that the proposed randomized comparative trial, with positive results, is appropriate as a single registration trial for a potential NDA filing?

FDA Response to Question 10: Possibly. Ultimately to support approval, the improvement in PFS should be statistically significant and clinically meaningful. Please request a Pre-NDA meeting with the Agency when your topline results are available.

Sponsor's June 13, 2018 Response: Discussion pursuant to clarity on response to Question 1.

Meeting Discussion: None.

Question 11: In October 2017, FDA granted Fast Track designation for the investigation of elacestrant for (b) (4) estrogen receptor positive (ER+) and human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer (b) (4)

(b) (4)

(b) (4)

FDA Response to Question 11: We do not agree (b) (4)

(b) (4)

Sponsor's June 13, 2018 Response: Radius acknowledges the FDAs comments.

Meeting Discussion: None.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active

ingredients (which includes new salts and new fixed combinations), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) 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 iPSP 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 iPSP, including an iPSP 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 Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide

feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>.

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

A copy of the handouts presented in the meeting is attached.

8 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

SHERRY C HOU
06/18/2018

LALEH AMIRI KORDESTANI
06/19/2018