CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217639Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: January 4, 2023

To: Amy Tilley, Regulatory Project Manager, Division of Oncology 1 (DO1)

William Pierce, Associate Director for Labeling, DO1

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Ray Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for ORSERDU® (elacestrant) tablets, for oral use

NDA: 217639

Background:
In response to DO1's consult request dated July 22, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for ORSERDU® (elacestrant) tablets, for oral use (Orserdu).

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on December 22, 2022, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on December 30, 2022.

Container Labeling:
OPDP has reviewed the proposed container labeling submitted by the sponsor to the electronic document room on December 16, 2022, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Koung Lee at 240-402-8686 or Koung.lee@fda.hhs.gov.

Section	Statement from Draft	OPDP Comments
6.1	The safety of ORSERDU was evaluated in 467 patients with ER+/HER2- advanced breast cancer following CDK4/6 inhibitor therapy in EMERALD, a randomized, open-label, multicenter study	OPDP is concerned that the description of the trial may suggest that this product is indicated for patients without any regards to their ESR1-mutation status. Consideration to revising this section to minimize any confusion about the indication would be helpful from a promotional perspective; however, OPDP defers to DO1 given that the description of the trial is otherwise accurate.

16 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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

/s/

KOUNG U LEE
01/04/2023 10:36:26 AM

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

PATIENT LABELING REVIEW

Date:	December 30, 2022
To:	Amy Tilley Regulatory Project Manager **Division of Oncology I (DO1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Koung Lee, RPh, MSHS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ORSERDU (elacestrant)
Dosage Form and Route:	tablets
Application Type/Number:	NDA 217639
Applicant:	Stemline Therapeutics, Inc.

1 INTRODUCTION

On June 17, 2022, Stemline Therapeutics, Inc., submitted for the Agency's review a New Drug Application (NDA) 217639 for ORSERDU (elacestrant) tablets. With this submission the Applicant seeks approval for the proposed indication for the treatment of postmenopausal women, and men, with (b) (4) positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer who have progressed following at least one line of endocrine therapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 1 (DO1) on July 22, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ORSERDU (elacestrant) tablets.

2 MATERIAL REVIEWED

- Draft ORSERDU (elacestrant) tablets PPI received on June 17, 2022 and received by DMPP and OPDP on December 22, 2022.
- Draft ORSERDU (elacestrant) tablets Prescribing Information (PI) received on June 17, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 22, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

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

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

---

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

/s/

SUSAN W REDWOOD
12/30/2022 11:47:39 AM

ALINE M MOUKHTARA
12/30/2022 11:51:31 AM
Signed for Koung Lee

BARBARA A FULLER
12/30/2022 11:54:23 AM

LASHAWN M GRIFFITHS
12/30/2022 11:58:45 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 21, 2022
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 217639
Product Name and Strength:	Orserdu (elacestrant) tablet, 86 mg and 345 mg
Applicant/Sponsor Name:	Stemline Therapeutics, Inc.
TTT ID #:	2022-244-1
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on December 16, 2022 for Orserdu. The Division of Oncology 1 (DO1) requested that we review the revised container labels for Orserdu (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Stewart, J. Label and Labeling Review for Orserdu (NDA 217639). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 NOV 22. TTT ID No.: 2022-244.

A. APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON DECEMBER 16, 2022

Container labels

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/

JANINE A STEWART
12/21/2022 01:42:39 PM

ASHLEIGH V LOWERY
12/23/2022 10:17:09 AM

Clinical Inspection Summary

Date	December 14, 2022
From	Yang-Min (Max) Ning, M.D., Ph.D. Min Lu, M.D., M.P.H. Jenn Seller, M.D., Ph.D. GCPAB/DCCE/OSI/CDER/FDA
To	Mirat Shah, M.D. Laleh Amiri Kordestani, M.D. Amy Tilley, RPM DO1/OOD/CDER/FDA
NDA #	217639
Applicant	Stemline Therapeutics, Inc., a subsidiary of Menarini Group Company
Drug	Elacestrant (RAD1901)
NME (Yes/No)	Yes
Therapeutic Classification	Estrogen receptor degrader
Proposed Indication	Treatment of postmenopausal women, and men, with (b) (4)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer who have progressed following at least one line of endocrine therapy
Consultation Date	08/10/2022
Summary Goal Date	12/16/2022
Action Goal Date	01/31/2023
PDUFA Date	02/17/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from a randomized Phase 3 study (Protocol RAD1901-308) were submitted to the Agency in support of a New Drug Application (NDA) for elacestrant for the proposed indication as listed above. Three clinical investigators, Drs. Patrick Dillon (Site 116), Alberto Montero (Site 108), and Hung Khong (Site 175), and the key contract research organization (CRO) Parexel International Corporation, responsible for the study conduct and management, were inspected.

The inspections found no significant regulatory violations in the conduct of Study RAD1901-308 by the three investigators and the CRO. The submitted clinical data were verifiable with source records reviewed at the sites, with no objectionable discrepancies identified. Overall, the inspection results demonstrate that this study appears to have been adequately conducted and the clinical data generated from these investigator sites are acceptable for this NDA.

II. BACKGROUND

Elacestrant is a selective estrogen receptor degrader (SERD) administered orally. Its investigational name was RAD1901, studied under IND 124748 since 2014. For this NDA, the Applicant submitted clinical data from Study RAD1901-308 and proposed an initial indication for elacestrant for use in patients with (b) (4)-positive, HER2-negative advanced or metastatic breast cancer previously treated with at least one line of endocrine therapy.

Study RAD1901-308 [NCT03778931] was a randomized, open-label, multicenter Phase 3 trial comparing the efficacy and safety of elacestrant to the standard of care (SOC) treatment options of either fulvestrant or an aromatase inhibitor (AI) in postmenopausal women and in men with advanced or metastatic HR-positive/HER2-negative breast cancer whose disease had relapsed or progressed on at least one or two prior lines of endocrine therapy. Subjects were required to have: 1) histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of either locally advanced disease not amenable to resection or radiation therapy with curative intent or metastatic disease not amenable to curative therapy; 2) confirmed evidence or documentation of ER-positive and HER2-negative tumor per local laboratory testing on their most recent biopsy specimen(s); 3) presence of evaluable lesion(s) confirmed by central radiology review at study entry; 4) prior treatment with a cyclin-dependent kinases 4/6 (CDK4/6) inhibitor in combination with either fulvestrant or an AI; 5) central laboratory testing of their circulating tumor DNA for estrogen receptor 1 (ESR1) mutation status [ESR-mutation (mut) or ESR1-wild type (WT)] before randomization. Eligible subjects consented were to be randomized (1:1) to receive elacestrant or one SOC treatment (fulvestrant, anastrozole, letrozole, or exemestane) at the Investigator's discretion. Randomization was stratified by ESR1 mutation status (ESR1-mut vs. ESR1-WT), prior treatment with fulvestrant (yes vs. no), and visceral metastasis (yes vs. no).

The primary endpoint was progression-free survival (PFS) as assessed by a blinded imaging review committee (IRC) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Key secondary endpoints included overall survival and the safety of study treatment.

Following randomization and study treatment assignments, subjects were to receive elacestrant 400 mg orally once daily or the Investigator-selected SOC treatment at the dose schedule(s) recommended. Study treatment was to be continued until disease progression, unacceptable toxicity, consent withdrawal, non-compliance, or other reasons specified in the protocol.

For the primary efficacy endpoint PFS, tumor assessments were to be performed with CT/MRI (of the chest, abdomen, and pelvis) at baseline and then every 8 weeks (± 7 days) from the date of randomization during the active treatment phase. For subjects with bone metastases, bone scans were to be performed every 24 weeks (±7 days) and as clinically indicated from the date of randomization. All scans were required to be collected and submitted to the sponsor's contracted imaging laboratory for blinded IRC per RECIST v1.1. For subjects who were discontinued from study treatment due to disease progression, their overall survival status was to be followed-up every 8 weeks (± 7 days) from the last dose of study treatment. For safety assessments, adverse events (AEs), serious adverse events (SAEs) and protocol-required examinations and laboratory tests were to be collected and/or conducted according to Schedule of Events of the protocol. All adverse events and laboratory abnormalities were to be graded

for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

From 05/10/2019 through 09/06/2021 [data cutoff date for the current submission], the study enrolled 478 subjects from 150 investigator sites across 17 countries, with 135 (28%) subjects from 46 sites in the United States (U.S.). Of the enrolled, 239 subjects were randomized to each study arm, 239 in the elacestrant arm and 239 in the SOC arm. Following randomization, 237 subjects in the elacestrant arm and 230 in the SOC arm received at least one dose of study treatment as planned and these subjects were included for safety analyses in the current submission. The study was ongoing as of the data cutoff date.

The DO1 and OSI review teams discussed the design of Study RAD1901-308 and related distribution of study subjects by geographical location and the risk ranking of investigator sites and selected the three domestic clinical investigators [Drs. Patrick Dillon (Site 116), Alberto Montero (Site 108), and Hung Khong (Site 175)] and a key CRO for clinical inspection. The study had sufficient data from the U.S. Relative to other domestic sites, these three investigators enrolled large numbers of study subjects and were associated with a relatively longer PFS in the elacestrant arm than in the SOC treatment arm, favoring treatment with elacestrant. Inspection of the key CRO Parexel International (MA) Corporation was requested based on the Applicant's responses to review teams' inquiries regarding the study conduct and management as well as the recent change in the sponsorship from the former sponsor Radius Health to the current Applicant in June 2022 for this NDA.

III. RESULTS

1. Patrick Dillon, M.D. [Site 116]
1215 Lee Street
Charlottesville, VA 22903

Dr. Dillon was inspected on October 11-14, 2022, as a surveillance and data audit for Study RAD1901-308. This was the first FDA inspection of the investigator. The site enrolled 6 subjects into the study, with 5 subjects randomized to the elacestrant arm and 1 to the SOC arm. All the subjects received study treatment following randomization. As of the data cutoff date, one subject (b) (6) in the elacestrant arm who started treatment on (b) (6) was transferred to another study site [Site 175] on (b) (6) secondary to relocation and the rest of subjects were discontinued from study treatment due to disease progression. No subjects were found to have been discontinued from study treatment due to adverse event(s) or withdrawal.

Source records for all the 6 subjects were reviewed during the inspection and source data were compared with the Applicant's submitted data for the site. The reviewed subject records included but were not limited to the informed consents, eligibility checklists, screening-enrollment log, randomization allocation, study treatment administered, tumor assessments, adverse events (AE)/serious adverse events (SAE), laboratory results, and protocol deviations. Regulatory documentation and oversight of the study at the site were also examined, including the institutional review board (IRB) approvals of the study protocol/amendments and informed consent forms and related correspondences,

delegation of authority log, site's training records (i.e., Good Clinical Practice (GCP) training and study specific training provided by the CRO Parexel), signed Form FDA 1572s, financial disclosures, study monitoring, study drug accountability records, and access to and data entry into the electronic case report form (eCRF) system [i.e., Medidata Rave] used for this study.

The inspection found no significant regulatory deficiencies at the site. All the subjects met the eligibility criteria and the submitted clinical data were verifiable with source records reviewed. All the AEs, SAEs and protocol deviations were reported to the sponsor. At the conclusion of this inspection, no Form FDA 483, Inspectional Observations, was issued to Dr. Dillon.

2. Alberto Montero, M.D. [Site 108]
1100 Euclid Ave LKS Ste 1200
Cleveland, OH 44106

Dr. Montero was inspected from 09/26/2022 through 10/03/2022 as a data audit for Study RAD1901-308. For the investigator, this was the first FDA inspection. Note that the inspection was initially issued for Dr. Paula Silverman based on the Applicant's submitted data. At the time of preannouncement for the inspection, it was found that Dr. Silverman retired in July 2020 and that Dr. Montero has since served as the Principal Investigator for continuation of this study at the site.

The site enrolled 9 subjects for the study, with 5 subjects randomized to the elacestrant arm and 4 to the SOC arm. Following randomization, all the enrolled subjects received study treatment as assigned. As of data cutoff, one subject (b) (6) in the elacestrant arm remained on study treatment and the rest of subjects in both arms were discontinued from study treatment due to disease progression or adverse events. At the time of this inspection, Subject (b) (6) was found to have discontinued study treatment since (b) (6) for disease progression, about (b) (6) after the data cutoff of 09/06/2021. This study was ongoing at the site for survival follow-up but was closed to enrollment.

The inspection involved a comprehensive review of source records for the 9 subjects, eligibility determination, informed consents, scans and radiology reports, AEs, laboratory reports, and data contained in the eCRFs. Source records and data were compared to the data listings submitted by the Applicant for the site. In addition, the inspection examined regulatory documentation and the study administration and related oversight (i.e., IRB's approvals and continuing reviews) at the site as well as financial disclosures, study monitoring records, and sponsor correspondences.

The inspection identified no regulatory issues with the study conducted by the current and previous investigators at this site. The Applicant's submitted data for the site were verifiable with source records reviewed at the site. There were no unreported AEs identified. No Form FDA 483 was issued to Dr. Montero at the conclusion of this inspection.

3. Hung Khong, M.D. [Site 175]
10920 Mckinley Drive
Tampa, FL 33612

Dr. Khong was inspected on September 19-23, 2022, as a surveillance and data audit for Study RAD1901-308. This was the initial FDA inspection of the investigator. The site enrolled 7 subjects into the study, with 2 subjects randomized to the elacestrant arm and 5 to the SOC arm. Following randomization, one subject (b) (6) in the SOC arm did not receive study treatment as assigned due to consent withdrawal and the rest of subjects received at least one dose of study treatment. In addition, this site accepted the subject (b) (6) transferred from Site 116 during the study. As of the data cut off, all the subjects enrolled at the site in both arms were discontinued from study treatment due to disease progression. At the time of this inspection, the subject transferred from Site 116 remained on study treatment, with the most recent study visit on (b) (6).

Source records for all the enrolled subjects were reviewed and compared with the submitted data listings. Records reviewed included the informed consents, inclusion/exclusion criteria, screening and enrollment log, randomization, study treatment administration and discontinuation, scans performed per protocol, adverse events, serious adverse events, concomitant medications, test article accountability, and protocol deviations. The inspection reviewed the activities and records related to the authority and administration of the study, including the IRB approvals and documentation, Form FDA 1572s, financial disclosures, site training activities and implementation of study procedures, source data collection and monitoring activities, adherence to and documentation of protocol-required visits, and sponsor monitoring activities.

The inspection found no significant regulatory violations at the site. The subjects' eligibility and source data were found to have been properly documented in source records reviewed and were verifiable for the submitted data listings. There was no evidence of underreporting of adverse events.

At the conclusion of the inspection, no From FDA 483 was issued to Dr. Khong.

4. Parexel International (MA) Corporation [CRO]
275 Grove St., Suite 101C
Newton, MA 02466

The CRO was inspected on November 01-09, 2022, to review its conduct and management of Study RAD1901-308. For this CRO, the most recent inspection was conducted in August 2019 and the final compliance classification was No Action Indicated (NAI).

The inspection reviewed the CRO's history, organizational chart, operating procedures, and service agreements, with an inspection focus on activities associated with the conduct of Study RAD1901-308. The activities included selection of monitors and related training for the study, selection and monitoring of clinical investigators,

management and monitoring of study sites including remote monitoring due to the COVID-19 pandemic, data collection and use of independent data monitoring committee (IDMC) and related IDMC charter, safety reporting and oversight, quality assurance procedures, and oversight of the outsourced services (i.e., electronic data capture (EDC) system and data management).

The inspection identified no objectionable compliance issues in the CRO's conduct and management of Study RAD1901-308. No clinical investigator sites were found to have been terminated or placed on hold due to non-compliance during the study. For the above three investigator sites, IRB approvals were verified prior to screening and enrollment of subjects, consistent with the CRO's specified requirements. The CRO has continued its agreed responsibilities from the initiation of this study through the change of sponsorship from the initial sponsor Radius Health to the current sponsor Stemline Therapeutics in June 2022.

Of note, one subject (b) (6) who was randomized to the SOC arm of the study was found not included initially in the NDA submission. This subject transferred study participation from Site 141 in New Jersey to Site 129 in Los Angeles, which occurred 5 weeks after randomization. About one month after the transfer, the subject died from breast cancer. The missed reporting of this subject was noted in June 2022 because of a discrepancy identified between the randomized subject count of 478 provided by Parexel and the reported data of 477 subjects in the interim analysis. The root cause for this discrepancy was analyzed and identified as "inadequate process information or documentation" due to the inadvertent transfer of the subject's data into a site within the EDC which was used to store duplicate files and other items such as erroneous entries of subject identification numbers. The corrective and preventive actions implemented for this issue were: 1) to have requested the CRO for responsible for randomization to reinstate the subject at the original Site 141; 2) to have notified the review division and resubmitted datasets and related reports and analyses; 3) to have evaluated the training material and update to reflect the best practices on Subject Data Transfers for new hires; 4) to have retrained Data Management group on the revised process to be defined in Data Management Plan.

<u>Reviewer's Comments</u>: The missed inclusion of the above subject (b) (6) was reported to the Agency in August 2022, with submission of the corrected datasets and analyses in September 2022. No additional subjects who were randomized in the study were not included in the analyses. This issue appears to be isolated. The CRO's corrective and preventive actions as listed above are timely, reasonable, and acceptable.

{See appended electronic signature page}

Yang-Min (Max) Ning, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Team Lead
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Jenn Seller, M.D., Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Room
Review Division/Division Director
Review Division/Project Manager
Review Division/Clinical Team Lead
Review Division/Clinical Reviewer
OSI/Office Director
OSI/DCCE/Division Director
OSI/DCCE/Acting Branch Chief
OSI/DCCE/Team Lead
OSI/DCCE/GCP Reviewer
OSI/ GCP Program Analysts
OSI/Database PM

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/

YANGMIN NING
12/14/2022 04:25:48 PM

MIN LU
12/14/2022 04:44:47 PM

JENN W SELLERS
12/14/2022 05:59:44 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	November 22, 2022
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 217639
Product Name, Dosage Form, and Strength:	Orserdu (elacestrant) tablet, 86 mg and 345 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Stemline Therapeutics, Inc.
FDA Received Date:	June 17, 2022 and July 11, 2022
TTT ID #:	2022-244
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the approval process for Orserdu (elacestrant) tablet, the Division of Oncology 1 (DO1) requested that we review the proposed Orserdu prescribing information (PI), patient information, and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the Patient Information found it acceptable from a medication error perspective.

Our review of the PI, patient information and the container labels identified areas that may be improved to support the safe and effective use of the product. We note portions of Section 2 and Section 3 can be revised for improved clarity and brevity.

We provide recommendations in Section 4 below.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Orserdu PI and container label can be improved to promote the safe use of the product. We provide recommendations for DO1 in Section 4.1 and recommendations for Stemline Therapeutics, Inc. in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 1 (DO1)

A. Prescribing Information

1. Dosage and Administration Section

a. Consider revising the product information in Section 2.1 *Recommended Dosage* for improved clarity and brevity to read as follows:

The recommended dosage of ORSERDU is 345 mg taken orally, once daily, (b) (4) until disease progression or unacceptable toxicity occurs (b) (4)

Swallow ORSERDU tablet(s) whole. Do not chew, crush, or split (b) (4) Do not take ORSERDU tablets that are broken, cracked, or that look damaged.

(b) (4)

2. Dosage Forms and Strengths Section

a. Consider revising the order of product information for improved clarity and brevity to read as follows:

Tablets:

- 86 mg (b) (4) light blue, unscored, round film-coated biconvex tablet, imprinted with "ME" on one side and plain on the other side.
- 345 mg (b) (4) light blue, unscored, oval film-coated biconvex tablet, imprinted with "MH" on one side and plain on the other side

4.2 RECOMMENDATIONS FOR STEMLINE THERAPEUTICS, INC.

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

A. Container Labels

1. The established name does not appear to be at least half the size of the proprietary name. Ensure the established name is at least half the font size of the proprietary name to be in accordance with 21 CFR 201.10(g)(2).

2. Product information on the principal display panel and on the side panels appears in small font size which may be difficult to read. Revise the presentation of the product information to appear in a larger font size for improved readability.

3. The [redacted] (b) (4) for the 86 mg strength and the 345 mg strength appear similar in color and may not adequately differentiate the two strengths to prevent wrong strength selection errors.
Revise the [redacted] (b) (4) color scheme for the 2 strengths so that each appears in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.

4. In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act.1 The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling.

   [1]The guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

5. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Orserdu received on July 11, 2022 from Stemline Therapeutics, Inc..

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Orserdu</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>elacestrant</td></tr>
<tr><td>Indication</td><td>ORSERDU® is indicated for the treatment of postmenopausal women, and men, with (b) (4)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer who have progressed following at least one line of endocrine therapy.</td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Dosage Form</td><td>tablet</td></tr>
<tr><td>Strength</td><td>86 mg and 345 mg</td></tr>
<tr><td>Dose and Frequency</td><td>
<table>
<tr><th>ORSERDU Dose Level</th><th>Dose and Schedule</th><th>Quantity and Tablet Strength</th></tr>
<tr><td>Starting dose</td><td>345 mg once daily</td><td>One 345 mg tablet</td></tr>
<tr><td>First-dose reduction</td><td>258 mg once daily</td><td>Three 86 mg tablets</td></tr>
<tr><td>Second-dose reduction</td><td>172 mg once daily[1]</td><td>Two 86 mg tablets</td></tr>
</table>
</td></tr>
<tr><td>How Supplied</td><td>Bottles of 30 tablets</td></tr>
<tr><td>Storage</td><td>Store (b) (4)</td></tr>
</table>

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Orserdu labels and labeling submitted by Stemline Therapeutics, Inc..

- Container label received on July 11, 2022
- Prescribing Information (Image not shown) received on June 17, 2022, available from \\CDSESUB1\EVSPROD\nda217639\0002\m1\us\114-label\1141-draft-label\proposed.doc

G.2 Label and Labeling Images

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

JANINE A STEWART
11/22/2022 04:41:14 PM

ASHLEIGH V LOWERY
11/22/2022 05:00:31 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 217639
Submission Number	001
Submission Date	6/17/2022
Date Consult Received	7/13/2022
Drug Name	Orserdu (elacestrant)
Indication	Treatment of metastatic breast cancer
Therapeutic Dose	345 mg QD
Clinical Division	DO1
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the Applicant's document.

This review responds to your consult dated 7/13/2022 regarding the Applicant's QT evaluation. We reviewed the following materials:

- Applicant's concentration - QT modelling report (NDA217639/SDN1);
- Previous IRT review dated 06/11/2019 in DARRTS;
- Applicant's proposed labeling (NDA217639/SDN2);
- Highlights of clinical pharmacology and cardiac safety (NDA217539 / SDN8).

1 SUMMARY

No large QTcF prolongation effect (i.e., >20 msec) was observed in this QTc assessment of elacestrant in studies RAD1901-004 and RAD1901-308 (ICH E14 Q&A 6.1). We are reluctant to conclude that elacestrant has no QTc effect because the studies lacked a positive control or large exposure margin over clinical exposures needed to waive the positive control.

Study RAD1901-004 was a Phase 1, randomized, double-blind, placebo-controlled, multiple ascending dose study in healthy postmenopausal women to determine safety, tolerability, MTD and PK of elacestrant. Study RAD1901-308 was a phase 3, randomized, open-label, active-controlled study in postmenopausal women and men with ER+/HER2- metastatic breast cancer. The highest dose evaluated in study RAD1901-004 was 1000 mg QD, which does not cover the high clinical exposure scenario (see Section 3.1). The highest dose that was evaluated in study RAD1901-308 was 400 mg QD with or without food, which covers the anticipated therapeutic exposure. These studies support the evaluation of QTc effects under ICH E14 Q&A 6.1 (Section 2.2).

Data from study RAD1901-004 were analyzed using exposure-response analysis while data from study RAD1901-308 were analyzed using by-time point analysis. Both analyses do not suggest that elacestrant is associated with mean increases >20 msec in the

QTcF interval (refer to section 4.5) – see Table 1: Point Estimates and the 90% CIs (FDA Analysis) for model predicted ΔΔQTcF based on results from study RAD1901-004.

Table 1: Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Concentration	ΔQTcF (msec)	90% CI (msec)
QTc	Elacestrant 400 mg QD	119.0 ng/mL	0.91	(-4.73 to 6.55)
QTc	Elacestrant 400 mg QD + Strong CYP4A4 inhibitor	559.3 ng/mL	1.84	(-9.14 to 11.83)

For further details of the FDA analysis, please see section 4.

1.1 Responses to questions posed by Applicant

We agree that treatment with elacestrant is not associated with mean increase > 20 msec in QTc interval (E14 Q&A 6.1). The data from your QTc assessment does not support excluding small increases in the QTc interval because the studies do not include a positive control or large exposure margin needed to waive the positive control.

1.2 Comments to the review division

None.

2 RECOMMENDATIONS

2.1 Additional Studies

None.

2.2 Proposed label

Below are proposed edits to the label submitted to SDN 001 (link) from the CSS-IRT. *Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Additionally, we are omitting section x, as we do not have any edits to that section. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.*

12.2 Pharmacodynamics Cardiac Electrophysiology [redacted] (b) (4) *At the [redacted] (b) (4) approved recommended dose, ORSERDU does not cause large mean increase (> 20 msec) in QTc interval.*
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 APPLICANT'S SUBMISSION

3.1 OVERVIEW

3.1.1 Relevant Regulatory History

The CSS-IRT reviewed the QT assessment proposal previously (see the Previous IRT review dated 06/11/2019). In brief, the Applicant proposed to conduct a robust ECG assessment in study RAD1901-308, a Phase 3 study in subjects with ER+/HER2- breast cancer. This study was randomized, open-label and active-controlled study in which subjects (n ≈ 466) were randomized in 1:1 ratio to receive standard-of-care or elacestrant 400 mg monotherapy. Triplicate ECGs were collected at screening, at pre-dose and 4 hours post-dose on Cycle 1 Day 1 (C1D1) and C1D15, at pre-dose on C2D1, C3D1, and C4D1, then on Day 1 of every-other cycle (eg, C6D1, C8D1, etc.) and at end of treatment. The ECGs were read by a central ECG vendor to ensure consistent evaluation across all subjects in the study. The Applicant also presented QTc assessments from study RAD1901-004 which indicated that elacestrant was not associated with concentration-dependent QT prolongation. The IRT agreed with the Applicant's QT assessment plan but noted that the ECG data in study RAD1901-004 were not of high quality; the ECGs were single, 12-lead, paper ECGs, interpreted by the Principal Investigator.

In the current submission, the Applicant has conducted concentration-QTc analysis of time matched PK and ECG data pooled from phase 1 studies (RAD1901-001, RAD1901-004, RAD1901-005, RAD1901-006, RAD1901-109, RAD1901-112, RAD1901-113, RAD1901-114, RAD1901-115, and RAD1901-116) and the phase 3 study (study RAD1901-308). The Applicant has also conducted categorical analyses of the ECG data, where these analyses are applicable. Summaries of the study designs, for each study, and PK and ECG assessments are presented in the Applicant's concentration-QT report (Table 3-1, page 21, and Table 3-2, page 29). Among those studies, only study RAD1901-001 and study RAD1901-004 had placebo control and intensive ECG sampling. All other studies had screening and pre-dose ECGs and sparse ECGs after treatment initiation. The maximum dose tested in study RAD1901-001 and study RAD1901-004 were 200 mg QD and 1000 mg respectively.

In this review, CSS-IRT's assessment of potential QT effects of elacestrant is focused on PK and ECG results from study RAD1901-004 and RAD1901-308 only. Pooling of data from phase 1 and 3 studies was considered inappropriate because of the potential for QT bias due to heterogeneities among the studies. Study RAD1901-004 was selected because it investigated potential QT effects of up to 1000 mg dose (2.5-fold of the maximum recommended elacestrant dose). Study RAD1901-308 was selected because of the high-quality ECG monitoring in the ER+ breast cancer patients undergoing treatment with elacestrant at the recommended dosing regimen.

3.1.2 Clinical Pharmacology

Elacestrant (RAD1901) is a tetrahydronaphthalene compound with tissue selective, estrogen receptor profile. Elacestrant tablet is being developed for the treatment of

advanced/metastatic ER+ breast cancer. The proposed dosing regimen is 345 mg (400 mg as salt form) once daily (QD), [redacted](b) (4)

Elacestrant clinical pharmacokinetics is summarized in the table of highlights of clinical pharmacology and cardiac safety. In brief, the drug product is formulated as an immediate release tablet for oral administration. The recommended dosage of 345 mg QD provides steady state geometric mean Cmax of 119 ng/mL with median (range) Tmax of 4 (2 - 8) hours post-dose. The drug exhibits greater than dose-proportional increase in exposure doses > 25 mg, and mean accumulation factor of 1.95-fold after 7 days of 200 mg QD dosing. According to the Applicant, intrinsic and extrinsic factors with clinically relevant impact on elacestrant Cmax are severe hepatic impairment (1.88-fold increase), strong CYP3A inhibitors (4.37-fold increase) and inducers (73% decrease), and high fat meal (1.42-fold increase). The Applicant has proposed to avoid elacestrant in patients taking strong CYP3A4 inhibitors (and inducers) and to reduce elacestrant dose to 258 mg [redacted](b) (4) QD in patients with moderate [redacted](b) (4) hepatic impairment.

Based on the presented information, the high clinical exposure scenario is when elacestrant is co-administered with strong CYP3A4 inhibitors (> 4-fold increase in Cmax). The highest tested dose in study RAD1901-004 of 1000 mg QD fasted for 7 days (n=3) provided a geometric mean Cmax of 543 ng/mL and therefore does not cover the anticipated high clinical exposure scenario (co-administration with strong CYP3A4 inhibitors). The dosage without regard to food in study RAD1901-308 provide coverage of the anticipated therapeutic exposure but not the anticipated worst-case exposure.

3.1.3 Nonclinical Safety Pharmacology Assessments

Cardiac safety in vitro:

In vitro effects of elacestrant were evaluated in a GLP-compliant study using the stably transfected HEK-293 cell line that expresses the hERG ion channel, IKr. Elacestrant demonstrated concentration-dependent inhibition of IKr potassium current at concentrations from 0.1 to 1.0 µM. The 1 µM concentration produced an 86.8% IKr blockade. The nominal IC_{50} for the inhibitory effect of elacestrant on hERG potassium current was 0.41 µM (407 nM, or 187 ng/mL).

In an in vitro GLP-compliant study using isolated rabbit Purkinje fibers, elacestrant increased the action potential duration at 60% repolarization (APD_{60}) 2.5 ± 3.3% to 8.0 ± 4.2% at 0.1 µM and 1µM, respectively, and reduced the APD_{60} 0.30 ± 3.2% to -4.3 ± 1.1% at 10 µM. Elacestrant increased the action potential duration at 90% repolarization (APD_{90}) (1.9 ± 2.4% to 4.7 ± 1.8%) at 0.1 µM and reduced the APD_{90} (-4.3 ± 3.6% to -5.9 ± 0.8%) at 10 µM. Elacestrant at 1 µM increased the APD_{90} (3.6 ± 2.6%) at 1 second stimulus interval and reduced the APD_{90} (-0.1 ± 1.6%) at 0.5 second stimulus interval. Elacestrant did not induce statistically significant changes in resting membrane potential (RMP), action potential amplitude (APA), or maximum rate of depolarization (Vmax) at concentrations of 0.1 µM and 1 µM. At 10 µM, elacestrant caused a significant depolarization of the RMP (5.7 ± 1.9 mV) at only one stimulus interval (basic cycle length [BCL] = 0.5 seconds), but a significant decrease of the APA at each stimulus

interval (-9.8 ± 2.5 mV to -20.3 ± 6.9 mV), and a statistically significant decrease in the Vmax (-53.3 ± 16.0%) at 0.5 second stimulus interval.

Cardiac safety in monkeys:

In a GLP-compliant 4-dose crossover study in cynomolgus monkeys, elacestrant administration produced only modest changes at the 100 mg/kg dose and no significant hemodynamic or ECG effects in 8 female monkeys at oral doses up to 50 mg/kg, with the exception of a shortened PR interval at 50 mg/kg that did not persist. A modest but statistically significant increase in diastolic (11%), systolic (6%), mean arterial BPs (8%) and HR (10% to 22%) were observed at the 100 mg/kg dose. All ECGs were within normal limits at doses ≥ 100 mg/kg. The PR interval of the ECG was decreased at doses ≥ 50 mg/kg while QRS duration was increased in the 100 mg/kg group. No significant changes in the QT interval or QTcB were observed in any of the elacestrant treated groups at estimated peak total plasma exposures from 314 to 550 ng/mL. With the exception of the increase in QRS duration at 8 hours postdose, all other changes occurred within the first 4 hours after dosing. All observed cardiovascular changes were reversible. No test article related effects were observed on arterial pulse pressure, inotropic state or body temperature. Based on the proposed therapeutic plasma concentration in patients, the 100 mg/kg treatment group, which was shown to be devoid of any electrocardiographic QT interval effects, represents an approximate 12-fold margin. Additional in vivo cardiac safety information, obtained from the ECGs in the repeat dose monkey study, indicated that exposure of monkeys to more than three weeks of elacestrant at 20, 50 and 100 mg/kg did not produce detectible ECG changes.

Reviewer's comment: *The IC50 from hERG assay is 407 nM, or 187 ng/mL. It is slightly higher than the estimated $C_{max,ss}$ at the 400 mg QD level. Assuming fu=0.01, the ratio between IC50 and free $C_{max,ss}$ is ~112-fold, the hERG safety margin is approximately 4-fold lower when considering high clinical exposures with CYP3A inhibition.*

3.2 APPLICANT'S RESULTS

3.2.1 By-Time Analysis

The by-time analysis was not provided in the Applicant's report. The primary analysis for elacestrant was based on exposure-response analysis, please see section 3.2.3 for additional details.

Reviewer's comment: *FDA reviewer conducted the by-time analysis for study RAD1901-004 and study RAD1901-308 separately. The largest ΔΔQTcF is 5.5 msec for elacestrant 200 mg in study RAD1901-004.*

3.2.1.1 Assay Sensitivity

Not applicable since elacestrant QT effects were evaluated under ICH E14 Q&A 6.1 section 2.2.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the Applicant.

3.2.2 Categorical Analysis

There were 2 QTcF observations > 500 msec from study RAD1901-005. There were 2 ΔQTcF observations > 60 msec, one each from study RAD1901-001 and RAD1901-005. The categorical analysis was not conducted on HR, PR and QRS.

Reviewer's comment: *FDA reviewers conducted categorical analysis on QTc (>500 msec and >60 msec over baseline), HR (>100 beats/min and 25% over baseline), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline) for study RAD1901-004 and study RAD1901-308. There were 21 subjects having HR>100 beats/min in study RAD1901-308.*

3.2.3 Exposure-Response Analysis

The Applicant's concentration-QTc analysis was based on pooled data from phase 1 and 3 studies (See section 3.1.1). The Applicant did not use the model recommended in the white paper. The Applicant used ECG data collected during placebo treatment and pre-dose to develop a structural placebo-QTc model which accounted for circadian rhythmicity of QTc interval (Cosine function). The potential QT effects of elacestrant concentration was added to the placebo-QTc model an additive term of $Slope \times concentration$. Equation 1 presents the Applicant's final concentration-QTc model. Where AMP is the amplitude of the cosine function (AMP1, and AMP2 for the first and second cosine functions, respectively), π=3.14159, t is clock time, and ACR is the acrophase parameter (ACR and ACR for the first, and second cosine functions). ACR was constrained to be between -0.5 and 0.5.

Equation 1. Concentration-QTc model accounting for Circadian Rhythm

$$QTc = (BQT + \eta_{BQT}) \times (1 + Placebo(t)) + (\text{SLPE} + \eta_{\text{SLPE}}) \times \text{elacestrant} + \varepsilon$$

$$Placebo(t) = AMP_1 . \exp(\eta_{AMP1}) . \cos\left(2\pi\left(\frac{t}{24} - ACR_1 . \exp(\eta_{ACR1})\right)\right) + AMP_2 . \exp(\eta_{AMP2}) . \cos\left(2\pi\left(\frac{t}{12} - ACR_2 . \exp(\eta_{ACR2})\right)\right)$$

Source: Adapted from the Applicant's concentration-QTc report

The results of the Applicant's analysis show an absence of concentration dependent QTc prolongation.

As there was no concentration-QTcF effect and the placebo QTcF parameters were fixed to final estimates from the placebo QTcF model, the final model estimates are the same as the placebo QTcF model apart from the residual variability. The final population concentration-QTc model estimates are presented in Table 5-8.

Table 5-8 Parameter Estimates of the Final Exposure-QTcF Model (Run QT002)

Parameter [Units]	NONMEM Estimates			
	Point Estimate	%RSE	95% CI	
BQT [msec]	408 fixed			
24- hr cycle amplitude	0.00801 fixed			
12- hr cycle amplitude	0.00244 fixed			
24- hr cycle acrophase[b]	0.126 (3.02 hr) fixed			
12- hr cycle acrophase[b]	0.056 (0.672 hr) fixed			
BQT~gender (proportional effect)	1.02 fixed			
Inter-individual variability				**CV%[a] or SD**
ω^2_{BQT}	215 fixed			SD = 14.7 (CV%=3.59)
$\omega^2_{12\text{-hr cycle amplitude}}$	2.38 fixed			CV%=313%
Residual variability				**CV%**
σ^2_{prop}	0.000623	7.91%	0.000526-0.000720	2.50

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate*100, 95% CI= 95% confidence interval on the parameter, BQT= baseline QT value after correction, ω^2_{BWT} = variance of random effect of BQT, $\omega^2_{12\text{-hr cycle amplitude}}$ = variance of random effect of 12- hr cycle amplitude, CV = Coefficient of variation of proportional error (=$[\sigma^2 prop]^{0.5}$*100), SD = standard deviation of additive error (=$[\sigma^2 add]^{0.5}$), $\sigma^2 prop$ = proportional component of the residual error model.

Source: Applicant's concentration-QTc report

Reviewer's comment: *The Applicants's C-QT analysis using pooled data from heterogeneous studies is not appropriate due to the potential for QT bias. The final model does not include elacestrant concentration term; therefore, cannot be used prediction of ΔQTcF effects at therapeutic and supratherapeutic exposure.*

In contrast to Applicant's analysis, the reviewers used the white paper model to analyze ECG data from study RAD1901-004 only. The sparseness of the PK/ECG data from study RAD1901-308 prevents adequate assessment of QTc effects at peak elacestrant concentration for individual subjects. Therefore, the reviewer's used by time-point analysis to analyze ECG data from study RAD1901-308.

The reviewers' findings show that elacestrant does not appear to cause concentration-dependent increase in QTc interval over the exposure range tested. However, the exposure range does not cover sufficiently high margin over the high clinical exposure scenario and cannot support concluding lack of an effect.

3.2.4 Cardiac Safety Analysis

Phase 3 study RAD1901-308

Cardiac related deaths occurred in 3 subjects: 1 subject (cardiac arrest) in the elacestrant group and 2 subjects (arrhythmia, myocardial infarction) in the SOC group. None of the AEs were considered related to drug.

There were 15 subjects (7%) with QTcF of > 450 msec in the elacestrant group versus 15 subjects (7%) in the SOC group. None of the subjects in either arm had a change from baseline that is > 60 msec or QTcF >480 msec.

Reviewer's comment: *In the elacestrant group, there were events of unexplained syncope, significant ventricular arrhythmias, or sudden cardiac deaths. None of the subject had significant QTc prolongation.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The Applicant used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall Quality

Waveforms for study 308 and 004 were submitted. Overall, ECG acquisition and interpretation in these studies appear acceptable.

4.2.2 QT Bias Assessment

No QT bias assessment was conducted by CSS-IRT as paper ECG data from study RAD1901-004 were analyzed separately from high quality ECG data from study RAD1901-308.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. The statistical reviewer evaluated the ΔQTcF effect using descriptive statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups for study RAD1901-004. Figure 2 displays the time profile of ΔQTcF for study RAD1901-308.

Figure 1: Median and 90% CI of ΔΔQTcF Time-course (unadjusted CIs) for study RAD1901-004.

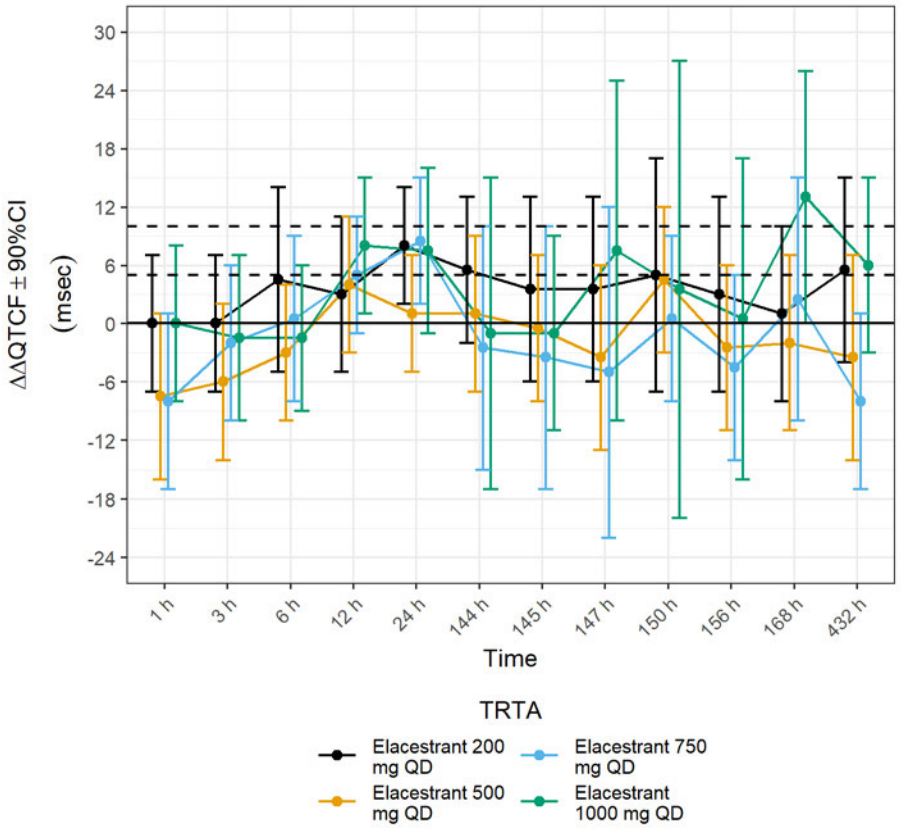
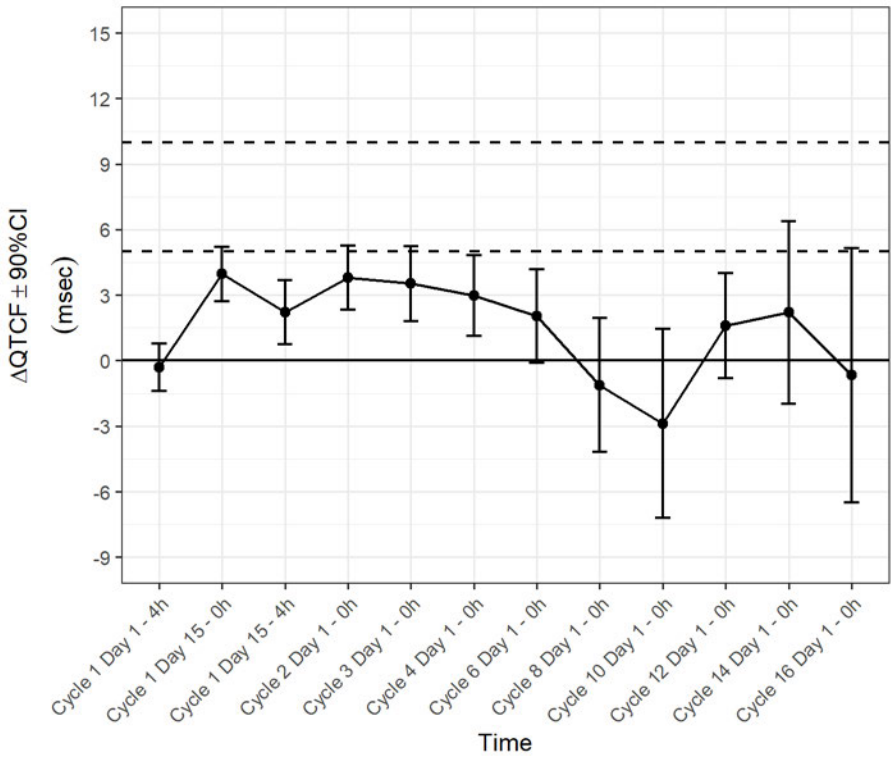


Figure 2: Mean and 90% CI of ΔΔ*QTcF* Time-course (unadjusted CIs) for study RAD1901-308.



4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 3 displays the time profile of ΔΔHR for different treatment groups for study RAD1901-004. Figure 4 displays the time profile of ΔHR for study RAD1901-308.

Figure 3: Median and 90% CI of ΔΔHR Time-course for study RAD1901-004.

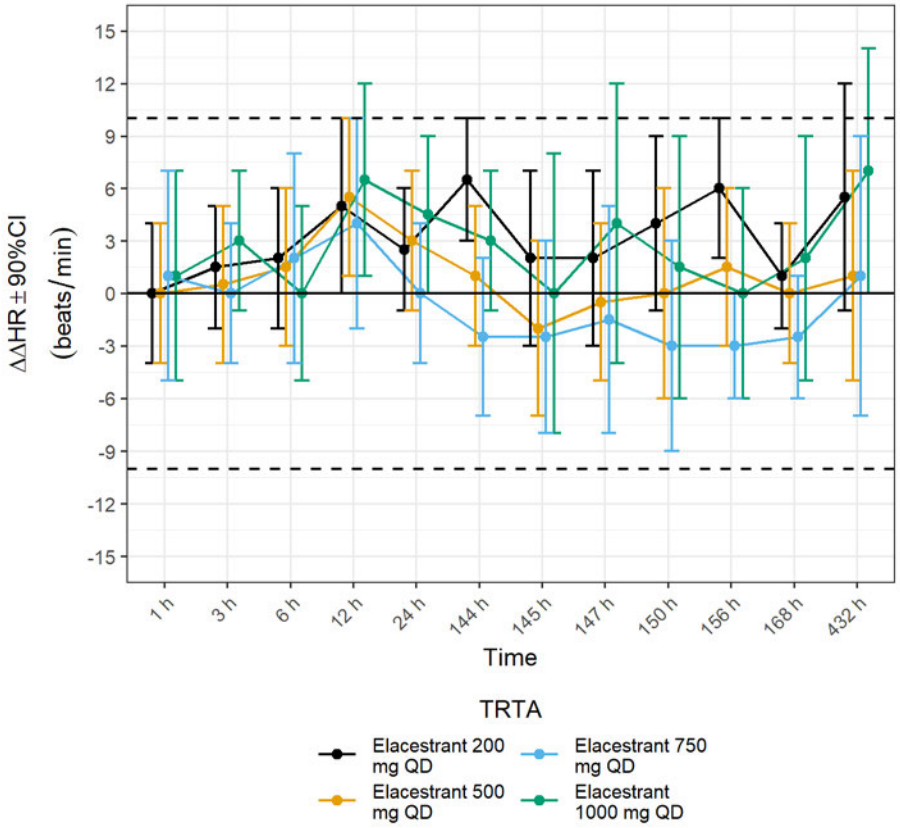
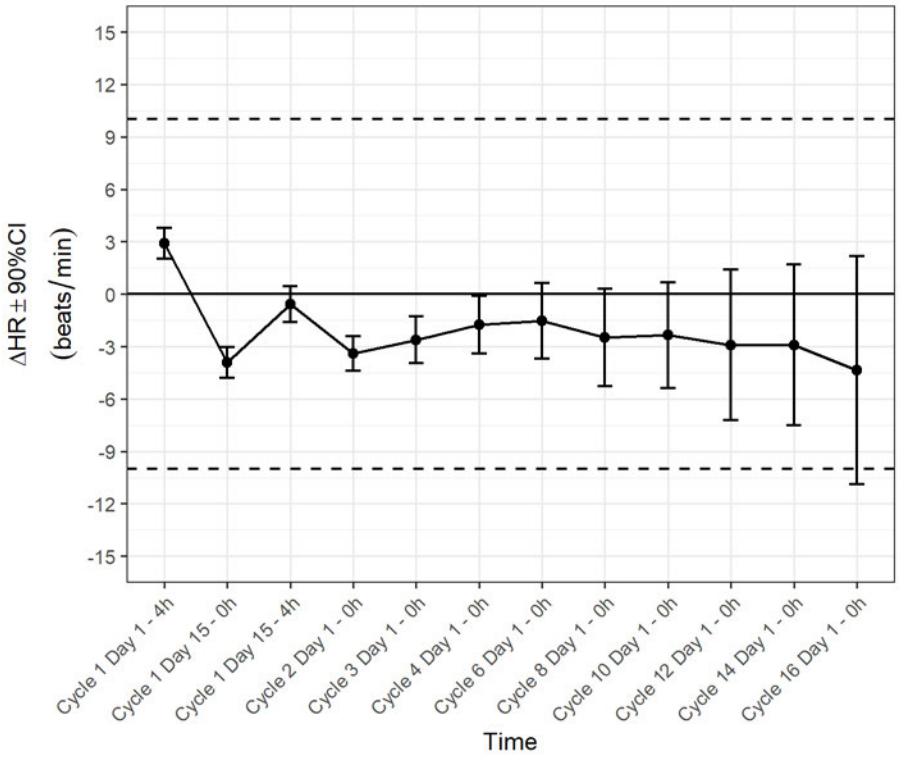


Figure 4: Mean and 90% CI of ΔHR Time-course for study RAD1901-308.



4.3.3 PR

Figure 5 displays the time profile of ΔΔPR for different treatment groups for study RAD1901-004. Figure 6 displays the time profile of Δ*PR* for study RAD1901-308.

Figure 5: Median and 90% CI of ΔΔPR Time-course for study RAD1901-004.

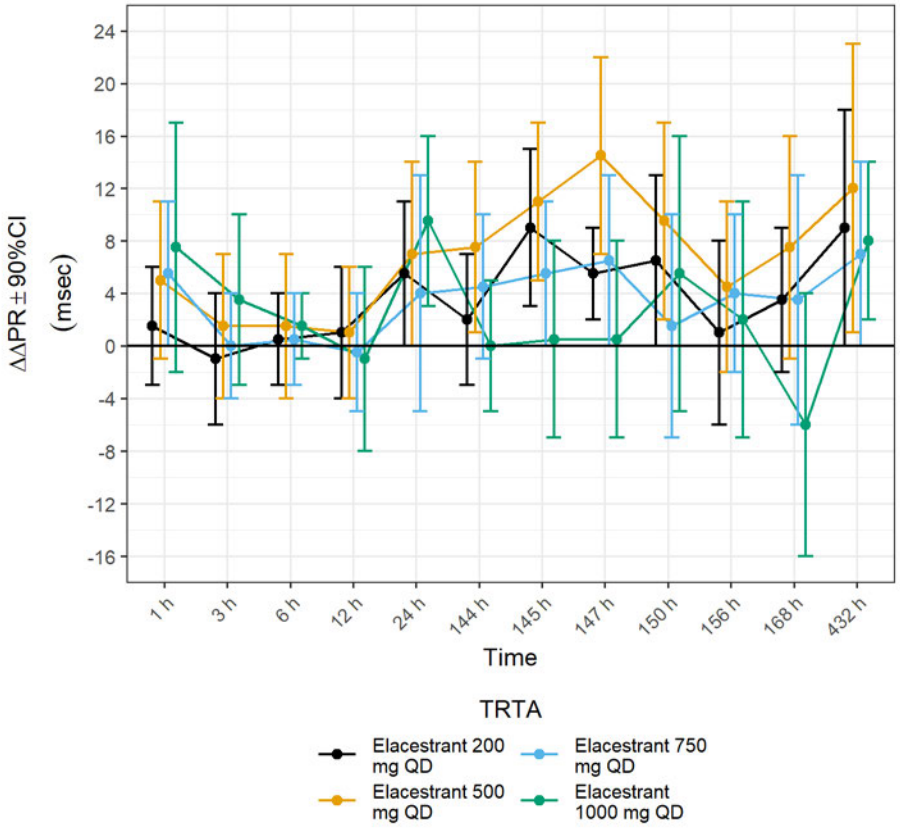
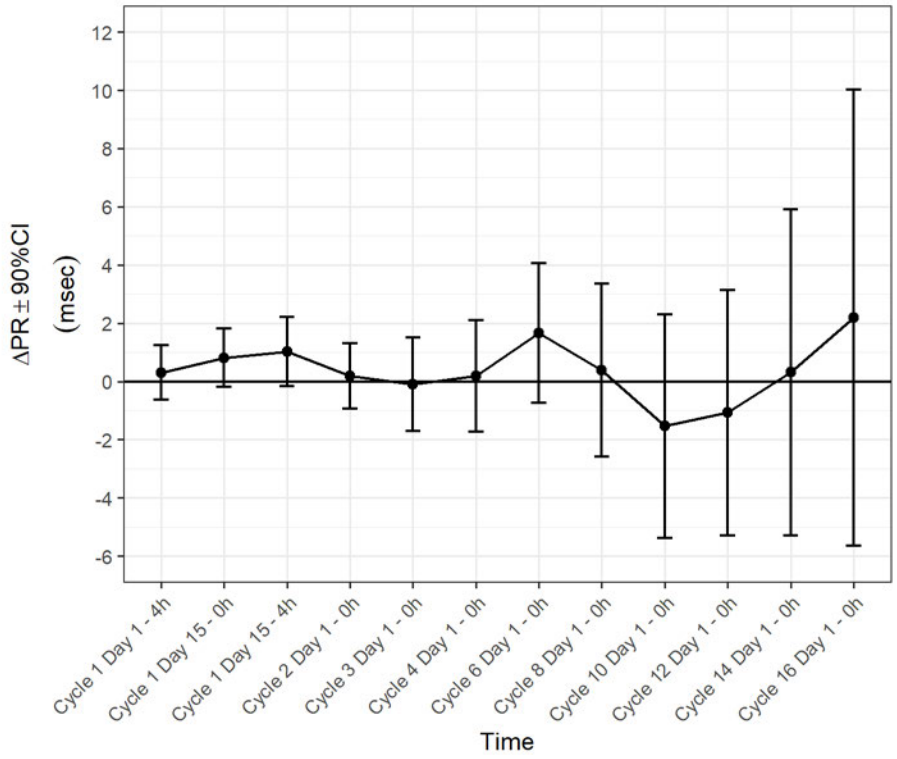


Figure 6: Mean and 90% CI of ΔPR Time-course for study RAD1901-308.



4.3.4 QRS

Figure 7 displays the time profile of ΔΔQRS for different treatment groups for study RAD1901-004. Figure 8 displays the time profile of Δ*QRS* for study RAD1901-308.

Figure 7: Median and 90% CI of ΔΔQRS Time-course for study RAD1901-004.

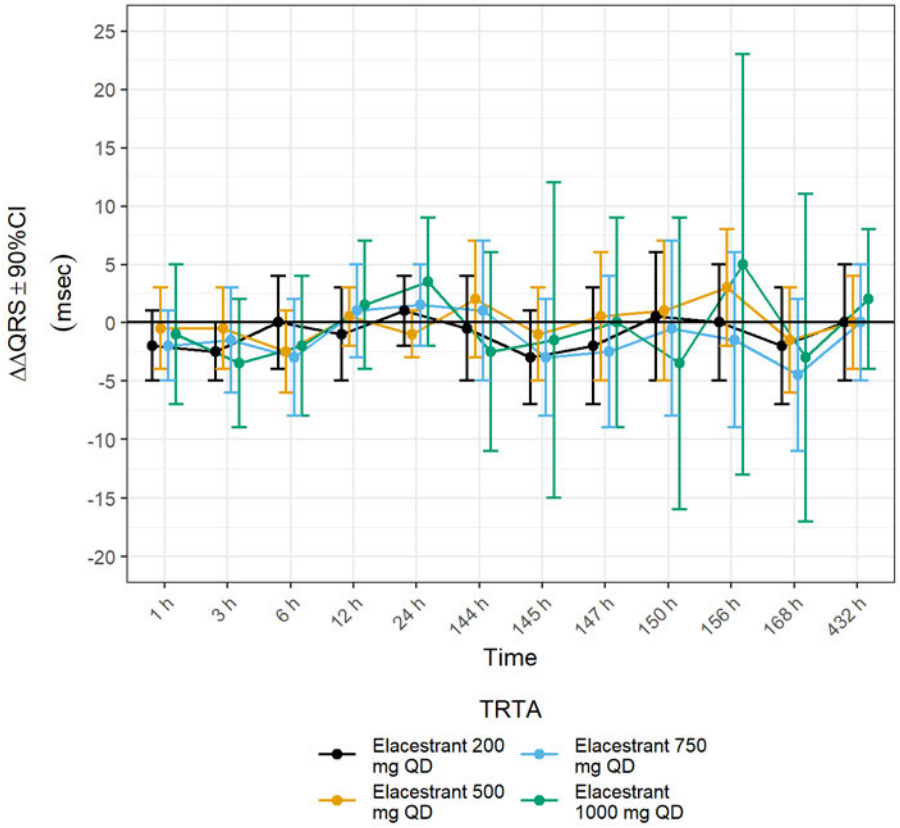
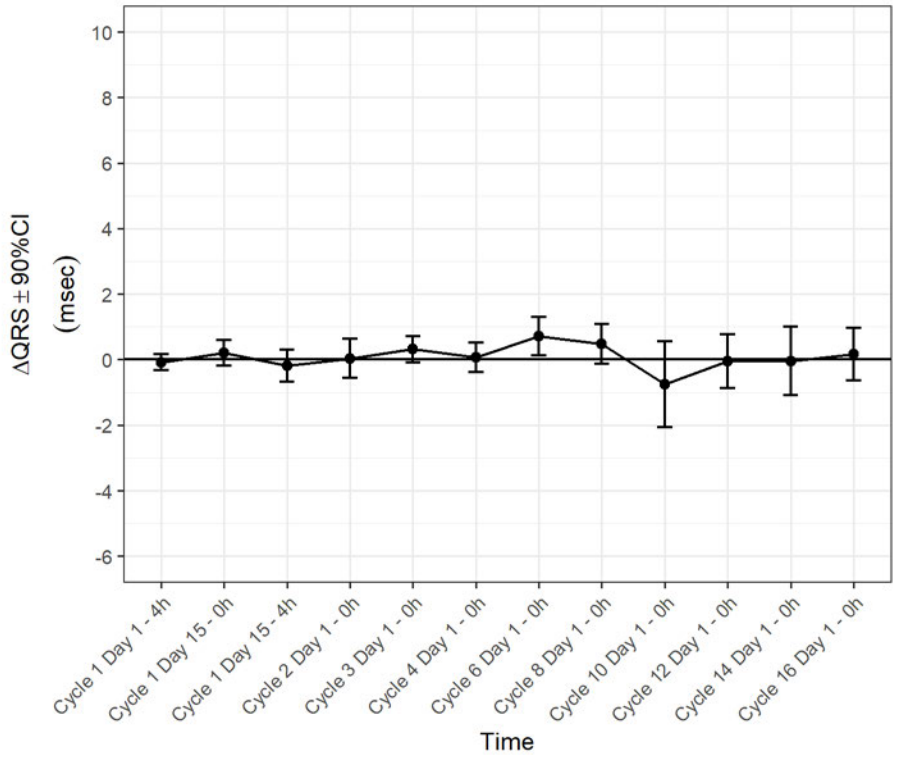


Figure 8: Mean and 90% CI of Δ*QRS* Time-course for study RAD1901-308.



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects had QTcF value >500 msec. None of the subjects had ΔQTcF value >60 msec.

4.4.2 HR

Table 2 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). There were 21 subjects having HR>100 beats/min in study RAD1901-308.

Table 2: Categorical Analysis for HR (maximum)

Study Identifier	Actual Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
RAD1901-004	Elacestrant 200 mg QD	15	195	14 (93.3%)	194 (99.5%)	1 (6.7%)	1 (0.5%)
	Elacestrant 500 mg QD	14	168	14 (100.0%)	168 (100.0%)	0 (0%)	0 (0%)
	Elacestrant 750 mg QD	8	93	8 (100.0%)	93 (100.0%)	0 (0%)	0 (0%)
	Elacestrant 1000 mg QD	7	69	7 (100.0%)	69 (100.0%)	0 (0%)	0 (0%)
	Placebo	8	105	8 (100.0%)	105 (100.0%)	0 (0%)	0 (0%)
RAD1901-308	Elacestrant 400 mg QD	236	1605	215 (91.1%)	1569 (97.8%)	21 (8.9%)	36 (2.2%)

4.4.3 PR

None of the subjects had PR value >220 msec and 25% over baseline.

4.4.4 QRS

None of the subjects had QRS value >120 msec and 25% over baseline.

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted for study RAD1901-004 using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK. The number of included subjects at each dose level from study RAD1901-004 was 15, 14, 8, and 7 for 200 mg, 500 mg, 750 mg, and 1000 mg, respectively.

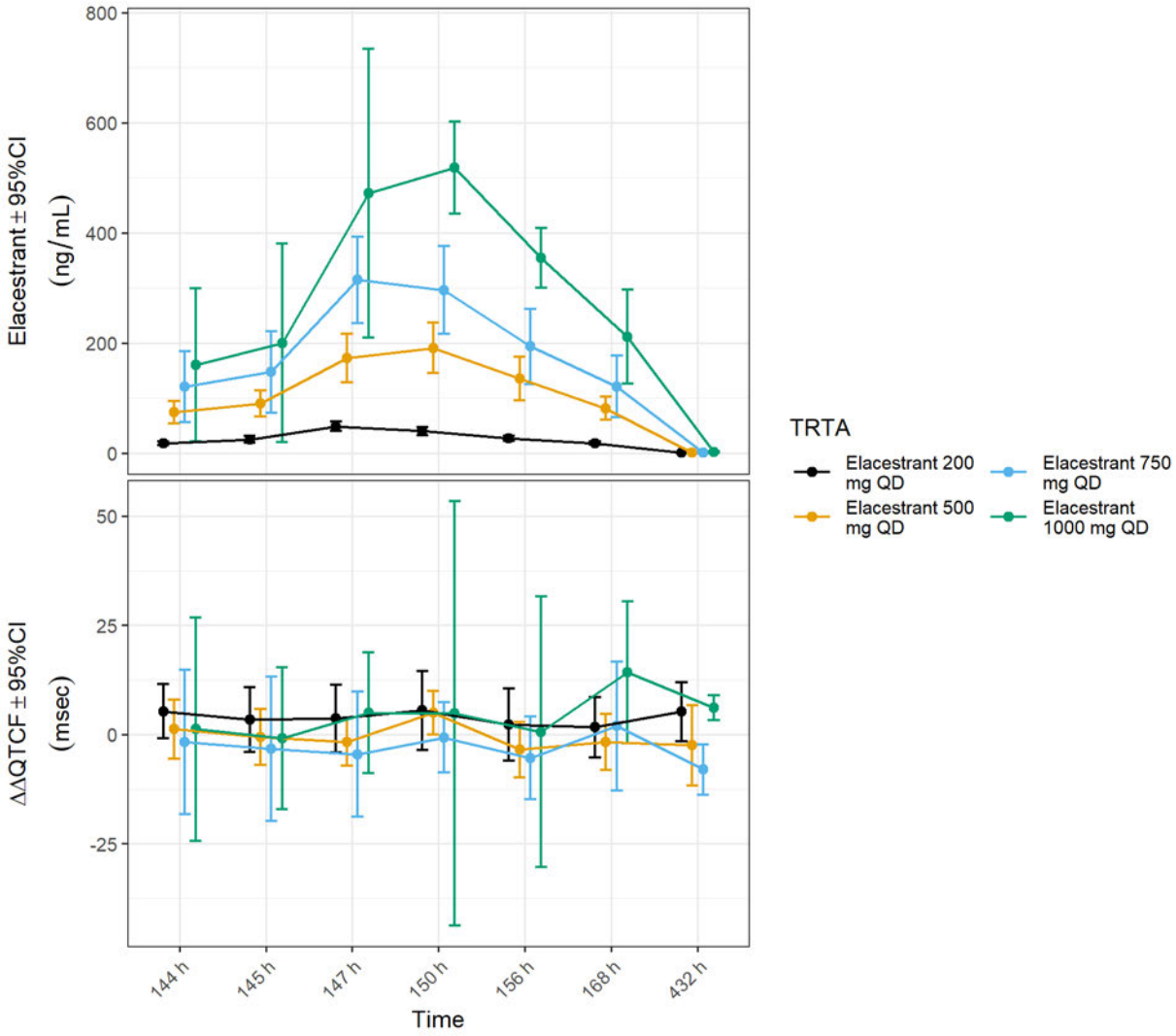
4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

Figure 3 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Figure 9 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF, with no appearance of significant hysteresis. Figure 10

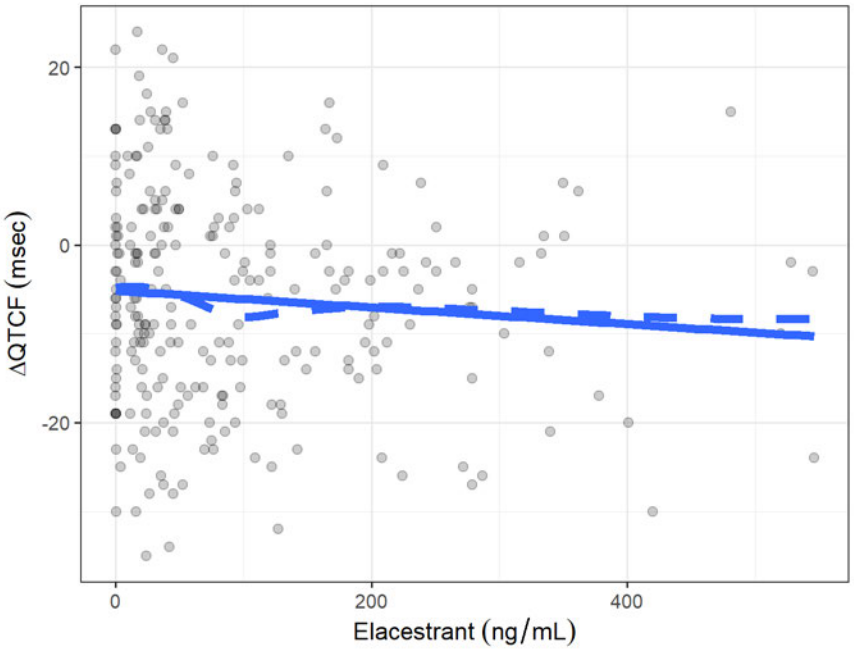
shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 9: Time-course of Drug Concentration (top) and QTcF (bottom)[1] for study RAD1901-004.



[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 10: Assessment of Linearity of the Concentration-QTcF Relationship for study RAD1901-004.



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 11. Predictions from the concentration-QTcF model are provided in Table 3.

Figure 11: Goodness-of-fit Plot for QTcF for study RAD1901-004.

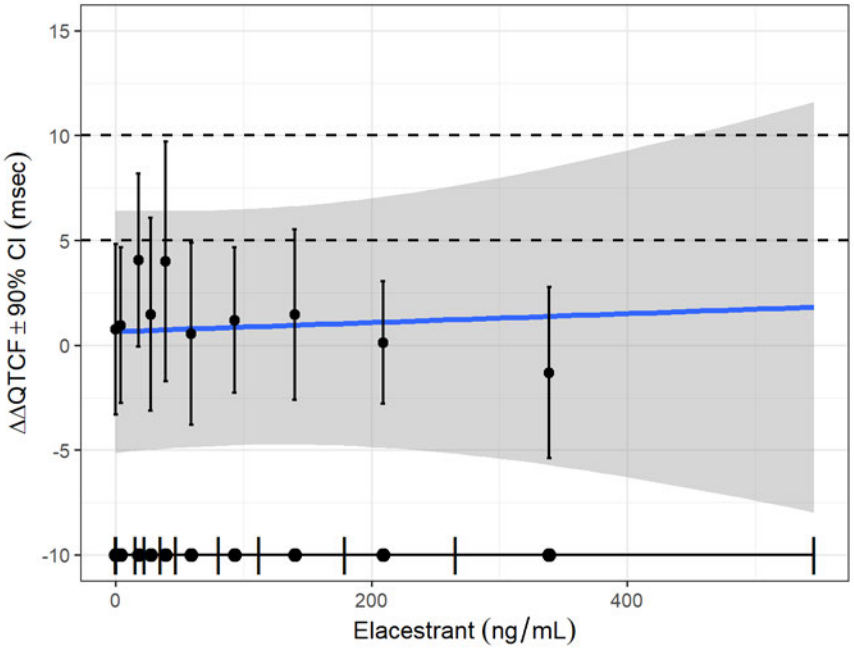


Table 3: Predictions from Concentration-QTcF Model for study RAD1901-004.

Actual Treatment	Analysis Nominal Period Day (C)	Elacestrant (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Elacestrant 200 mg QD	1	47.5	0.8	(-4.9 to 6.4)
Elacestrant 500 mg QD	1	190.9	1.1	(-4.8 to 6.9)
Elacestrant 750 mg QD	1	306.2	1.3	(-5.4 to 8.1)
Elacestrant 1000 mg QD	1	523.1	1.8	(-7.7 to 11.2)

4.5.1.1 Assay Sensitivity

Not applicable since elacestrant QT effects were evaluated under ICH E14 Q&A 6.1 section 2.2.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted

---

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/

ELIFORD N KITABI
10/12/2022 12:31:55 PM

XUTONG ZHAO
10/12/2022 12:33:37 PM

DALONG HUANG
10/12/2022 12:51:56 PM

MICHAEL Y LI
10/12/2022 12:53:11 PM

LARS JOHANNESEN
10/12/2022 02:25:45 PM

CHRISTINE E GARNETT
10/12/2022 02:28:22 PM

M E M O R A N D U M

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

DATE: 9/28/2022

TO: Division of Oncology I (DO I)
Office of Oncologic Diseases (OOD)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 217639

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

OSIS is not able to initiate an inspection or remote regulatory assessment (RRA) for the clinical sites listed below due to resource constraints.

Celerion (Tempe, AZ): The Office of Regulatory Affairs (ORA) inspected the site in June 2019. The inspection was conducted under the following submissions: NON-RESPONSIVE

The final classification for the inspection was Voluntary Action Indicated (VAI) for the following observation:

NON-RESPONSIVE

After reviewing a written response from this site, OSIS recommended that data from NON-RESPONSIVE be accepted for Agency review and that data from NON-RESPONSIVE be excluded. (Final OSIS Review - June 2019).

Celerion (Lincoln, NE): ORA inspected the site in November 2019. The inspection was conducted under the following submission: NON-RESPONSIVE The final classification for the inspection was No Action Indicated (NAI).

(b) (4) OSIS conducted a Remote Regulatory Assessment (RRA) for the analytical site in (b) (4) which falls within the surveillance interval. The RRA were conducted under the following submission: NON-RESPONSIVE OSIS concluded that data from the reviewed studies were reliable.

Sites

Facility Type	Facility Name	Facility Address
Clinical	Celerion	2420 West Baseline Road, Tempe, AZ
Clinical	Celerion	621 Rose Street, Lincoln, NE
Analytical	(b) (4)	

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/

FOLAREMI ADEYEMO
09/28/2022 01:23:31 PM