CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218881Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: September 2, 2025

To: Ja'Kaya Wilson, Regulatory Project Manager, Division of Oncology I (DO1)

From: Courtney Leach, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for INLURIYO (imlunestrant) tablets, for oral use

NDA: 218881

Background:
In response to DO1's consult request dated November 19, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for INLURIYO (imlunestrant) tablets, for oral use.

PI/PPI
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 22, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI/Medication Guide/IFU, and comments were sent under separate cover on August 28, 2025.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on August 29, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Courtney Leach at (301) 796-1044 or Courtney.Leach@fda.hhs.gov.

PI:

Section(s)	Statement from Draft (if applicable)	OPDP Comments
HIGHLIGHTS OF PRESCRIBING INFORMATION: Adverse Reactions	The most common (incidence ≥10%) adverse reactions, including laboratory abnormalities were: hemoglobin decreased, musculoskeletal pain, neutrophils decreased, AST increased, fatigue, diarrhea, ALT increased, triglycerides increased, nausea, platelets decreased, constipation, (b) (4), cholesterol increased, and abdominal pain. (6.1)	We note that "Calcium decreased" is included in Table 4 at an incidence ≥10%. This information is not included in the Adverse Reactions section of the HIGHLIGHTS or in the most common adverse reactions list in section 6.1. We recommend revising the most common adverse reactions in the HIGHLIGHTS and the most common adverse reactions list in section 6.1 to match Table 4.
17 PATIENT COUNSELING INFORMATION	"Instruct patients to take INLURIYO at approximately the same time each day and to swallow the tablet(s) whole." (emphasis added)	Section 2.2 **Recommended Dosage and Administration** does not indicate INLURIYO should be taken at the same time each day. For consistency, we recommend including this information with the administration instructions in section 2.2, we defer to DO1/DMEPA.

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

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/s/

COURTNEY L LEACH
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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:	August 28, 2025
To:	Ja'Kaya Wilson, MS Regulatory Project Manager **Division of Oncology I (DO1)**
Through:	Barbara Fuller, MSN, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Courtney Leach, PharmD, BCCCP, BCP Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	INLURIYO (imlunestrant)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 218881
Applicant:	Eli Lilly and Company

1 INTRODUCTION

On October 31, 2024, Eli Lilly and Company submitted for the Agency's review an original New Drug Application (NDA) 218881 for INLURIYO (imlunestrant) tablets, for oral use. The Applicant proposes an indication for the treatment of adults with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, estrogen receptor-1 (ESR1)-mutated advanced or metastatic breast cancer previously treated with an endocrine-based regimen.

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 I (DO1) on November 19, 2024, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for INLURIYO (imlunestrant) tablets.

2 MATERIAL REVIEWED

- Draft INLURIYO (imlunestrant) tablets PPI received on October 31, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 19, 2025, and August 22, 2025.
- Draft INLURIYO (imlunestrant) tablets Prescribing Information (PI) received on October 31, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 19, 2025, and August 22, 2025.

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 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.

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/s/

SUSAN W REDWOOD
08/28/2025 08:18:24 AM

COURTNEY L LEACH
08/28/2025 08:39:04 AM

BARBARA A FULLER
08/28/2025 09:04:12 AM

CLINICAL INSPECTION SUMMARY

Date	8/6/2025
From	Leigh Marcus, M.D., Senior Physician Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Ja'Kaya Wilson, Regulatory Project Manager Joshua Donaldson, M.D., Clinical Reviewer Preeti Narayan, M.D., Team Leader Laleh Amiri-Kordestani, M.D., Division Director Division of Oncology 1 (DO1) Office of Oncologic Diseases (OOD)
NDA/BLA #	NDA 218881
Applicant	Eli Lilly and Company
Drug	Imlunestrant
NME	Yes
Review Priority	Standard
Proposed Indication	Treatment of adult patients with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2-negative, estrogen receptor-1-mutated advanced or metastatic breast cancer previously treated with an endocrine-based regimen
Consultation Request Date	1/13/2025
Summary Goal Date	8/29/2025
Action Goal Date	9/26/2025
PDUFA Date	10/31/2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study J2J-OX-JZLC were submitted to the Agency in support of this New Drug Application (NDA) for imlunestrant for the treatment of adult subjects with breast cancer.

Two foreign clinical investigators (CIs), Dr. Monica Lis Casalnuovo (Site #33334), and Dr. Jose Angel Garcia Saenz (Site #74489), one domestic CI, Dr. Komal Jhaveri (Site #99301), and the

Sponsor were inspected for Study J2J-OX-JZLC.

Based on the inspections of three CIs and the Sponsor, no significant regulatory violations were identified. The clinical data generated by these CI sites are verifiable. Study J2J-OX-JZLC appears to have been conducted adequately, and the data generated by these sites and reported by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Imlunestrant is an orally bioavailable, estrogen receptor (ER) antagonist and degrader, designed to support continuous ER inhibition throughout the dosing period, with a large volume of distribution and high intratumoral accumulation compared to plasma. Imlunestrant has shown antitumor activity within multiple preclinical models, including *ESR1*-mutant models, along with an acceptable toxicity profile in nonclinical species. Imlunestrant is being investigated for the treatment of ER-positive, human epidermal growth factor receptor 2 (HER2)-negative, estrogen receptor-1-mutated (*ESR1*) advanced or metastatic breast cancer previously treated with an endocrine-based regimen.

Study J2J-OX-JZLC (EMBER-3)

*Title: "*A Randomized, Open-Label, Phase 3 Study of LY3484356 vs Investigator's Choice of Endocrine Therapy, in Patients with Estrogen Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer Previously Treated with Endocrine Therapy*"*

Study J2J-OX-JZLC was a Phase 3 global, randomized, open label 3-arm study of imlunestrant, investigator's choice of endocrine therapy of either fulvestrant or exemestane, and imlunestrant plus abemaciclib in subjects with ER+, HER2- locally advanced or metastatic breast cancer previously treated with an AI, with or without a CDK4/6 inhibitor.

Eligible subjects included adults greater than 18 years of age who had ER+, HER2- breast cancer per ASCO-CAP guidelines per local testing and either locally advanced or metastatic disease. Subjects must have relapsed with evidence of progression while on or within 12 months of completion of (neo)adjuvant aromatase inhibitor (AI), alone or in combination with a CDK4/6 inhibitor, with no treatment for advanced disease; relapsed with evidence of progression after 12 months from completion of (neo)adjuvant endocrine therapy (ET): tamoxifen, or AI, with subsequent progression on or after only 1 line of therapy with an AI, alone or in combination with a CDK4/6 inhibitor; presented with de novo metastatic disease, with subsequent progression on or after only 1 line of therapy with an AI, alone or in combination with a CDK4/6 inhibitor. Additionally, per RECIST v1.1, subjects were required to have either measurable disease or nonmeasurable bone-only disease. Baseline *ESR1*-mutation status was determined by circulating tumor DNA analysis of plasma collected prior to initiating study treatment.

The study consisted of a 28-day screening phase; followed by a treatment phase; and a post-treatment phase, which included safety, efficacy, and survival follow-up. Investigator's Choice Endocrine Therapy (fulvestrant or exemestane) was selected prior to randomization.

Subjects were randomized 1:1:1 between the 3 treatment arms:

1. Arm A: imlunestrant monotherapy (hereinafter referred to as "imlunestrant arm")
2. Arm B: investigator's choice of ET (fulvestrant or exemestane, SOC arm)
3. Arm C: imlunestrant in combination with abemaciclib (imlun+abema arm)

Subjects were stratified by:

- Previous treatment with any CDK4/6 inhibitor (yes versus no)
- Presence of visceral metastases (yes versus no); visceral includes lung, liver, brain, pleural, and peritoneal involvement, and
- Region (East Asia versus North America/Western Europe versus Others).

Subjects received:

1. Imlunestrant arm received imlunestrant 400 mg orally once daily as monotherapy
2. SOC arm received investigator's choice of exemestane or fulvestrant, administered per labelled doses and schedules
3. Imlun+abema arm received imlunestrant 400 mg once daily in combination with abemaciclib in accordance with abemaciclib's labeled dose and schedule.

Subjects were treated until disease progression, development of unacceptable toxicity, withdrawal of informed consent or other discontinuation criteria as outlined in the protocol.

The primary objective of Study J2J-OX-JZLC was to compare the progression-free survival (PFS) of imlunestrant (Arm A) to the standard comparator of Investigator's Choice Endocrine Therapy of either fulvestrant or exemestane (Arm B), to compare the PFS of Arm A to Arm B in the *ESR1-mutation* detected population, and to compare the PFS of imlunestrant plus abemaciclib (Arm C) to imlunestrant (Arm A).

The primary efficacy outcome for the study submitted for approval was Investigator-assessed PFS data from subjects in the *ESR1-mutation* sub-population comparison of Arm A versus Arm B. PFS was defined as the time from randomization to the date of first documented progression of disease or death from any cause in the absence of disease progression using RECIST version 1.1, as below "PFS Censoring Scheme". Subjects known to be alive and without disease progression were censored at the last known date of progression-free assessment. Response to treatment was determined based on investigator assessment.

A total of 874 subjects were enrolled: 331 patients enrolled and 326 treated in the imlunestrant arm; 330 patients enrolled and 324 treated in the SOC arm (292 treated with fulvestrant; 32 treated with exemestane); 213 patients enrolled and 209 treated in the imlun+abema arm. A

total of 256 subjects with *ESR1-mutation* were assessed for data analysis to support the application, 138 subjects were enrolled on the imlunestrant arm.

To provide the overall safety profile of imlunestrant in subjects with breast cancer, the primary safety review in the submission included the safety data from the pivotal Study J2J-OX-JZLC. The safety population included all subjects randomly assigned to study treatment who took at least 1 dose of study treatment (N=859). A data monitoring committee reviewed the safety of study treatment assessed by evaluation of adverse events (AEs) (e.g., frequency, seriousness, severity, and type), including treatment-emergent AEs of special interest (AESIs), changes from baseline in laboratory values and incidence of measurements, and clinically meaningful changes in physical examination findings including vital signs.

The study was conducted at 195 centers in 22 countries. Subjects first enrolled to Study J2J-OX-JZLC on October 15, 2021. Data cut-off date for the primary analysis was June 24, 2024. The study was ongoing during the time of the inspection.

III. RESULTS

1. Monica Lis Casalnuovo/Site #33334
   Juncal 2222, Ground and First Floor
   Caba, Ciudad Autónoma De Buenos Aires C1125
   Argentina

   Inspection Dates: 4/1/2025, 4/3/2025 – 4/4/2025, 4/7/2025

   This was a comprehensive, BIMO review based inspection of Monica Lis Casalnuovo. This was the first FDA inspection of this CI.

   At this site for Study J2J-OX-JZLC, 15 subjects were screened, and 9 subjects were enrolled, 5 of which had the ESR1-mutation. At the time of the inspection, all subjects had discontinued treatment due to disease progression.

   During the inspection, subject records reviewed included informed consent documents (ICDs), subject case history records, eligibility criteria, protocol deviations, primary outcome data, and adverse event reporting. The regulatory documents reviewed included independent ethics committee submissions, protocol amendments, financial disclosures, investigational product (IP) accountability records, and training.

   The primary efficacy endpoint data were verifiable. There was no underreporting of adverse events (AEs) or serious AEs (SAEs). ICDs did not contain the required statement related to ClinicalTrials.gov in any of their versions of the main ICF document.

   Reviewer's comments: There was a discussion to ensure the site has the required statement

related to clinicaltrials.gov in all versions of the main informed consent form going forward.

The inspection verified adequate source data for the study subjects.

2. Jose Angel Garcia Saenz, M.D./Site #74489
   C/o Martin Lagos s/n, Pabellon B, Planta Baja
   Madrid 28040
   Spain

   Inspection Dates: 5/19/2025 – 5/22/2025

   This was a comprehensive, BIMO review based inspection of Dr. Jose Angel Garcia Saenz. This was the first FDA inspection of this CI.

   At this site for Study J2J-OX-JZLC, 15 subjects were screened, 3 subjects were screen failures, 12 subjects were enrolled, 4 subjects of which were on the imlunestrant arm and ESR-1 mutated. Of the 4 subjects enrolled on imlunestrant, 3 subjects had disease progression.

   During the inspection, subject records reviewed included ICDs, subject case history records, eligibility criteria, protocol deviations, primary outcome data, and adverse event reporting. The regulatory documents reviewed included independent ethics committee submissions, protocol amendments, financial disclosures, investigational product (IP) accountability records, and training.

   The primary efficacy endpoint data were verifiable. All AEs and SAEs were reported from the site. However, there were SAE's that were not reported within the 24-hour time frame during the follow-up period (Subject # (b) (6) [emesis, and COVID-19] and Subject # (b) (6) ["pharmacological pneumonitis" defined as drug-induced pneumonitis, a type of interstitial lung disease]).

   Reviewer's comment: Late reporting of SAEs was unlikely to have a significant impact on the safety or results of the study, and AEs are already listing under labelling in Section 6. Additionally, the research team had training to make sure that even in the follow-up phase that SAEs must be reported to the sponsor within the 24-hour timeframe.

   In general, the inspection verified adequate source data for the study subjects.

3. Komal Jhaveri, M.D./Site #99301
   225 Summit Avenue
   Montvale, NJ 07645

   Inspection Dates: 3/10/2025 –3/14/2025

This was a comprehensive, BIMO review based inspection of Dr. Komal Jhaveri. The previous FDA inspection in 7/2024 showed an outdated protocol version being used, 2 minor AEs and a concomitant medication was not reported for 1 subject, and a discrepancy in eligibility status was observed in one subject.

At this site for Study J2J-OX-JZLC, 21 subjects were screened; 19 subjects enrolled in which 5 subjects were *ESR1* mutated. Of the 5 subjects with *ESR1-mutation*, 4 subjects had progressive disease and one subject was in active treatment.

During the inspection, 9 subject records were reviewed including all of the 5 subjects with *ESR1-mutation*. The review included ICDs, AE reporting, subject case history records, eligibility criteria, protocol deviations, adverse event reporting, study visit assessments, and concomitant medications. The regulatory documents reviewed Institutional Review Board (IRB) submissions for initial approval and continuing reviews, protocol amendments, financial disclosures and FDA Form 1572s, IP accountability records, and training.

The primary efficacy endpoint data were verifiable. There was underreporting of one AE in 1 subject (Subject # (b) (6)) "hip pain" missing from the sponsor data listing. There was no evidence of under-reporting of SAEs. An outdated ICD was used for one subject (Subject # (b) (6)), and the site did not properly calculate the proper window of dates to obtain scans which resulted 2 subjects having multiple "out of window (OOW)" +/- 3-day scans, 1 of whom with the *ESR1-mutation* (Subject # (b) (6)) in the indicated population.

Reviewer's comments: The underreported AE in Subject # (b) (6) was added into electronic data capture (EDC) by site after data cut-off and the AE (hip pain) was likely due to underlying cancer. The OOW scans were off by 1-3 days, therefore no clinical significance was seen. Protocol deviations were filed for all OOW assessments. Subject # (b) (6) was consented with an outdated ICD that was on a shared computer drive and was reconsented with the current ICD after the inspection. The site agreed to no longer share documents on an open electronic platform, and in the future, will only be performing e-consent via their EPIC electronic medical record (EMR) software.

In general, the inspection verified adequate source data for the study subjects.

4. Eli Lilly and Company
   Lilly Corporate Center
   Indianapolis, Indiana 46285

   Inspection Dates: 3/24/2025 – 3/27/2025

   This inspection covered the Sponsor's study conduct related to Study J2J-OX-JZLC. The previous FDA inspection in 9/2022 had no significant regulatory violations.

Records reviewed during the inspection included:

- Standard operating procedures (SOP)
- Monitoring plan, procedures, and activities (CRO: (b) (4))
- IRB approvals
- Data collection and handling (CRO: (b) (4))
- Primary efficacy data
- Electronic records and record retention
- IP accountability
- Safety reporting and handling including reporting of SAEs, i.e., deaths
- Selection of clinical investigators, sites, and monitors
- Form FDA 1572s for CIs in the U.S.; GCP agreements for foreign CIs
- Financial disclosures
- Contract agreements

Lilly had agreements with a CROs to assist in monitoring sites. Four sites: Site #11738, Site #14248, Site #29299, and Site #96527, were reviewed for monitoring reports and other documents during this inspection. Site #29299 was put on enrollment hold due to noncompliance, and the site of Dr. Satheesh Thungappa was terminated due to noncompliance. Dr. Thungappa was notified of Good Clinical Practice (GCP) noncompliance for a different study, Study (b) (4); consequently, Lilly decided to end the site's participation in Study J2J-OX-JZLC. Lilly determined that subject safety and safety data, and data integrity in general, were not compromised for study.

A review of all MRI reports was completed for all subjects randomized to the standard regimen or enhanced titration at the four clinical sites chosen for CI inspections: Sites #55999 (n=12), #87714 (n=35), #91581 (n=15), and #98053 (n = 15). A review of PET centiloid data was completed for all subjects randomized to the standard regimen or enhanced titration enrolled at the four clinical sites chosen for CI inspections. No data discrepancies were identified. The sponsor was asked to provide a list of all data changes to PET data for Study 15T-MC-AACQ. The review of these centiloid values did not identify any significant changes, of note, the values were recorded up to 9 significant figures. No PET data discrepancies were identified. The primary efficacy endpoint of PFS was verified from the data listings provided.

Overall, the sponsor's oversight and monitoring for Study J2J-OX-JZLC appears to have been conducted adequately.

{See appended electronic signature page}

Leigh Marcus, M.D. Senior Physician
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation

Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

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

cc:

Central Document Room/NDA #218881
Division of Oncology (DO1)
Division Director/Laleh Amiri-Kordestani
Medical Team Leader/Preeti Narayan
Medical Officer/Joshua Donaldson
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Min Lu
OSI/DCCE/GCPAB/Senior Physician/Leigh Marcus
OSI/GCPAB Program Analyst/Yolanda Patague

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/s/

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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)

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

Date of This Review:	July 2, 2025
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 218881
Product Name, Dosage Form, and Strength:	Inluriyo (imlunestrant) tablet, 200 mg
Applicant Name:	Eli Lilly and Company
FDA Received Date:	June 27, 2025
TTT ID #:	2024-11855-1
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF MEMORANDUM

Eli Lilly and Company submitted revised container labels received on June 27, 2025 for Inluriyo. The Division of Oncology 1 (DO1) requested that we review the revised container labels for Inluriyo (Appendix A) to determine if they are 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

Eli Lilly and Company implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Mahmoud, S. Label and Labeling Review for Inluriyo (NDA 218881). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 APR 25. TTT ID: 2024-11855.

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 218881
Submission Number	0001
Submission Date	10/31/2024
Date Consult Received	12/17/2024
Drug Name	Imlunestrant
Indication	Advanced or metastatic breast cancer
Therapeutic Dose	400 mg QD
Clinical Division	DO1

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 12/17/2024 regarding the Applicant's QT evaluation. We reviewed the following materials:

- Summary of clinical pharmacology studies, including integrated QT risk assessment (appendix) (NDA 218881/ SN0001; link);
- QT evaluation checklist (NDA 218881/ SN0006; link);
- Clinical study report for study EMBER (J2J-MC-JZLA) (NDA 218881/ SN0001; link);
- Protocol for study EMBER (J2J-MC-JZLA) (IND 145311/ SN0001; link);
- Protocol addenda for study EMBER (J2J-MC-JZLA) (NDA 218881/ SN0001; link);
- Clinical study report for study EMBER-3 (J2J-OX-JZLC) (NDA 218881/ SN0001; link);
- Proposed label (NDA 218881/ SN0001; link);
- Highlights of clinical pharmacology and cardiac safety (IND 145311 / SN0158; link); and
- Applicant's responses to IR (NDA 218881/ SN0008, SN0013, SN0017).

1 SUMMARY

Based on data from study EMBER (J2J-MC-JZLA), imlunestrant does not demonstrate mean QTc interval prolongation ≥20 msec (Table 1). In the absence of a positive control and a placebo group there is a reluctance to conclude a lack of an effect of imlunestrant on the QTc interval.

The Applicant supplemented the alternative QTc assessment with an integrated nonclinical risk assessment and the cardiovascular safety database. If these data are negative, then the totality of evidence could support concluding a low likelihood of proarrhythmic risk due to delayed repolarization (ICH E14 Q&A 6.1). While the cardiovascular safety database based on EMBER-3 does not show an increased

proarrhythmic risk, we do not agree that the integrated nonclinical risk assessment (in vitro hERG and in vivo QT study) is negative. Consequently, the available data for imlunestrant do not support concluding a low likelihood of proarrhythmic risk due to delayed repolarization.

The clinical study EMBER was an open-label study consisting of a Phase 1a dose escalation of imlunestrant monotherapy followed by Phase 1b dose expansions of imlunestrant administered as monotherapy or in combination with other targeted therapeutic agents. The highest dose provided (b) (4) fold high clinical exposure. Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that imlunestrant is associated with ≥20 msec mean increases in the QTcF interval (section 4.5). The findings of the primary analysis are corroborated by the by-time analysis (section 4.3).

The hERG safety margin for imlunestrant ((b) (4) x) exceeds the hERG safety margins of reference drugs associated with QTc prolongation based on hERG assays following best practice recommendations. In contrast, the in vivo studies failed to show low risk of QTc prolongation. This is because QTc prolongation was observed in the 600 mg/kg dose group at multiple visits in the 3-month toxicology study, which had sufficient sensitivity based on a historical positive control study. The Applicant also submitted a 28-day toxicology study, which did not show QTc prolongation. It is unclear why QTc prolongation was not observed at the 600 mg/kg dose group in this study. Considering that QTc prolongation was observed in the 3-month toxicology study, we do not agree that the nonclinical data supportive of low risk as defined in ICH S7B Q&A 1.1 (section 3.1.2 and section 6).

In EMBER-3, there was no increase in percent of patients experiencing AEs within the broad SMQ query of Torsade de Pointes/QT prolongation + seizure in the imlunestrant/ imlunestrant + abemaciclib (I+A) arms than the standard of care (SOC) arm (1.5%/2.9% versus 1.9%). More patients experienced QTc prolongation in the imlunestrant/I+A arms than the SOC arm (0.9%/1.9% versus 0%), which could be due to the lack of ECG collection on the SOC arm. Most patients who experienced QTc prolongation had other confounding factors, including electrolyte imbalance, comorbidities, and concomitant medications (section 4.6). Four patients (three patients receiving I+A and one receiving imlunestrant) experienced significant QTc prolongation (>500 msec and ΔQTc >60 msec) where contribution of imlunestrant cannot be excluded, including dose discontinuation for one patient because of QTc prolongation (I+A). Altogether, the cardiovascular safety database based on EMBER-3 does not indicate an increased proarrhythmic risk for imlunestrant.

Table 1: Summary of findings

QTc assessment pathway	☐ *Thorough QT study* ☐ *Substitute for thorough QT study (5.1)* ☒ *Alternative QT study when a thorough QT study is not feasible (6.1)*
Clinical QT study findings	• Cmax at the maximum recommended dose (400 mg QD without food) was 141 ng/mL. (b) (4) 1.9-fold

<table>
<tr><td></td><td>increase with strong CYP3A4 inhibitors, which resulted in Cmax of 266 ng/mL (section 3.1).
• At the highest dose in study EMBER (1200 mg QD without food), Cmax was 253 ng/mL, covering clinical exposure by 1.8-fold and high clinical exposure by (b) (4) fold.
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Concentration (ng/mL)</th><th>ΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>QTcF</td><td>Imlunestrant 400 mg QD</td><td>141.9</td><td>1.1</td><td>(-0.6 to 2.8)</td></tr>
<tr><td>QTcF</td><td>Imlunestrant 1200 mg QD (highest dose)</td><td>253.0</td><td>0.6</td><td>(-2.0 to 3.3)</td></tr>
</table></td></tr>
<tr><td>In vitro findings</td><td>
<table>
<tr><th></th><th>Safety Margin</th><th>Reference Drugs</th><th>Best Practice Deviations</th></tr>
<tr><td>imlunestrant</td><td>(b) (4) x</td><td>Dofetilide: 38x
Moxifloxacin: 36x
Ondansetron: 4x</td><td>Only one concentration was tested for positive control</td></tr>
</table></td></tr>
<tr><td>In vivo findings</td><td>• It is unclear why QTc prolongation was not observed in the 600 mg/kg dose group in study 8002569 (28-day toxicology study).
• Data from Week 15 of study 8003147 (3-month toxicology study) demonstrated sufficient assay sensitivity and showed QTc prolongation at the 600 mg/kg dose group after 10 hours postdose at Weeks 4, 8, and 15.</td></tr>
</table>

2 RECOMMENDATIONS

2.1 PROPOSED LABEL

Below are proposed edits to the label submitted to SN0001 (link).

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

(b) (4)

At 2 times the mean maximal concentration provided by the highest recommended dose of imlunestrant, a mean increase in the QTc interval >20 ms was not observed.

Reviewer's comment: We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance (link).

3 APPLICANT'S SUBMISSION

3.1 OVERVIEW

Imlunestrant (INLURIYO™) is an estrogen receptor antagonist indicated for treatment of adults with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer, previously treated with an endocrine-based regimen. The recommended dosage is 400 mg (tablet) QD without food.

The CS-IRT has not previously reviewed the QTc assessment conducted by the Applicant. The Applicant proposed QT evaluation under the 6.1 pathway with integrated risk assessment.

The clinical QTc assessment was based on study EMBER (study JZLA), a single-arm, open-label dose escalation (Phase 1a) and dose expansion (Phase 1b) study in patients with metastatic breast cancer and endometrial cancer. During Phase 1a, imlunestrant was administered as monotherapy in 5 dose cohorts (200-1200 mg QD) and 81 patients were treated. During Phase 1b, imlunestrant 400 mg QD or 800 mg QD (before 400 mg QD was finalized as RP2D) was administered as monotherapy (E3 and E8, 71 treated, 8 at 800 mg QD) or in combination with other targeted agents. Concentration-QTc analysis was used as the primary analysis, performed on Phase 1a and Phase 1b monotherapy cohorts only (E3 and E8). All the cohorts used in C-QTc analysis were dosed in 28-day cycles without food (1 hour before and 2 hours after). See section 5 for a detailed review of the Applicant's QTc assessment. Automatic ECG readings were used for FDA's analysis since the Applicant did not have ECG waveforms with annotated manual overread.

The Applicant's cardiac safety assessment was based on study EMBER and EMBER-3. EMBER-3 was a phase 3, randomized, open-label study of imlunestrant, investigator's choice of endocrine therapy (standard of care), and imlunestrant plus abemaciclib (I +A) in patients with estrogen receptor positive, HER2 negative locally advanced or metastatic breast cancer previously treated with endocrine therapy. See section 3.2.4 and 4.6 for more details.

The nonclinical assessment included in vitro hERG assay (study 190112-fmd) and in vivo QT evaluations in monkeys (28-day study 8002569 and 3-month study 8003147). See section 3.1.2 and section 6 for more details.

3.1.1 Clinical Pharmacology

The clinical pharmacology of imlunestrant was summarized in the table of highlights of clinical pharmacology and cardiac safety. Briefly, median time to peak concentration of imlunestrant (Tmax) was 4 hours and time to steady state after once daily dosing was 5 to 8 days (accumulation factor: 2 to 3-fold). Imlunestrant accounted for 20% of total drug in circulation. It was mainly eliminated by metabolism, with phenolic glucuronide conjugate (M1), sulfate conjugate (M2), and oxidative sulfate conjugate (M12) accounting for 20%, 4%, and 5% of total drug moiety. About 97% was excreted through feces (20% unchanged) and 0.3% in urine.

Strong CYP3A4 inhibition with itraconazole increased imlunestrant Cmax approximately 87%. Moderate and severe hepatic impairment did not increase Cmax but increased imlunestrant AUC (0-∞) by approximately 2.2-fold and 3.1-fold.

Low-fat meal increased Cmax and AUC (0-∞) by approximately 3.6-fold and 2-fold respectively. The Applicant proposed imlunestrant to be taken without food.

The Applicant also proposed to reduce imlunestrant dosage to 200 mg QD for patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. No dosage adjustment was recommended for patients with mild hepatic impairment (Child-Pugh A). There's no proposed dose reduction for CYP3A4 inhibitors.

Table 2 presents the highest dose in the Applicant's QTc assessment and coverage of exposures at therapeutic and anticipated high clinical exposure scenario.

Table 2. Summary of Dose and Exposure Assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	400 mg QD, oral tablets, without food	141 ng/mL ($C_{max,ss}$)
Applicant's High clinical exposure scenario	[redacted] (b) (4)	
Highest dose in QTc assessment	1200 mg QD, oral tablets, fasted	253 ng/mL[1]
C_{max} Ratio	1.8 over clinical exposure and [redacted] (b) (4) over high clinical exposure	

[1] n = 3 for the 1200 mg QD dose cohort. The next highest dose group was 800 mg QD with Cmax of 247 ng/mL on C1D15 (n = 15).

3.1.2 Nonclinical Safety Pharmacology Assessments

Original electrophysiology records for the hERG assay and in vivo studies were provided by the Applicant. We reanalyzed these records of hERG assay and the in vivo studies to assess data quality and verify study report conclusions (see section 6).

In summary, the hERG assays met the best practice recommendations according to the ICH S7B Q&A 2.1. The hERG safety margin for imlunestrant was [redacted] (b) (4) x of the high clinical exposure (unbounded), higher than those computed under the similar experimental conditions for reference drugs of dofetilide (38x), moxifloxacin (36x) and ondansetron (4x) over the clinical critical concentrations (the mean concentration that gives a 10-msec mean increase in ΔΔQTc in clinical study). The findings suggested that imlunestrant may exhibit a low risk for QTc prolongation by direct inhibition of the hERG channel at the high clinical exposure.

The Applicant submitted two toxicology studies in monkeys with intensive ECG monitoring and a reference study of moxifloxacin in monkeys as historical positive control. The 28-day toxicology study (8002569) showed no QTc effect of imlunestrant. It is unclear why QTc prolongation was not observed in this study. Data from Week 15 of the 3-month toxicology study (8003147) demonstrated sufficient assay sensitivity. However, QTc prolongation was observed at the 600 mg/kg dose group after 10 hours postdose at Weeks 4, 8, and 15.

Altogether, the nonclinical studies do not support a double negative conclusion for 6.1 integrate risk assessment.

3.2 APPLICANT'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for imlunestrant was based on exposure-response analysis, please see section 3.2.3 for additional details.

The Applicant applied descriptive statistics for the by-time analysis with pooled Phase 1a and Phase 1b data. The maximum estimated 90% CI upper limit was below 10 msec at time points with the number of patients more than 7.

Reviewer's comment: *Due to different ECG schedules in Phase 1a and 1b, the reviewer evaluated the ΔQTcF effect using descriptive statistics for the two phases separately. The time points with the number of patients fewer than 7 were excluded. The reviewer's analysis showed that the maximum estimated 90% CI upper limit was below 10 msec in Phase 1b but above 10 msec at several time points in Phase 1a. Please see Section 4.3 for more details.*

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the Applicant.

Reviewer's comment: *The reviewer did not conduct bias analysis. ECGs were read automatically.*

3.2.2 Categorical Analysis

The Applicant performed outlier analysis by phases:

- QTc (i.e., >500 msec or >60 msec over baseline): Phase 1a (n=2), Phase 1b (n=0)

- HR (>100 beats/min and 25% over baseline): Phase 1a (n=0), Phase 1b (n=1).

- PR (>200 msec and 25% over baseline): Phase 1a (n=2), Phase 1b (n=4).

- QRS (>120 msec and 25% over baseline): Phase 1a (n=0), Phase 1b (n=1).

Reviewer's comment: *The reviewer performed categorical analysis with pooled Phase 1a and Phase 1b data. The reviewer's analysis results were similar to the Applicant's. The minor discrepancy was due to a different cutoff for PR and a slight variation in the population for QTc. Please see section 4.4 for additional details.*

3.2.3 Exposure-Response Analysis

The Applicant conducted concentration-QTc analysis using time-matched PK-ECG data collected from 79 patients receiving imlunestrant monotherapy (doses ranging from 200 mg QD to 1200 mg QD). The Applicant claimed to have used a linear mixed effect model recommended by the white paper. The results of the Applicant's analysis showed no significant C-QTc relationship. The model predicted mean (90% CI) ΔΔQTcF of 1.72 (90% CI -0.43, 3.87) msec at Cmax of 164 ng/mL for the 400 mg dose.

Reviewer's comment: *The Applicant's C-QTc model deviated from the white paper. They included time as a fixed effect in their model while the study had no placebo control. Findings from the Applicant were consistent with the reviewer's findings that imlunestrant is not associated with concentration-dependent increase in QTc interval at the range of exposures investigated.*

3.2.4 Safety Analysis

In EMBER, 152 patients received imlunestrant monotherapy. Dose ranged from 200 mg QD to 1200 mg QD and 83 received the therapeutic dose of 400 mg QD. There were 2 (1.3%) nonserious Grade 1 treatment emergent adverse events (TEAEs) of electrocardiogram QT prolonged, one at 200 mg and the other at 400 mg QD. Both patients recovered the events while continued on imlunestrant. No TEAEs of torsade de pointes, ventricular tachycardia, ventricular fibrillation or flutter, sudden death, or seizures were reported. There was 1 SAE of syncope reported on Day 584. The patient recovered from the event. There were no discontinuations, dose interruptions, or dose reductions due to QTc prolongation or syncope.

EMBER-3 was an open-label, Phase 3 pivotal study in patients with ER+, HER2-locally advanced or metastatic breast cancer previously treated with endocrine therapy. Patients were randomly assigned 1:1:1 to receive oral imlunestrant, or investigator's choice of standard of care (SOC) endocrine monotherapy (exemestane or fulvestrant), or imlunestrant plus oral abemaciclib. In total, 327 patients received imlunestrant monotherapy (median exposure of 6 cycles), 324 patients received SOC (292 received fulvestrant with median exposure of 5 cycles; 32 received exemestane with median exposure of 5 cycles), and 208 received imlunestrant plus abemaciclib (median exposure of 9 cycles).

As of the data cutoff date of 24 June 2024, 11 of 535 patients treated with imlunestrant monotherapy or in combination with abemaciclib and 4 of 324 patients treated in the standard of care arm reported TEAEs that can signal potential for proarrhythmic effects as per ICH E14 (Table 3). No TEAEs of Torsade de Pointes, ventricular tachycardia, or ventricular fibrillation/flutter were reported.

Table 3. TEAEs with Potential for Proarrhythmic Effects as Per ICH E14

TEAE (PT)	Imlunestrant (N = 327)		Imlunestrant + Abemaciclib (N = 208)		Standard of Care (N = 324)	
	All Grade n (%)	Grade ≥3 n (%)	All Grade n (%)	Grade ≥3 n (%)	All Grade n (%)	Grade ≥3 n (%)
ECG QTc prolonged	3 (0.9%)	0	4 (1.9%)	2 (1.0%)[a]	0	0
Myocardial infarction[b]	0	0	1 (0.5%)	1 (0.5%)	0	0
Syncope	1 (0.3%)	0	2 (1.0%)	2 (1.0%)	3 (0.9%)	1 (0.3%)
Seizure	0	0	0	0	1 (0.3%)	0

Source: Applicant's summary of clinical pharmacology studies, Appendix 1

Reviewer's comment: *In EMBER, two patients ([(b) (6)] from Phase 1a 200 mg QD and [(b) (6)] from Phase 1a 400 mg QD) reported TEAEs of electrocardiogram QT prolonged on Day 15. The maximum QTcF on C1D15 was 478 msec (at 2-hour postdose; baseline: 460 msec) for patient [(b) (6)] and 462 msec (at 4-hour postdose; baseline: 423 msec) for patient [(b) (6)]. One patient ([(b) (6)]) experienced 1 SAE of syncope on Day 584. The patient permanently discontinued from the study treatment due to progressive disease on Day 571 and died due to study disease on Day 597.*

See section 4.6 for the reviewer's analysis on EMBER-3.

4 REVIEWERS' ASSESSMENT

In by-time analysis, dose levels included 200 mg QD (subtherapeutic), 400 mg QD (therapeutic), and 600 mg QD and above (supratherapeutic). The 600 mg QD and above treatment group included 600 mg, 800 mg, and 1200 mg QD. Data from Phase 1a and Phase 1b were analyzed separately due to different ECG schedules. Categorical analysis and exploratory plot of the exposure response analysis used the same pooling of dose groups as the by-time analysis, except that Phase 1a and Phase 1b were presented together, instead of separately.

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

ECG waveforms were submitted for review. Since annotations for digital ECGs were not available, automatic ECG measurements as provided by the ECG devices at the clinical sites were used for all analysis. No QT bias assessment was conducted.

4.3 By-Time Analysis

The analysis population used for by-time analysis included all patients with a baseline and at least one post-dose ECG. The patients at time points with the number of patients fewer than 7 were excluded. Phase 1a and Phase 1b were analyzed using descriptive statistics separately.

4.3.1 QTc

Figure 1 and Figure 2 displayed the time profiles of ΔQTcF with different treatment groups for Phase 1a and Phase 1b, respectively. There was no dose dependent QTc effect observed in Phase 1a.

The maximum ΔQTcF values by treatment for Phase 1a and Phase 1b were shown in Table 4 and Table 5, respectively. The maximum estimated 90% CI upper limits were below 10 msec in the Phase 1b but were above 10 msec at several time points in the Phase 1a.

Figure 1. Mean and 90% CI of ΔQTcF Time-Course (Unadjusted CIs) for Phase 1a

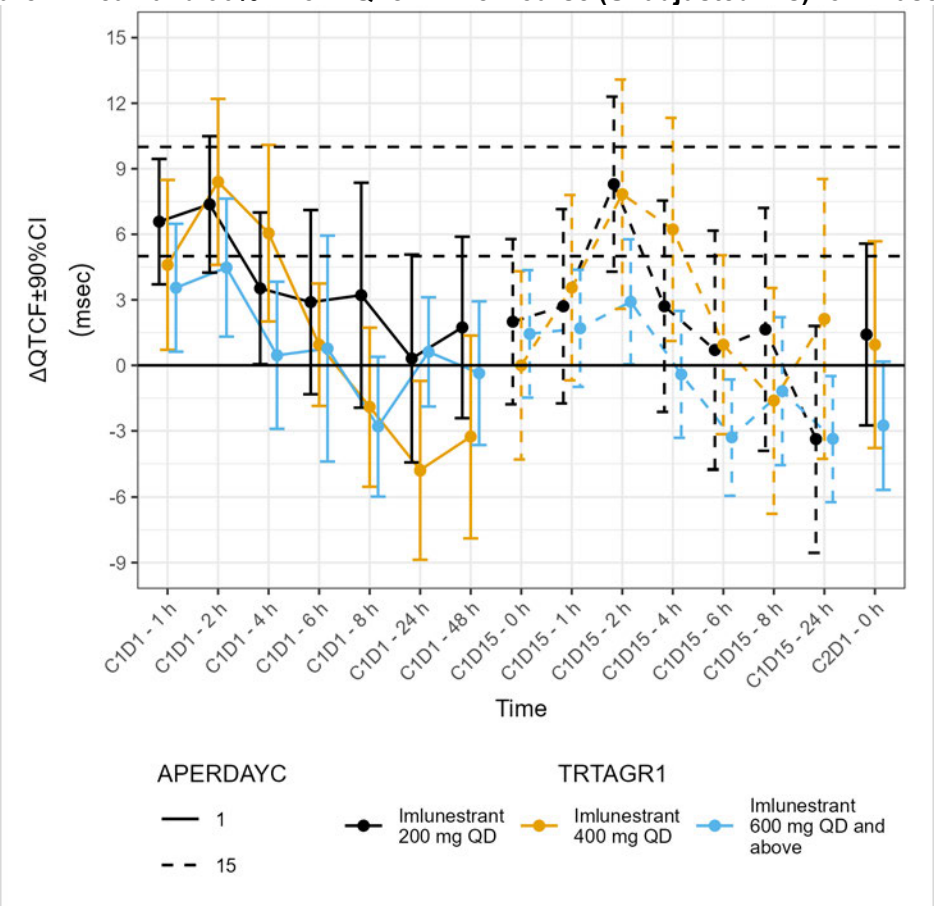


Figure 2. Mean and 90% CI of ΔQTcF Time-Course (Unadjusted CIs) for Phase 1b

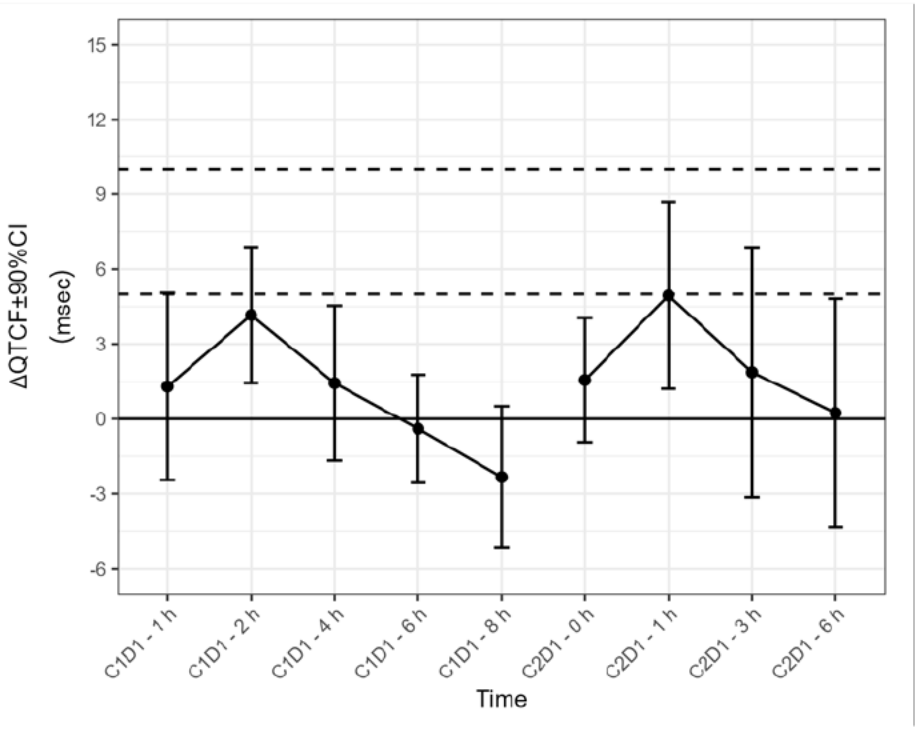


Table 4. Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF for Phase 1a

TRTAGR1	Cycle (C)	Analysis Nominal Cycle Day (C)	N	Time (hour)	ΔQTCF (msec)	90.0% CI (msec)
Imlunestrant 200 mg QD	1	15	17	2.0	8.3	(4.3 to 12.3)
Imlunestrant 400 mg QD	1	15	18	2.0	7.8	(2.6 to 13.1)
Imlunestrant 600 mg QD and above	1	1	38	2.0	4.5	(1.3 to 7.6)

Table 5. Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF for Phase 1b

TRTAGR1	Cycle (C)	N	Time (hour)	ΔQTCF (msec)	90.0% CI (msec)
Imlunestrant 400 mg QD	1	50	2.0	4.2	(1.4 to 6.9)
Imlunestrant 400 mg QD	2	37	1.0	4.9	(1.2 to 8.7)

4.3.2 HR

Figure 3 and Figure 4 displayed the time profiles of ΔHR with different treatment groups for Phase 1a and Phase 1b, respectively. There was no dose dependent HR effect observed in Phase 1a. HR effect was less than 10 bpm in both Phase 1a and Phase 1b.

Figure 3. Mean and 90% CI of ΔHR Time-Course for Phase 1a

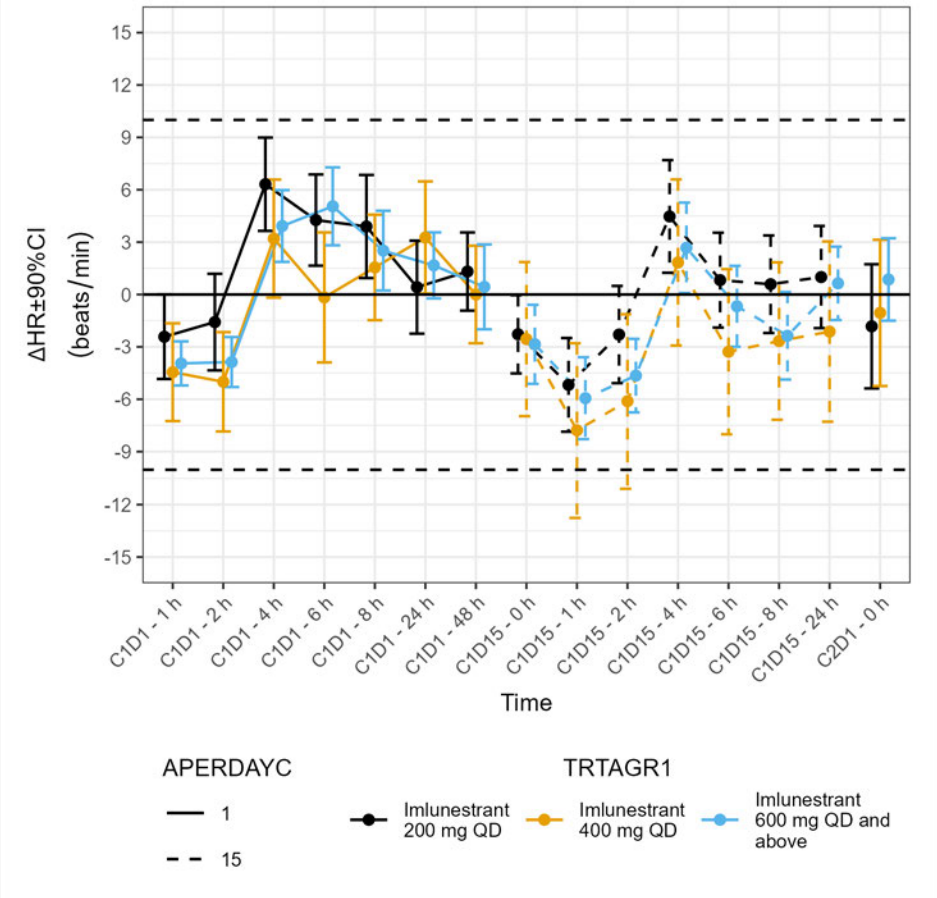
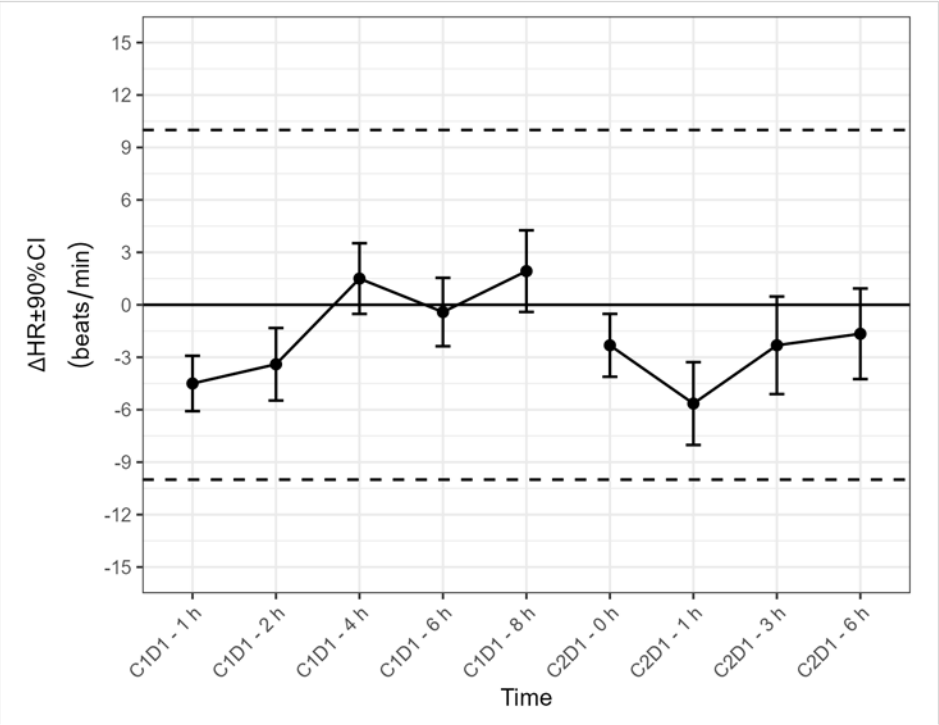


Figure 4. Mean and 90% CI of ΔΔHR Time-Course for Phase 1b



4.3.3 PR

Figure 5 and Figure 6 displayed the time profiles of ΔPR with different treatment groups for Phase 1a and Phase 1b, respectively. The magnitude of the mean ΔPR was less than 10 msec in Phase 1b. The 90% CI upper limits reached 14.8 msec at C1D1 2-hour postdose with the imlunestrant 400 mg QD treatment in Phase 1a (n = 20). Altogether, we do not consider the increase in PR to be significant.

Figure 5. Mean and 90% CI of ΔPR Time-Course for Phase 1a

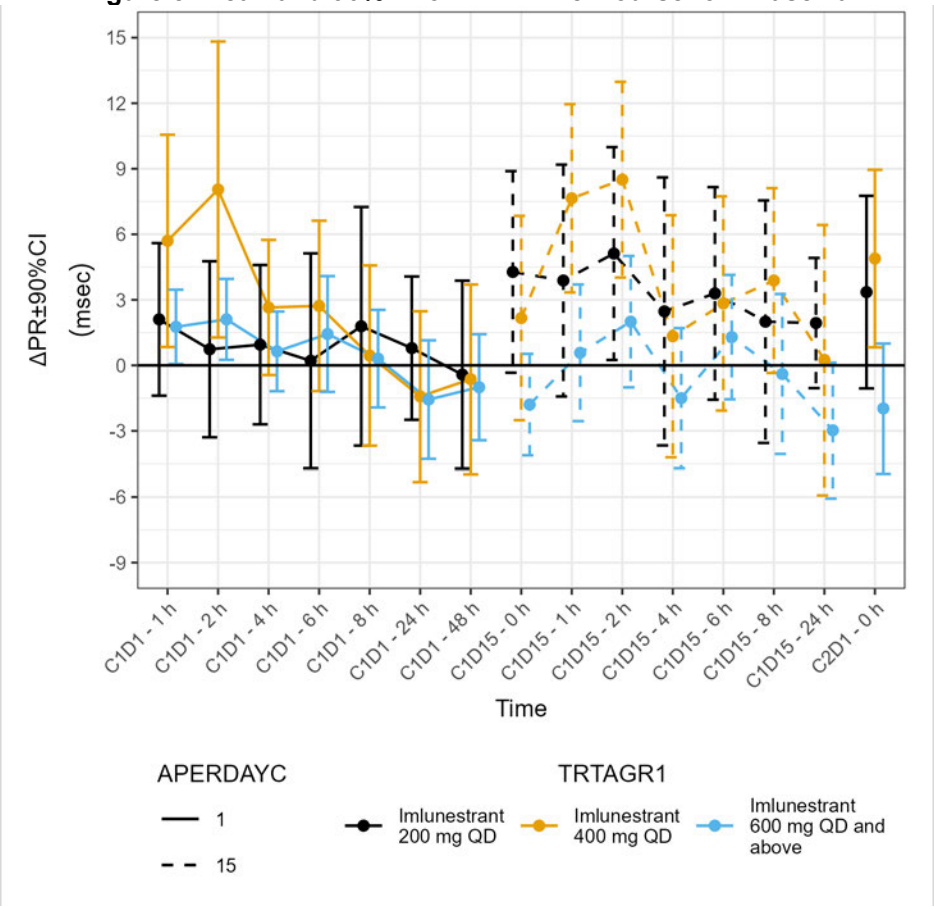
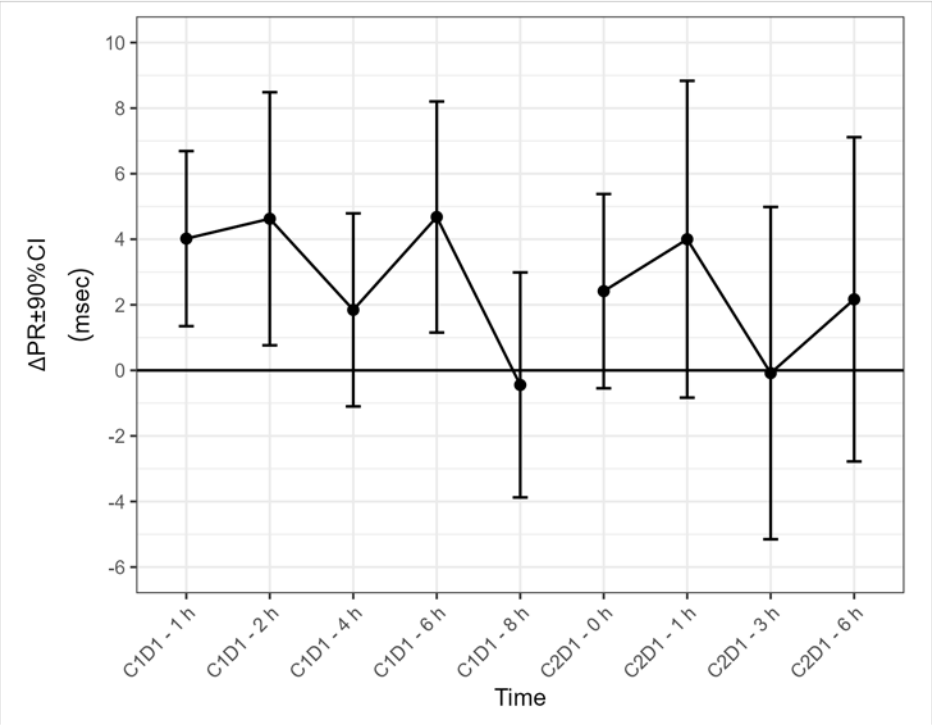


Figure 6. Mean and 90% CI of ΔPR Time-Course for Phase 1b



4.3.4 QRS

Figure 7 and Figure 8 displayed the time profiles of ΔQRS with different treatment groups for Phase 1a and Phase 1b, respectively. QRS prolongation was not observed at any of the doses studied.

Figure 7. Mean and 90% CI of ΔQRS Time-Course for Phase 1a

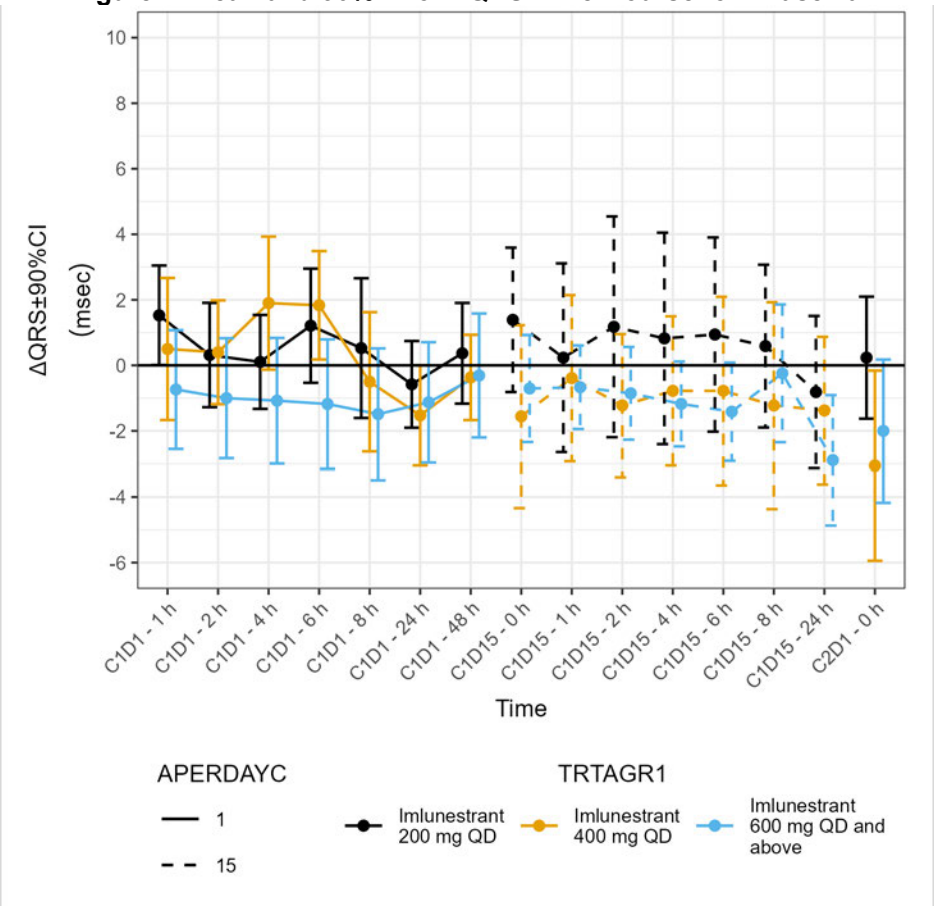
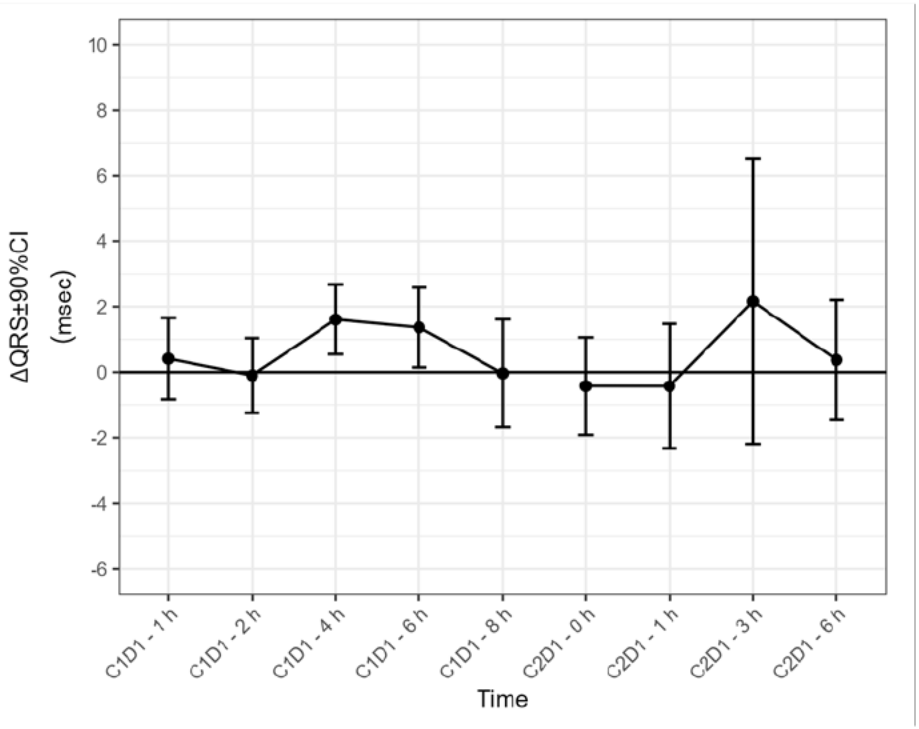


Figure 8. Mean and 90% CI of ΔQRS Time-Course for Phase 1b



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.

4.4.1 QTc

There were no patients having observed QTcF above 500 msec in any of the treatment groups.

Table 6 listed the categorical analysis results for ΔQTcF (<30 msec, >30 and <60, and >60 msec). One patient had observed QTcF change from baseline above 60 msec in the imlunestrant 600 mg QD and above treatment group. QTcF was 396 msec at baseline and was 496 msec at C1D1 6-hour postdose. At all other time points, QTcF were below 450 msec.

Table 6. Categorical Analysis for ΔQTcF (Maximum)

TRTAGR1	Total (N)		Value <=30 msec		30 msec < Value <=60 msec		Value >60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Imlunestrant 200 mg QD	19	274	17 (89.5%)	267 (97.4%)	2 (10.5%)	7 (2.6%)	0 (0%)	0 (0%)
Imlunestrant 400 mg QD	70	668	66 (94.3%)	661 (99.0%)	4 (5.7%)	7 (1.0%)	0 (0%)	0 (0%)

TRTAGR1	Total (N)		Value <=30 msec		30 msec < Value <=60 msec		Value >60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Imlunestrant 600 mg QD and above	45	628	43 (95.6%)	626 (99.7%)	1 (2.2%)	1 (0.2%)	1 (2.2%)	1 (0.2%)

4.4.2 HR

Table 7 listed the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). There were 13 patients having observed maximum HR above 100 beats/min. Among them, one patient (J2J-MC-JZLA-[redacted] (b) (6)) showed a 25% increase over baseline in the imlunestrant 400 mg QD treatment group at follow-up on Day 35 (HR: 106 bpm, baseline: 84 bpm). Treatment ended on Day 7.

Table 7. Categorical Analysis for HR (Maximum)

TRTAGR1	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Imlunestrant 200 mg QD	21	297	18 (85.7%)	287 (96.6%)	3 (14.3%)	10 (3.4%)
Imlunestrant 400 mg QD	81	750	78 (96.3%)	746 (99.5%)	3 (3.7%)	4 (0.5%)
Imlunestrant 600 mg QD and above	48	672	41 (85.4%)	660 (98.2%)	7 (14.6%)	12 (1.8%)

4.4.3 PR

Table 8 listed the categorical analysis results for PR (<200 msec, >200 and ≤220 msec, and >220 msec; with and without 25% increase over baseline). There were two patients in the imlunestrant 400 mg QD treatment group and one patient in the imlunestrant 600 mg QD and above treatment group having observed PR above 220 msec with 25% increase over baseline. There was no reporting of atrioventricular block.

Table 8. Categorical Analysis for PR

TRTAGR1	Total (N)		Value <=220 msec		Value >220 msec & <25%		Value >220 msec & >=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Imlunestrant 200 mg QD	19	274	19 (100.0%)	274 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Imlunestrant 400 mg QD	68	649	64 (94.1%)	639 (98.5%)	2 (2.9%)	6 (0.9%)	2 (2.9%)	4 (0.6%)
Imlunestrant 600 mg QD and above	46	642	44 (95.7%)	640 (99.7%)	1 (2.2%)	1 (0.2%)	1 (2.2%)	1 (0.2%)

4.4.4 QRS

Table 9 listed the categorical analysis results for QRS (<120 msec and >120 msec; with and without 25% increase over baseline). There was one patient having observed QRS above 120 msec with 25% increase over baseline in the imlunestrant 400 mg QD treatment group.

Table 9. Categorical Analysis for QRS

TRTAGR1	Total (N)		Value <=120 msec		Value >120 msec & <25%		Value >120 msec & >=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Imlunestrant 200 mg QD	19	274	19 (100.0%)	274 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Imlunestrant 400 mg QD	70	668	66 (94.3%)	641 (96.0%)	3 (4.3%)	26 (3.9%)	1 (1.4%)	1 (0.1%)
Imlunestrant 600 mg QD and above	46	642	45 (97.8%)	627 (97.7%)	1 (2.2%)	15 (2.3%)	0 (0%)	0 (0%)

4.5 Exposure-Response Analysis

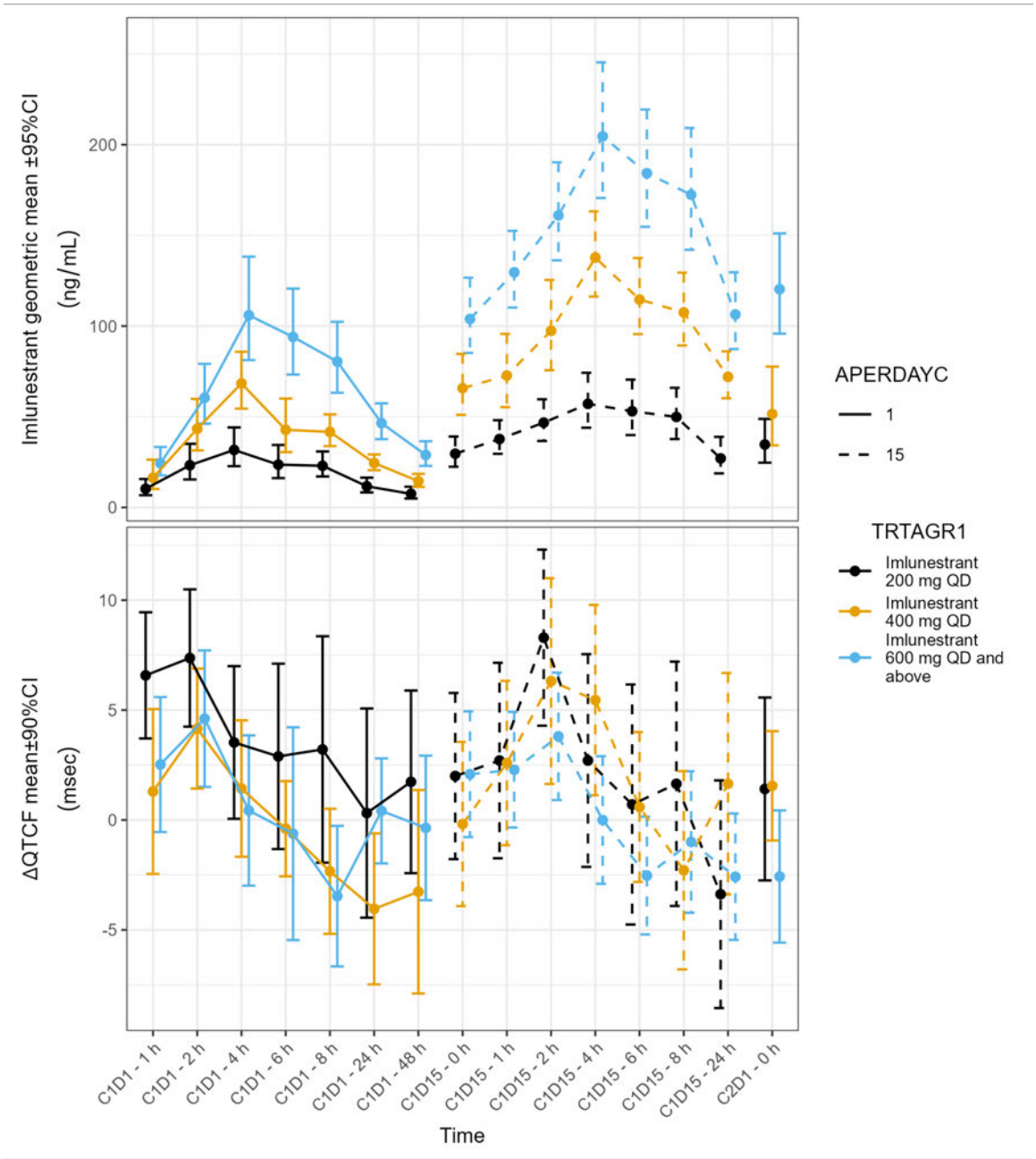
Exposure-response analysis was conducted using all patients with baseline and at a least one post-baseline ECG, with time-matched PK.

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 ΔQTcF; and 3) absence of a nonlinear relationship.

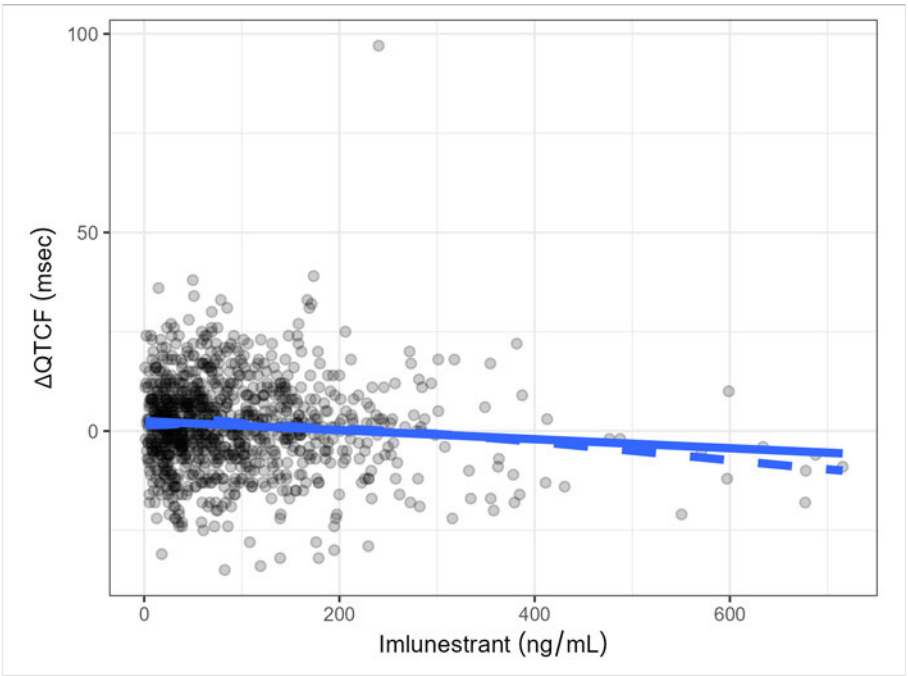
Figure 3 showed the time-course of ΔHR, with an absence of significant ΔHR changes. Figure 9 offered an evaluation of the relationship between time-course of drug concentration and ΔQTcF, with no appearance of significant hysteresis. Figure 10 showed the relationship between drug concentration and ΔQTcF and supported the use of a linear model.

Figure 9. Time-Course of Drug Concentration (Top) and QTcF (Bottom)[1]



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

Figure 10. Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot was shown in Figure 11. Predictions from the concentration-QTcF model were provided in Table 10.

Figure 11. Goodness-of-Fit Plot for QTcF

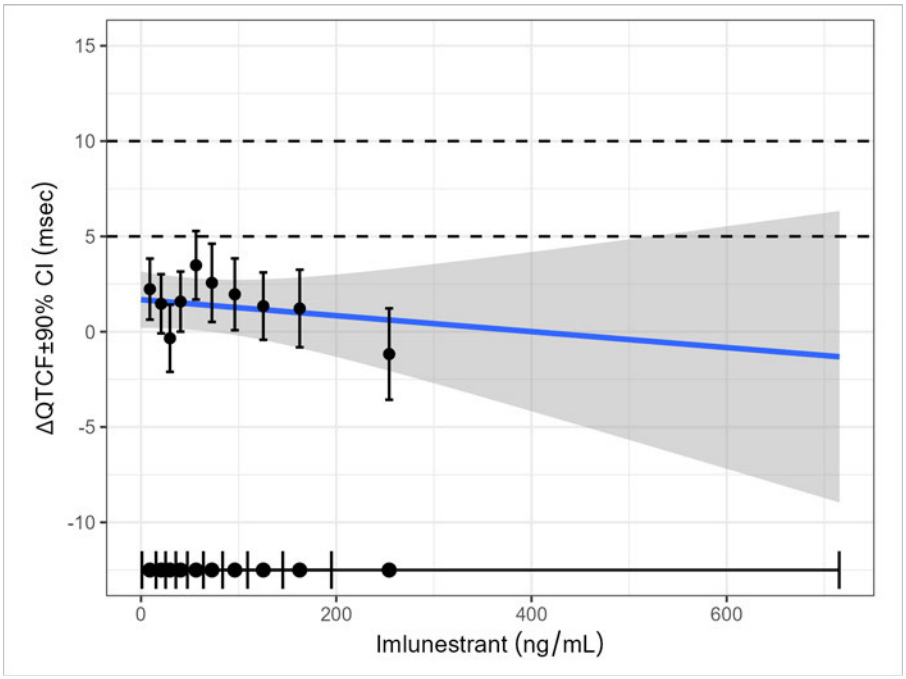


Table 10. Predictions From Concentration-QTcF Model

TRTAGR1	Analysis Nominal Period Day	Imlunestrant (ng/mL)	ΔQTCF (msec)	90.0% CI (msec)
Imlunestrant 200 mg QD	1	37.3	1.5	(0.2 to 2.9)
Imlunestrant 200 mg QD	15	60.3	1.4	(0.1 to 2.8)
Imlunestrant 400 mg QD	1	83.6	1.3	(-0.1 to 2.7)
Imlunestrant 600 mg QD and above	1	126.9	1.1	(-0.5 to 2.8)
Imlunestrant 400 mg QD	15	141.9	1.1	(-0.6 to 2.8)
Imlunestrant 600 mg QD and above	15	215.4	0.8	(-1.5 to 3.1)
Imlunestrant 1200 mg QD (highest dose)		253.0	0.6	(-2.0 to 3.3)

4.6 SAFETY ASSESSMENTS

The reviewer's safety analysis was based on all three treatment arms in EMBER-3: imlunestrant monotherapy, imlunestrant+abemaciclib (I+A), and SOC. In the proposed label section 6, TEAEs and lab results were reported for the imlunestrant monotherapy and the SOC arms only. Abemaciclib does not cause large mean increases (i.e., 20 ms) in the QTc interval.

Patients with QTcF ≥470 msec were excluded from EMBER-3. Single local ECGs were performed at baseline for all patients. For patients receiving imlunestrant, ECGs were collected at 2-4 hr postdose on C1D1, then predose on C2D1 and C4D1, and at short-term follow-up (FU). Most patients receiving SOC did not have postbaseline ECGs.

Overall, there was no imbalance in percent of patients experiencing TEAEs of torsade de pointes/QT prolongation (broad SMQ) + seizure (preferred term [PT]) between the imlunestrant/I+A and the SOC arm (Table 11). All three cardiac arrests were SAEs (fatal) and led to treatment discontinuation. Additionally, one electrocardiogram QT prolonged from the I + A arm led to treatment discontinuation (patient ID: (b) (6)). No other events were SAEs, led to treatment discontinuation, or dose adjustment (reduction, omission, or delay).

- Patient (b) (6) was a 72-year-old white female who had a relevant medical history of hypertension, hypercholesterolemia, and Type 2 diabetes mellitus (DM). She was randomized to the imlunestrant arm. On Day 54, the patient had symptoms of heart racing, vomiting and profuse sweating. On the way to the hospital within 30 min of the onset of the symptoms, she died. The cause of death was reported as cardiac arrest (SAE, Grade 5). The last dose of imlunestrant was on the same day. Radiographic tumor assessments performed 2 days prior to the event revealed progressive disease.
  Assessment: *There were no ECGs at the time of the event. ECG reported at screening and on Day 30 were normal. The patient had disease progression and other relevant comorbidities. There were no imbalance in cardiac arrest between the imlunestrant/I + A arms and placebo.*

All 3 patients reported syncope in the imlunestrant or the I + A arms did not have ECG at the time of the event. One patient from the imlunestrant arm (ID: (b) (6)) experienced the syncope event 30 days after the end of treatment (EOT). This patient had no ECG data. Two patients from the I + A arm had all their available QTcF below 450 msec.

Table 11. Treatment Emergent Adverse Events of Torsade de Pointes/QT Prolongation (Broad SMQ) + Seizure, Safety Population, EMBER-3

TEAE Preferred Term	Imlunestrant N = 327 n (%)	Imlunestrant+Abemaciclib N = 208 n (%)	Standard of Care N = 324 n (%)
Total	5 (1.5)	6 (2.9)	6 (1.9)
Cardiac arrest	1 (0.3)	0	2 (0.6)
Electrocardiogram QT prolonged	3 (0.9)	4 (1.9)	0
Seizure	0	0	1 (0.3)
Syncope	1 (0.3)	2 (1.0)	3 (0.9)

Abbreviations: n, number of patients with events; N, number of patients in the treatment group; SMQ, standard MedDRA Query; TEAE, treatment emergent adverse event

All 7 patients reported TEAEs of electrocardiogram QT prolonged were in the imlunestrant or the I + A arms. One in each arm had QTcF > 500 msec (ID: (b) (6) and (b) (6)).

Of the 3 patients with reported TEAEs of ECG QT prolonged in the imlunestrant arm, two had confounding factors: one had QTc prolonged at baseline (ID: (b) (6), baseline: 466 msec, maximum postbaseline: 475 msec on Day 1), one had QTc prolonged at baseline and had concomitant medication that prolonged QTc (ID: (b) (6), baseline: 470 msec, maximum postbaseline: 504 msec at FU, 28 days after EOT, concomitant medication at FU: ribociclib [prolongs QTc by ~20 msec]). The third patient (ID: (b) (6)) had QTc prolongation reported at FU, 42 days after the EOT (baseline: 433 msec, maximum postbaseline: 472 msec on Day 109, EOT: Day 67).

Of the 4 patients reported TEAEs of ECG QT prolonged in the I +A arm, two had confounding factors: one had potassium below lower limit of normal (LLN) at the time of the event (ID: (b) (6), baseline: 425 msec, maximum postbaseline: 467 msec) and one had QTc prolonged at baseline (ID: (b) (6), baseline: 458 msec, maximum postbaseline: 477 msec). The other two cases were evaluated below:

- Patient (b) (6) is a 77-year-old Asian female. Ongoing medical history included dyslipidemia. Her baseline QTcF was 438 msec. She experienced Grade 3 TEAE of ECG QT prolonged from Day 87 to Day 99 (maximum QTcF: 625 msec on Day 87). On Day 87, I + A were withheld for 12 days due to the event and was resumed with reduced doses on Day 99 after QTcF returned to baseline level. The concomitant medication included loperamide from Day 15 to Day 108 (W&P for TdP [overdose setting], syncope, and ventricular tachycardia]). Then she experienced a second Grade 3 TEAE of ECG QT prolonged from Day 109 to Day 183 (maximum QTcF: 628 msec on Day 113), which led to I + A discontinuation on Day 127. Both events were resolved.
  Assessment: *This patient experienced two separate QTc prolongations of ~200 msec above baseline and the second event reappeared after resuming a lower I +A dose.*

Concomitant medication with conditional QTc prolonging risk (based on CredibleMeds) was administered during the first event but not the second. Based on timing of these events, the QTc prolongation was likely related to the investigational treatment.

- Patient (b) (6) is a 59-year-old Asian female. Ongoing medical history included type 2 DM and hyperlipidemia. TEAE of ECG QT prolonged was reported from Day 1 to Day 29 (Grade 3) and on Day 155 (Grade 2, unresolved, EOT: Day 120). Though no ECG measurements were available from the dataset. At the time of the first event from Day 1 to Day 29, concomitant medication included ondansetron (Day 1 to Day 84, label bears W&P for QTc prolongation [~20 msec]) and loperamide (Day 1 to Day 84, W&P for TdP [overdose setting], syncope, and ventricular tachycardia). At the time of the second event on from Day 155 onward, concomitant medication included famotidine (Day 120 onward, label noted prolonged QT intervals in patients with moderate and severe renal impairment) and loperamide (Day 143 onward).
  Assessment: *Though this patient had concomitant medications with QTc prolonging risks, since the magnitude of QTc prolongation and the baseline values were unknown, the reviewer cannot determine whether the concomitant medication alone contributed to the QTc prolongation.*

In total, 2 patients from the imlunestrant arm (0.6%), 4 patients from the I + A arm (1.9%), and no patients from the SOC arm had QTcF > 500 msec, though only 2 were reported as TEAEs (ID: (b) (6) and (b) (6)).

Of the two patients who had QTcF > 500 msec in the imlunestrant arm, one of them reported it as TEAE and had confounding factors (ID: (b) (6), see above). The other case was evaluated below:

- Patient (b) (6) is an 80-year-old white female. Ongoing medical history included atrial fibrillation (AF), blood cholesterol increased, type 2 DM, hypokalemia, and hypertension. Her baseline QTcF was 407 msec and HR was 82 bpm (it was 113 bpm at screening). She experienced an SAE of AF (Grade 3) on Day 44 and was resolved on Day 46. On Day 63, she experienced dizziness (SAE, Grade 2, resolved on Day 63), lethargy (SAE, Grade 2, resolved on Day 63), dehydration (non-serious, Grade 2, resolved on Day 63), hyponatremia (non-serious, Grade 1, resolved on Day 63), urinary tract infection (non-serious, Grade 3, resolved on Day 68), acute kidney injury (non-serious, Grade 3, unresolved, creatinine unreported for this patient), and bradycardia (non-serious, Grade 2, resolved on Day 63, HR value unreported). Narratives were not found for SAEs. On Day 85 (C4D1), QTcF was 521 msec, HR was 106 bpm. Electrolytes were within normal range. She was receiving concomitant medication of amiodarone (antiarrhythmic, prolongs QTc by 10%) from Day 44 to Day 86. At FU on Day 171 (30 days after EOT), her QTcF was 519 msec and HR was 90 bpm. Ca was lower than LLN and K was borderline LLN. Concomitant medication included capecitabine (warning for cardiotoxicity: MI, angina, ECG change etc.). The patient died on Day 350.
  Assessment: *The QTc prolongation at FU was unlikely due to IP. Contribution from imlunestrant to the QTc prolongation on Day 85 cannot be excluded.*

Of the four patients who had QTcF > 500 msec in the I + A arm, one of them reported it as TEAE and the event was considered related to study drug (ID: (b) (6), see above). One (ID: (b) (6)) had QTcF of 502 msec reported at FU, 27 days after the EOT, and had both Ca and K below LLN. Except for the FU visit, QTcF did not exceed 450 msec. The QTc prolongation at FU visit is unlikely to be related to imlunestrant. The other two cases were evaluated below:

- Patient (b) (6) is a 75-year-old white female. Ongoing medical history included cardiac failure chronic and type 2 DM. Her QTcF was 427 msec at baseline. On Day 86 (C4D1) she reported QTcF of 534 msec. Ca and K were normal. Concomitant medication included omeprazole (conditional risk based on CredibleMeds, label bears W&P for rare hypomagnesemia; magnesium not collected in this study)
- Patient (b) (6) is a 64-year-old female. Ongoing medical history included hypertension. Her baseline QTcF was 426 msec. On Day 245 (C9D1) she reported QTcF of 551 msec. Concomitant medication included loperamide (W&P for TdP [overdose setting], syncope, and ventricular tachycardia) and escitalopram (~10 msec QTc prolongation at supratherapeutic dose in TQT study).
  Assessment: *Even though patients* (b) (6) *and* (b) (6) *had concomitant medication that were associated with risks of QTc prolongation, the magnitude of QTc prolongation they experienced (>100 msec compared to baseline) was unlikely caused by the concomitant medications solely.*

In conclusion, there was no imbalance in percent of patients experiencing TEAEs of torsade de pointes/QT prolongation (broad SMQ) + seizure (preferred term [PT]) between the imlunestrant/I+A and the SOC arm. More patients experienced QTc prolongation in the imlunestrant/I+A than the SOC arm, which could be due to the lack of ECG collection on the SOC arm. Most patients experienced QTc prolongation, whether based on AE reporting or ECG data, had other confounding factors. The safety data does not suggest imlunestrant has increased risk for proarrhythmic effects.

5 APPENDIX I: EVALUATION OF THE APPLICANT'S CLINICAL QT ASSESSMENT

5.1 EVALUATION OF THE APPLICANT'S CLINICAL QT STUDIES

1. QT Studies					
Study	**ECG Quality**	**Treatments**		**Sample Size**	**ECG & PK Assessments**
		Arms	**Dose Coverage**		
Protocol Number: EMBER (J2J-MC-JZLA) Population: Patients Design: Other (open-label)	Digital: No Central Read? Yes Blinded? No Replicates? Yes Single ECGs at screening	Highest Dose: 1200 mg QD Placebo: No Positive Control: No	Above therapeutic	About 135 patients had baseline ECG parameters, 79 patients had matching PK/QTcF samples	Baseline: Pre-dose baseline Matching PK/ECG Timing: Phase 1a: C1D1 and C1D15: predose, 1, 2, 4, 6, 8, 24, 48 (C1D1 only) hours post-dose; C2D1: predose Phase 1b: C1D1 and C2D1: predose, 1-2, 3-4, 6-8 hours post-dose
Reviewer's comments: QT evaluation was conducted in Phase 1a and 1b monotherapy Cohorts E3 and E8. Digital ECG waveforms were not available. Automatic measurements were used for analysis.					

5.2 Evaluation of the Applicant's Clinical QT Analysis Plan

1. Analysis plan	
1.1 Study Objectives Related to QT	
What QTc effect size is the analysis trying to exclude?	Unclear
Reviewer's comments: Based on the proposed label language, [redacted] (b) (4)	
1.2 Data Pooling	
Data pooling?	No
Did Applicant propose an assessment for heterogeneity?	N/A
Is the data pooling appropriate?	N/A
1.3 QT Correction Method	
Is an HR increase or decrease greater than 10 beats/min?	No
Primary method for QT correction	QTcF
1.4 Assay Sensitivity	
Assay sensitivity methods proposed by Applicant	☐ Moxifloxacin ☐ Exposure-margin ☐ QT bias assessment ☐ Other ☒ Not applicable (objective is large mean effects)
Reviewer's comments: The regulatory pathway is 6.1 with integrated risk assessment.	
1.5 By-Time Analysis	
1.5.1 Investigational Drug	

Primary analysis	No
Did the Applicant use IUT or descriptive statistics?	Descriptive statistics
For IUT: Does the Applicant use MMRM to analyze longitudinal values that consider the correlation across time-points, or use ANCOVA by-time-point without considering correlation?	N/A
For IUT: Is the MMRM model specified correctly with regard to covariance structure, covariates, or if ANCOVA, is the model specified correctly with regard to covariates?	N/A
1.5.2 Positive Control	
Primary analysis	N/A
Did the Applicant adjust for multiplicity?	N/A
1.6 Exposure-Response Analysis	
1.6.1 Investigational Drug	
Primary analysis	Yes
What is the dependent variable in the Applicant's model?	Single delta
White paper model?	No
Which concentration covariate(s) are included in the model?	Parent
Which methods did the Applicant use for predicting the QT effect?	☒ Model-based confidence intervals ☐ Bootstrap-derived confidence intervals
Reviewer's comments: The Applicant incorrectly included time as a fixed effect without a placebo control.	
1.6.2 Positive Control	
Primary analysis	N/A
Same model as investigational drug	N/A

1.7 Categorical Analysis			
QTcF / ΔQTcF?	Yes	QRS?	Yes
PR?	Yes	HR?	Yes

6 APPENDIX II: EVALUATION OF THE APPLICANT'S NONCLINICAL QT ASSESSMENT

The Applicant proposed integrated clinical and nonclinical risk assessment to support ICH E14 Q&A 6.1. The Applicant submitted the raw data of hERG assay and in vivo studies for review.

6.1 IN VITRO HERG ASSAY

6.1.1 Applicant's Submission

The GLP hERG study report 190112.FMD (link) described the potential effects of imlunestrant on the hERG current in HEK293 cells. The hERG current was assessed at near-physiological temperature (33-35ºC), using a voltage protocol that was similar to the hERG protocol recommended by the FDA (link). A full blocker (0.5 µM E-4031) was added at the end of the experiment to assess the contribution of the non-hERG currents. The positive control terfenadine (60 nM) inhibited hERG potassium current by 75.1%. Solution samples collected at the outflow of the recording chamber were used for drug concentration verification. The analysis results met the acceptance criteria ((b) (4) % of nominal concentrations).

Imlunestrant inhibited hERG current by 4% at 0.3 µM and 27.8% at 1 µM. The IC50 for the inhibitory effect of imlunestrant on hERG potassium current could not be calculated but was expected to be larger than 1 µM. Concentrations greater than 3 µM were not evaluated due to the solubility of the test article in the vehicle.

Another hERG study (study ID: 220502.FMD, link) assessed the effects of positive control drugs (dofetilide, moxifloxacin, ondansetron, terfenadine and cisapride) on hERG current in HEK293 cells. The hERG current was assessed at near-physiological temperature (35-37ºC), using a voltage protocol that was recommended by the FDA. A full blocker (0.5 µM E-4031) was added at the end of the experiment to assess the contribution of the non-hERG currents.

Dofetilide, moxifloxacin, ondansetron, terfenadine and cisapride concentration-dependently blocked the hERG current with IC50 values of 11.1 nM, 79.4 µM, 1.1 µM, 16.5 nM and 31.8 nM, respectively.

6.1.2 Reviewer's Assessment and Data Reanalysis

Original electrophysiology records for the hERG assays (study ID: 190112.FMD and 220502.FMD) were provided by the Applicant. The reviewer reanalyzed these records to assess data quality and verify study report conclusions. For data quality assessment, current from all traces were examined to verify stability, and time course plots were constructed to verify that current amplitude in control solution were stable prior to drug application, and that drug effects reached steady state.

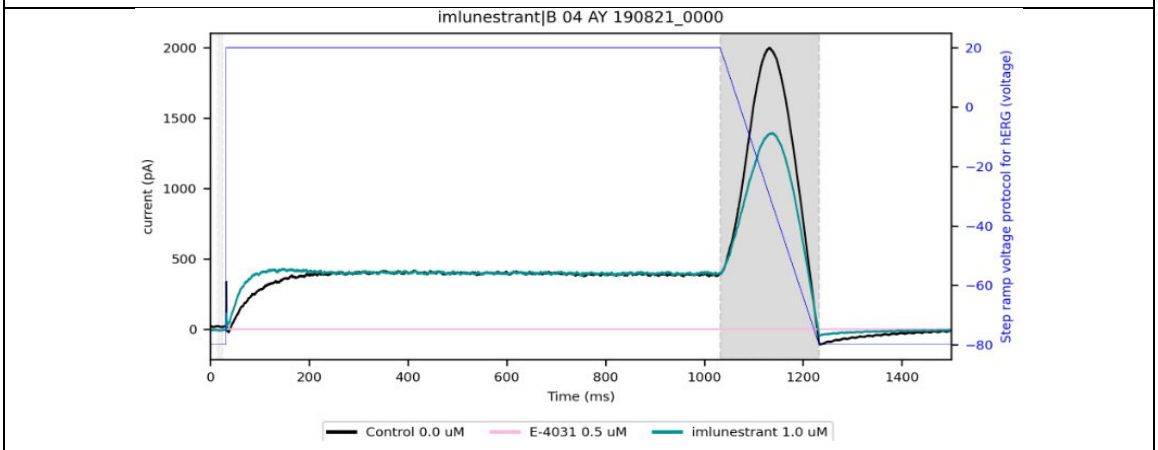
The hERG assay for imlunestrant was assessed at near-physiological temperature (33-35ºC), at the stimulating frequency of 0.2 Hz (every 5 seconds), using a voltage protocol that's similar to the recommended hERG voltage protocol available at IRT's website (link). The positive control drugs were evaluated at near physiological temperature (35-37ºC) using a voltage protocol recommended by the FDA. A full hERG blocker (0.5 µM E-4031) was added at the end of the experiment to assess the non-hERG currents evoked by the

voltage protocol. Solution samples were collected at the outflow of the recording chamber at the time of experiment for drug concentration verification. The analysis results met the acceptance criteria ([redacted]% of nominal concentrations). Therefore, the nominal concentrations were used to describe the drug effects.

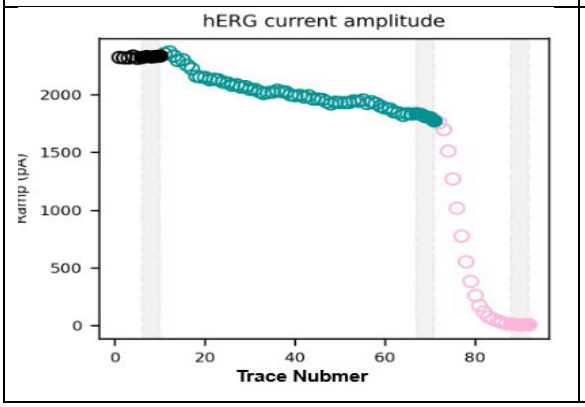
Representative analysis from one cell of hERG study (Cell ID: B04 AY 190821_0000) was shown in Figure 12. Panel A showed recorded traces of each treatment group from this cell. The voltage waveform used to evoke hERG current was shown in blue. The shaded gray areas on the left showed measurement cursors used to calculate baseline currents at -80 mV. The gray shade on the right highlighted the region where peak hERG tail current was measured. Traces recorded in control solution were shown in black, following 1.0 µM imlunestrant application in dark green; and 0.5 µM E-4031 in pink at the end of the experiment. Time course for peak ramp current and holding current were shown on panels B and C, respectively.

Figure 12 Representative Analysis (Cell ID: B 04 AY 190821_0000)

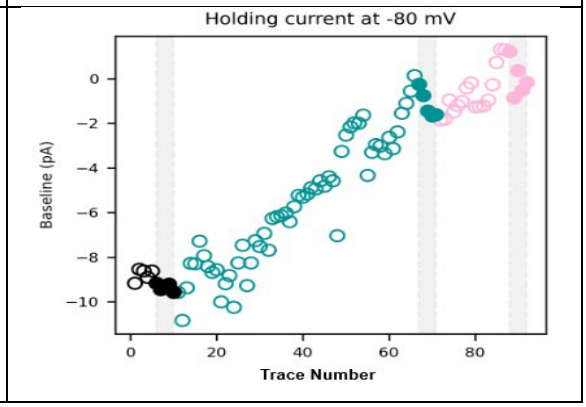
A. hERG current traces



B. Peak ramp current



C. Baseline current



The hERG current amplitudes from the last 5 traces acquired in control (black solid circles) and in drug solution (dark green solid circles represent drug concentration at 1.0 µM) were then averaged to calculate % inhibition by that concentration.

Results (with E-4031 subtraction) of imlunestrant, positive control drugs on hERG current were summarized in **Table 12**.

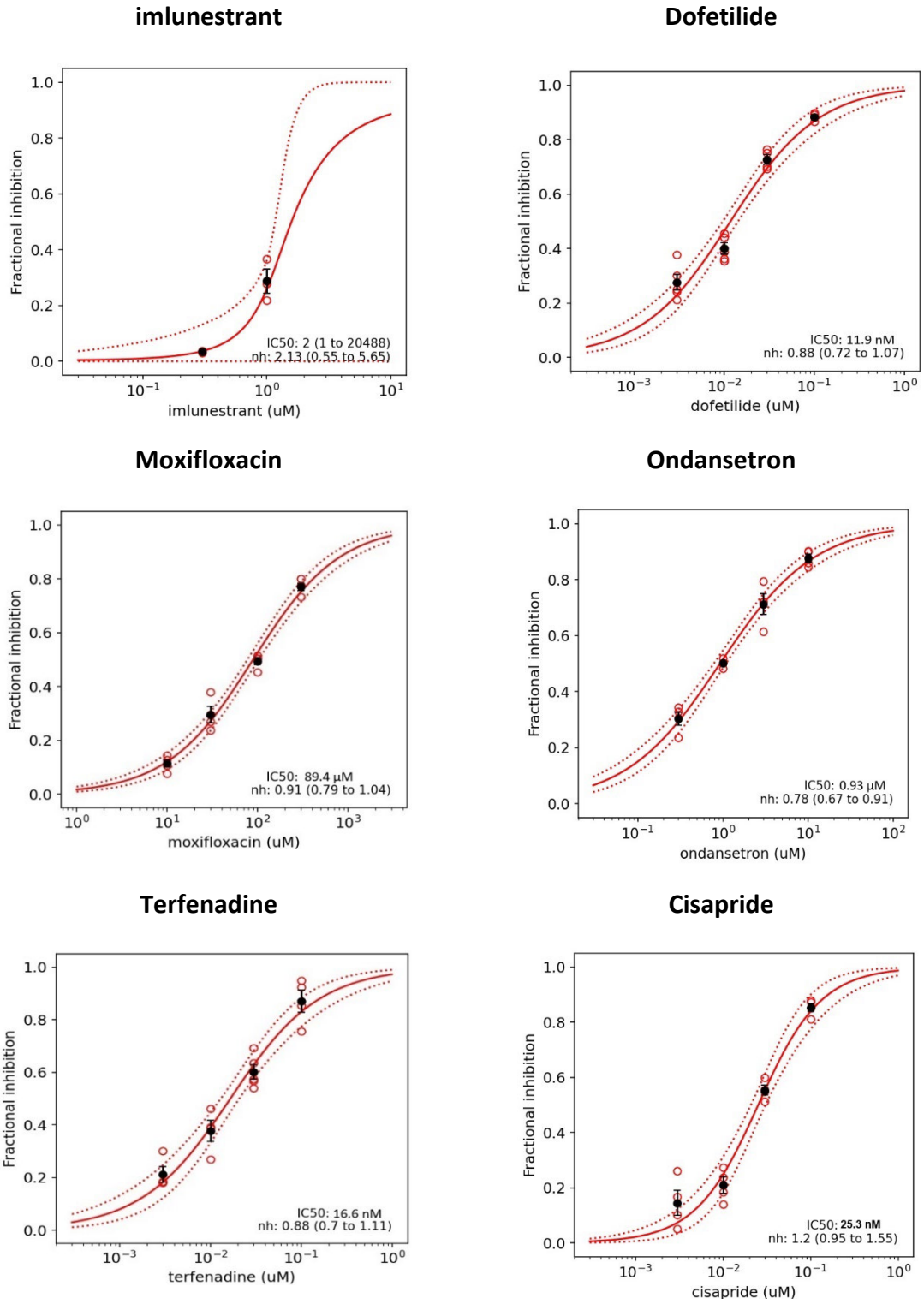
Table 12 Effects of Imlunestrant and Positive Controls on hERG Current

Test article	N	Inhibition (fraction)	SEM	IC50
Imlunestrant 0.3 µM	5	0.03	0.00	1.58 µM
Imlunestrant 1 µM	5	0.29	0.04	
Dofetilide 3 nM	5	0.28	0.03	11.8 nM
Dofetilide 10 nM	5	0.40	0.03	
Dofetilide 30 nM	4	0.713	0.02	
Dofetilide 100 nM	4	0.82	0.01	
Moxifloxacin 10 µM	4	0.11	0.00	89.4 µM
Moxifloxacin 30 µM	4	0.30	0.03	
Moxifloxacin 100 µM	4	0.49	0.01	
Moxifloxacin 300 µM	4	0.77	0.01	
Ondansetron 0.3 µM	4	0.30	0.02	0.93 µM
Ondansetron 1 µM	4	0.50	0.01	
Ondansetron 3 µM	4	0.71	0.04	
Ondansetron 10 µM	4	0.88	0.01	
Terfenadine 3 nM	4	0.21	0.03	16.6 nM
Terfenadine 10 nM	4	0.38	0.04	
Terfenadine 30 nM	5	0.60	0.03	
Terfenadine 100 nM	4	0.87	0.04	
Cisapride 3 nM	4	0.14	0.05	25.3 nM
Cisapride 10 nM	4	0.21	0.03	
Cisapride 30 nM	4	0.55	0.02	
Cisapride 100 nM	4	0.85	0.01	

While there were numerical differences in the results from FDA's independent analysis compared to the Applicant's, they did not change the overall conclusions. Imlunestrant concentration-dependently inhibited hERG current with an estimated IC50 of 1.58 µM. The positive controls dofetilide, moxifloxacin, ondansetron, terfenadine and cisapride concentration-dependently inhibited hERG current with IC50s of 11.8 nM, 89.4 µM, 0.93 µM, 16.6 nM and 25.3 nM, respectively. The IC50 values of those reference drugs were similar to the IC50 values (12.7 nM, 69.9 µM, 1.4 µM, 37.5 nM and 25.6 nM for dofetilide, moxifloxacin, ondansetron, terfenadine and cisapride, respectively) from the HESI-BAA

study by the FDA using the same experimental protocol. The concentration-response curves of imlunestrant were summarized in **Figure 13**.

Figure 13. Effects of Imlunestrant and Positive Controls on hERG Current



6.1.3 In Vitro Summary

The comparisons of Applicant's hERG assay and the best practice recommendations by the new ICH S7B Q&A 2.1 were summarized in **Table 13**. The hERG safety margins of imlunestrant and positive controls were summarized in **Table 14** .

Table 13 Comparison of Applicant's hERG Assay with the New Draft ICH S7B Q&As Best Practice Recommendations

Best Practice Elements	Deviations/limitations	Impact from Deviations
Temperature (35-37°C)	33-35°C	Experiment was conducted at near physiological temperature
Voltage protocol	No hyperpolarized step at -90 mV before the test step pulse for imlunestrant.	The input resistance cannot be assessed; however, this will not impact the drug's potency.
Recording quality	None	
IC50 Calculation	None	
Concentration verification	None	
Positive Control	Only one concentration was tested	Unable to calculate the IC50 value but the inhibition (75.1%) was within the range of historical data.
Negative Control (vehicle)	None	

Table 14 Safety Margins of Imlunestrant on hERG Current

Drug	Cmax (ng/mL)	Protein Binding (%)	Free Cmax (ng/mL)	hERG IC50 (μM)	Mol Weight (g/mol)	Safety Margin (Ratio)
imlunestrant	(b) (4)	99	(b) (4)	1.58	525	(b) (4)x
dofetilide	0.396*	65	0.138	0.0119	442	38x
moxifloxacin	1663*	40	997.8	89.4	401	36x
ondansetron	249*	73	67.2	0.93	293	4x

**Critical concentration is the mean concentration that gives a 10 msec mean increase in ΔΔQTc. It was estimated by drug and study using the concentration-QTc white paper model and assuming log-normal distribution (see Lars Johannesen et al, Poster for SPS 2024 meeting).*

In summary, the hERG assay met the best practice recommendations for in vitro assays according to the new ICH S7B Q&A 2.1 (link) except only one concentration was tested for the positive control. The hERG results showed that imlunestrant has a hERG safety margin of (b) (4)x, which is larger than the safety margins of reference controls, suggesting

that imlunestrant may have a low risk for QTc prolongation by directly inhibiting the hERG current at the high clinical exposure.

6.2 In Vivo QT Study

6.2.1 Applicant's Submission

The in vivo tox study (**8002569**, link) assessed the effects of imlunestrant on ECG parameters following repeat oral doses (30, 150, and 600 mg/kg/day) to conscious telemetrized monkeys (n = 3/sex/dose) for 28 days.

ECG were collected at ~ 25-hr recordings pretreatment (x2), Day 3, Day 23 in 28-day study. ECG waveforms were collected at least 1 hour prior to dosing and continued for at least 24 hours postdose. QT were corrected for each animal based on individual correction factors (QTca).

Full PK collection in the same animals were conducted on Day 1 and Day 28. Cmax values on Day 1 were 112 ng/mL ((b) (4) x high clinical exposure), 349 ng/mL ((b) (4) x high clinical exposure) and 725 ng/mL ((b) (4) x high clinical exposure) for 30, 150 and 600 mg/kg/day doses, respectively.

There were no drug-related changes in QTca, HR, PR and QRS intervals throughout the course of the study. No positive control drugs were used in the study. The minimal detectable differences (MDD) required to attain statistical significance with 80% certainty was 12.6 msec for QTc interval based on Day 3 QTca data.

Another in vivo tox study (**8003147**, link) assessed the effects of imlunestrant on ECG parameters following repeat oral doses (15, 100, and 600 mg/kg/day) to conscious telemetrized monkeys (n = 4/sex/dose) for 3 months.

ECG were collected at ~ pretreatment (x1) and Weeks 4, 8, and 15. ECG waveforms were collected at least 1 hour prior to dosing and continued for at least 24 hours postdose. QT were corrected for each animal based on individual correction factors.

Full PK collection was conducted in the same animals on Day 1 and Day 105. Cmax values on Day 1 were 68 ng/mL ((b) (4) x high clinical exposure), 191 ng/mL ((b) (4) x high clinical exposure) and 759 ng/mL ((b) (4) x high clinical exposure) for 10, 100 and 600 mg/kg/day doses, respectively.

There were no drug-related changes in QTca, HR, PR and QRS intervals throughout the course of the study. No positive control drugs were used in the study. The minimal detectable differences (MDD) required to attain statistical significance with 80% certainty was 16.4 msec for QTc interval based on Week 4 QTc data.

Sensitivity justification was based on exposure from Day 1 of both studies and MDD from Day 3 and Week 4 for studies 8002569 and 8003147, respectively.

Reviewer's Comment: *We do not agree with the Applicant that there were no drug-related changes in QTca. See section 6.2.2.3.*

The Applicant used moxifloxacin from the **reference study**[2,3] as historical positive control. The reference study split 48 cynomolgus monkeys into 4 equally sized single sex cohorts. The QTc (individual corrected) data collection was carried out for each cohort in 5 periods:

- Period 1 was a 24-hour telemetry recording for pre-dose baseline evaluation.
- Period 2 was a collection of 2 hours of baseline data and 48 hours of post-dose vehicle data (V1).
- Period 3 involved 48 hours of data collection after an 80 mg/kg oral dose of moxifloxacin (M1).
- Periods 4 and 5 were repeats of Periods 2 and 3 (V2 and M2).

For parallel design analysis, cohort of 12 animals were randomly divided into 4 groups of 3. Data for only one treatment was considered for each group of animals. Combining the 4 cohorts this resulted in a parallel analysis design with four groups (V1, M1, V2, M2) of n = 12/group with balanced sexes in each group (no sex difference).

Baseline was 24-hour average QTc from pre-treatment day.

The treatment effect was compared to the Vehicle 1 treatment period using a linear regression QTc ~ Treatment + Baseline. Median sigma was 8.2 msec and MDD was 12.7 msec for n = 6 and 10.7 msec for n = 8.

6.2.2 Reviewer's Assessment and Data Reanalysis

The in vivo studies to support a negative conclusion for 6.1 integrated risk assessment need to satisfy the following criteria:

- Achieve exposures covering high clinical exposure in humans.
- Have sensitivity to detect a QTc prolongation effect of a magnitude similar to dedicated clinical QT studies, taking into consideration interspecies differences in the normal range of values for the QTc interval. For example, this can be achieved by demonstrating MDD ≤ 10 msec at 2x high clinical exposure if pharmacological sensitivity was reduced by half in the studied animals compared to humans. If historical positive control was used, the reference study should have sufficient sensitivity described above and MDD of the in vivo studies should be similar to the reference study. An increased MDD could be addressed via an increased exposure margin.
- Show no QTc prolongation.

The reviewer's assessment was based on these three criteria.

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[2] Leishman DJ, Holdsworth DL, Best DD, Roche BM. Comparing the sensitivity of cross-over and parallel study designs for QTc assessment: An analysis based on a single large study of moxifloxacin in 48 nonhuman primates. J Pharmacol Toxicol Methods. 2023 Sep-Oct;123:107299. doi: 10.1016/j.vascn.2023.107299. Epub 2023 Jul 24. PMID: 37495163.

[3] Holdsworth D, Best DD, Haist K, O'Donohue K, Phillips A, Abernathy MM, Roche B, Leishman DJ. Comparison of validity of standard nonclinical group size selection versus standard clinical group sizes for nonhuman primate QTc prolongation evaluation. J Pharmacol Toxicol Methods. 2023 Mar-Apr;120:107253. doi: 10.1016/j.vascn.2023.107253. Epub 2023 Feb 16. PMID: 36806737.

6.2.2.1 Comparison of Pharmacological Sensitivity Between Humans and Monkeys

Based on the moxifloxacin reference study, pharmacological sensitivity of monkeys is reduced compared with humans (Table 15). In humans, critical concentration (Cmax corresponding to a 10 msec QTc prolongation) of moxifloxacin was 1663 ng/mL[4], corresponding to free Cmax of 998 ng/mL (based on PB of 40%, mean of 30-50% from Moxi label[5]).

In the reference study, the observed geometric mean Cmax was 5020 ng/mL[3], corresponding to ΔΔQTc of approximately 20 msec. Assuming a linear relationship, the critical Cmax is ~2510 ng/mL. Protein binding of moxifloxacin in monkeys was reported to be 18% according to Komatsu et al.[6], 28% according to Watson et al.[7], and 38% according to Siefert et al.[8]. Ratio of free critical Cmax between monkeys and humans ranged between 1.6 to 2.1, depending on the choice of protein binding (Table 15).

In their response to the FDA's information request, the Applicant chose Siefert et al. as their source for protein binding, in which humans and monkeys reported similar free unbound values (fu: 62% for monkeys and 55% for humans). However, in the reference study[3], Komatsu et al. was used as the source for protein binding, which resulted in the critical concentration ratio between monkeys and humans to be 2.1-fold.

Based on dofetilide data, pharmacological sensitivity of monkeys is also reduced compared with humans (Table 15). In humans, critical Cmax of dofetilide was 0.4 ng/mL[4], corresponding to free Cmax of 0.14 ng/mL (based on PB of 65%, mean of 60-70% from dofetilide label[9]). According to Leishman et al.[10], the plasma concentration corresponding to 10 msec QTc prolongation based on an Emax model using a conventional analysis was 0.8 ng/mL. Protein binding of dofetilide in monkeys was 71% according to Komatsu et al.[6]. Ratio of free critical Cmax between monkey and human was 1.7-fold.

In conclusion, pharmacological sensitivity of monkeys was reduced compared with humans based on both moxifloxacin and dofetilide data. Ratio of free critical concentration between monkeys and humans was 2.1-fold for moxifloxacin and 1.7-fold

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[4] Reviewer's database.
[5] Moxi USPI
[6] Komatsu R, Mizuno H, Ishizaka T, et al. Exposure-response analysis of drug-induced QT interval prolongation in telemetered monkeys for translational prediction to human. J Pharmacol Toxicol Methods. 2019. Sep-Oct;99:106606. doi: 10.1016/j.vascn.2019.106606
[7] Watson KJ, Gorczyca WP, Umland J, Zhang Y, Chen X, Sun SZ, Fermini B, Holbrook M, Van Der Graaf PH. Pharmacokinetic-pharmacodynamic modelling of the effect of Moxifloxacin on QTc prolongation in telemetered cynomolgus monkeys. J Pharmacol Toxicol Methods. 2011 May-Jun;63(3):304-13. doi: 10.1016/j.vascn.2011.03.002. Epub 2011 Mar 17. PMID: 21419854.Chemother. 1999 May;43 Suppl B:69-76. doi: 10.1093/jac/43.suppl_2.69.
[8] Siefert HM, Domdey-Bette A, Henninger K, et al. Pharmacokinetics of the 8-methoxyquinolone, moxifloxacin: a comparison in humans and other mammalian species. J Antimicrob Chemother. 1999 May;43 Suppl B:69-76. doi: 10.1093/jac/43.suppl_2.69.
[9] Dofetilide USPI.
[10] Leishman DJ, Holdsworth DL, Best DD, Abernathy MM, Roche BM. Demonstrating the statistical and pharmacological sensitivity of nonclinical QTc analysis using a dofetilide dose-response in nonhuman primates. J Pharmacol Toxicol Methods. 2025 Feb;131:107572. doi: 10.1016/j.vascn.2024.107572. Epub 2024 Dec 15. PMID: 39689735.

for dofetilide, using protein binding from Komatsu et al. This means to achieve the same sensitivity as clinical QT study, the in vivo studies would need to cover ~2x high clinical exposure in humans (unbound) with MDD ≤ 10 msec.

Table 15. Comparison of Pharmacological Sensitivity Between Humans and Monkeys

Drug	Species	Critical Concentration (ng/mL)	Protein Binding (%)	Free Critical Concentration (ng/mL)	Ratio of Free Critical Cmax between Monkeys and Humans
Moxifloxacin	Human	1663	40	998	
	Monkey	2510	18	2058	2.1
			28	1807	1.8
			38	1556	1.6
Dofetilide	Human	0.4	65	0.14	
	Monkey	0.8	71	0.24	1.7

6.2.2.2 Assess Exposures and MDDs of the Two Tox Studies

The reviewer adopted the analysis methods from the reference study (section 6.2.1). Modeling was based on hourly averaged QTc data. Each time point was modeled independently. The comparison of MDD was conducted on the MDDs corresponding to the median residual error among all time points on a given day. The reviewer can reproduce similar MDDs of the reference paper (Table 16).

We then applied the same model to the two tox studies. Table 16 summarizes MDDs and exposures by day. The resulted MDDs were similar to the ones reported by the Applicant (median adjusted MDD from different statistical models in Applicant's analysis).

On most of the study days of the two tox studies, MDDs were higher than the reference study. MDD on Day 23 from study 8002569 and MDD at Week 4 and Week 8 from study 8003147 were 40-50% higher than the reference study.

MDD on Day 3 from study 8002569 was similar to the reference study. However, the exposure (measured on Day 1) was only (b) (4)-fold of high clinical exposure in human and while this exposure margin exceeds 2-fold (based on reduced pharmacological sensitivity between monkeys and humans), the MDD was 12.6 msec compared to 10 msec.

MDD of Week 15 from study 8003147 was similar to the reference study. The exposure was also higher at Week 15. Assay sensitivity was sufficient at Week 15 from study 8003147.

Table 16. Exposure and MDD of the Reference Study and the Tox Studies

Study	Day/Week	n	Cmax[1] (ng/mL) [Day]	Exposure ratio[2]	Applicant's or reference study MDD	Reviewer's MDD

Reference study		6			12.7	11.2
		8			10.7	9.5
8002569	Day 3	6	725 [D1]	(b) (4)	12.6	12.2
	Day 23	6	893 [D28]		18.9	17.6
8003147	Week 4	8	750 [D1]		16.4	15.9
	Week 8	8			14.6	15.2
	Week 15	8	1400 [D105]		11.8	12.5

1 Cmax of the highest dose (600 mg/kg)
2 Ratio of unbound Cmax to unbound high clinical exposure; protein binding is 1% for human and NHP.

6.2.2.3 By-Time Analysis Results

Figure 14 showed the estimated mean effect of vehicle and baseline adjusted QTc of study 8002569, using model from the reference study (QTc ~ Treatment + Baseline, each time point modeled independently). Error bars represented 95% confidence interval (CI). The time course showed no effect of QTc in any dose group on either study day.

Figure 14. Estimated Mean Effect of Vehicle and Baseline Adjusted QTc, Study 8002569

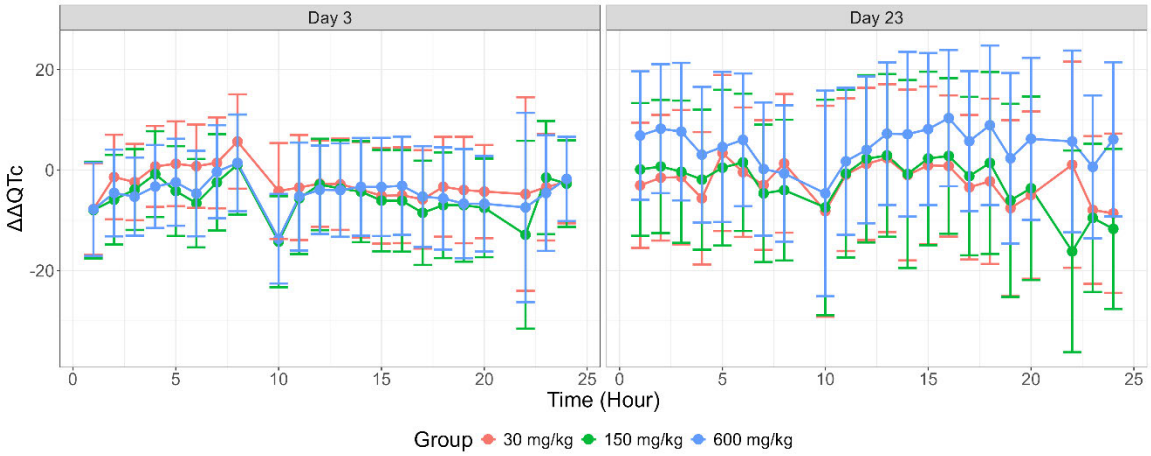


Figure 15 showed the estimated mean effect of vehicle and baseline adjusted QTc of study 8003147. QTc increased after 10 hours postdose in all three weeks at the highest dose group (600 mg/kg). Note that at Week 15, when the assay sensitivity might be sufficient (section 6.2.2.2), the lower bounds of 95% CI were consistently above 0 msec after 10 hours postdose. This trend can also be seen from unadjusted QTc. Figure 16 showed mean and 95% CI of QTc by week (descriptive statistics). QTc was increased by ~20 msec after 10 hours postdose in the 600 mg/kg dose group at Week 4, 8, and 15. This trend was not observed at prestudy. The reason for this QTc prolongation is unknown. The QTc prolongation did not follow the time course of the plasma concentration (Figure 17, Applicant's figure).

Figure 15. Estimated Mean Effect of Vehicle and Baseline Adjusted QTc, Study 8003147

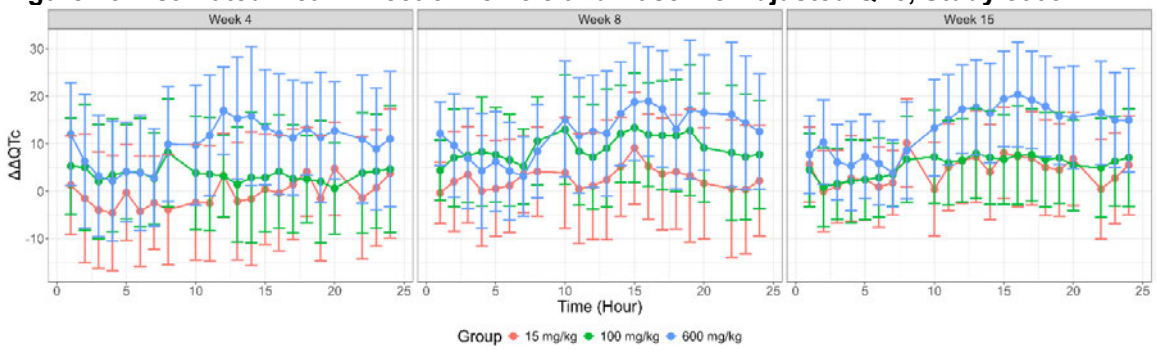


Figure 16. Mean and 95% Confidence Interval of QTc, Study 8003147

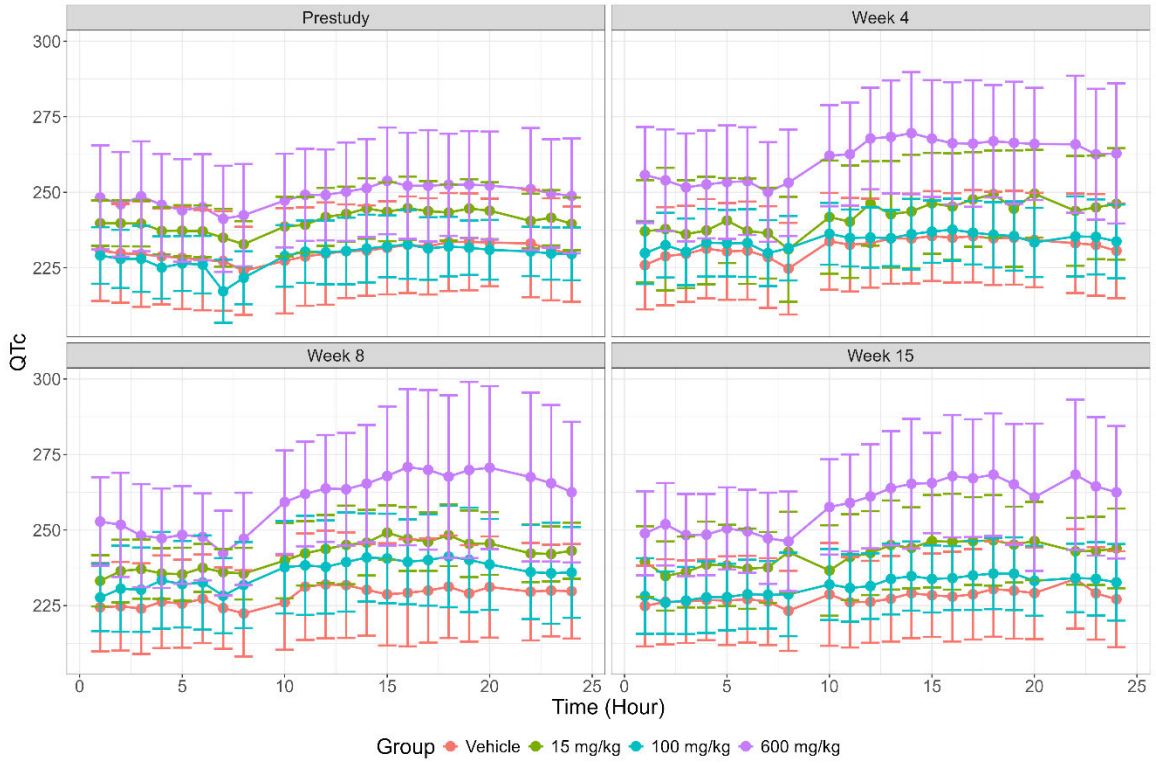
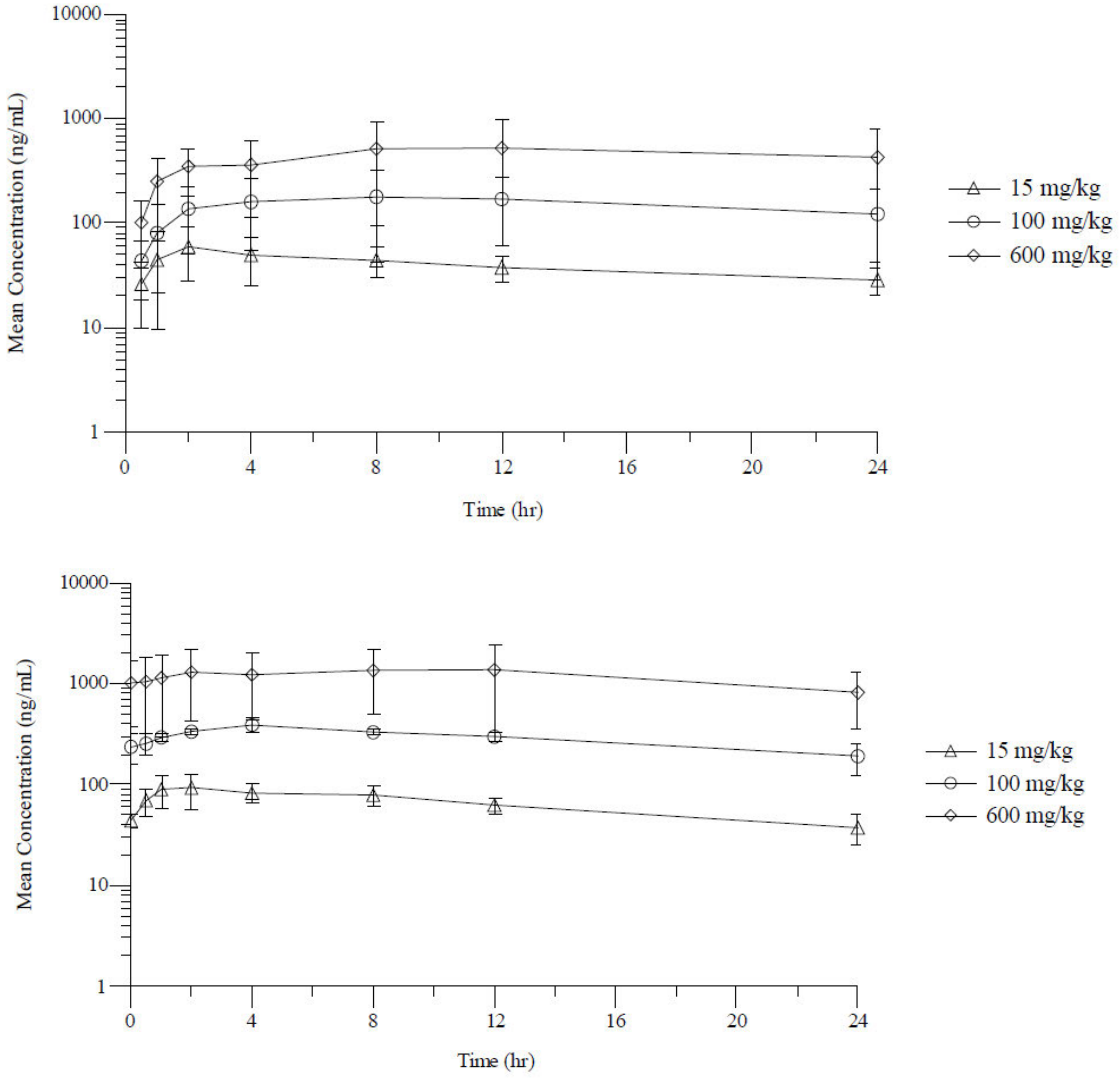


Figure 17. Summary (Mean ± SD) Male Cynomolgus Monkey Plasma Concentrations on Day 1 (Top) and Day 105 (Bottom), Study 8003147



Source: Applicant's study 8003147 report

6.2.3 In Vivo Summary

The Applicant submitted two toxicology studies in monkeys with intensive ECG monitoring and a reference study of moxifloxacin in monkeys as historical positive control. Pharmacological sensitivity was reduced by half in monkeys compared with humans. Study 8002569 showed no QTc effect of imlunestrant. It is unclear why QTc prolongation was not observed in this study. Data from Week 15 of study 8003147 had sufficient assay sensitivity. However, QTc prolongation was observed at the 600 mg/kg dose group after 10 hours postdose at Week 4, Week 8, and Week 15. In summary, the in vivo studies do not support a negative finding for 6.1 integrated risk assessment.

6.3 NONCLINICAL SUMMARY

The hERG results showed that imlunestrant has a hERG safety margin of (b) (4) x, which is larger than the safety margins of reference drugs over the clinical critical concentrations (the mean concentrations that give a 10-ms mean increase in ΔΔQTc in clinical study). The finding suggests that imlunestrant may present a low risk for QT prolongation by directly inhibiting the hERG current at the high clinical exposure.

The in vivo studies do not support a negative conclusion for 6.1 integrated risk assessment. Study 8002569 showed no QTc effect of imlunestrant. It is unclear why QTc prolongation was not observed in this study. Data from Week 15 of study 8003147 had sufficient assay sensitivity. However, QTc prolongation was observed at the 600 mg/kg dose group after 10 hours postdose at Week 4, Week 8, and Week 15.

Altogether, the nonclinical studies do not support double negative for 6.1 integrate risk assessment.

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Mike is OOO

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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:	April 25, 2025
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 218881
Product Name, Dosage Form, and Strength:	Inluriyo (Imlunestrant) tablet, 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Eli Lilly and Company
FDA Received Date:	October 31, 2024
TTT ID #:	2024-11855
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 INTRODUCTION

As part of the approval process for Inluriyo (Imlunestrant) tablet, the Division of Oncology 1 (DO1) requested that we review the proposed Inluriyo Prescribing Information (PI), Patient Package Insert (PPI), and container label(s) for areas of vulnerability that may lead to medication errors.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	**Appendix Section**
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

The proposed Inluriyo Prescribing Information (PI), Patient Package Insert (PPI), and container label(s) may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Oncology 1 (DO1) in Section 4 and for Eli Lilly and Company in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 1 (DO1)

A. Prescribing Information

1. Highlights of Prescribing Information (HPI), Section 2 Dosage and Administration

a. We recommend deleting "INLURIYO" from this section to increase the prominence of dosage and administration information in the HPI. Additionally, we recommend adding important administration instructions regarding swallow tablets whole for consistency across labeling.

- Select patients for treatment [redacted] (b) (4) based on the presence of *ESR1* mutations. (2.1)
- The recommended dosage [redacted] (b) (4) is 400 mg [redacted] (b) (4) orally once daily, without food. Swallow tablets whole. Do not split, crush, or chew tablets. (2.2)

b. The statement [redacted] (b) (4) does not describe increasing the dose for concomitant use with strong CYP 3A inducers which is described in section 2.5. We recommend revising to "[redacted] (b) (4)".

c. Consider adding dosing information for hepatic impairment for consistency with prescribing information. Add "Hepatic impairment: Reduce dosage for patients with moderate (Child-Pugh B) or severe hepatic impairment (Child-Pugh C). (2.4)".

2. Full Prescribing Information, Section 2 Dosage and Administration

   a. We recommend revising the title of section "2.3 Dose Modifications" to "2.3 Dose Modifications for Adverse Reactions" to facilitate information retrieval.

3. Patient Package Insert (PPI)

   a. The pronunciation "en-loo-ree-yoh" in the PPI does not match the pronunciation "ihn-LUUR-EE-oh" provided in the proprietary name submission. Please clarify the correct pronunciation of the proprietary name, Inluriyo.

   b. Currently the title states "(b) (4)." This is inconsistent with prescribing information and container label which can lead to patient confusion. Delete the phrase "(b) (4)" from the title of the Patient Package Insert.

   c. The following statements are inconsistent with the prescribing information.

      - (b) (4)
      - Swallow tablets whole.
        - Do not chew, crush, or split the tablets.

      (b) (4)

      Inconsistent information can lead to wrong technique errors. We recommend aligning the bulleted information to give each bullet point equal prominence and revising to:

      • Take on an empty stomach, at least (b) (4) before food or (b) (4) after food.
      • Swallow tablets whole. Do not split, crush, or chew the tablets.
      • (b) (4)

5 RECOMMENDATIONS FOR ELI LILLY AND COMPANY

A. Container Label(s)

1. As currently presented, important administration information is not on the container label, which may cause wrong administration errors. For clarity, we recommend adding the following information to the side panel "Take the tablets on an empty stomach, at least (b) (4) before food or (b) (4) after food. Swallow the tablets whole. Do not split, crush, or chew the tablets." if space permits.

2. As currently presented on the principal display panel (PDP), the net quantity statement is [redacted] (b) (4), which may be overlooked. This layout affects the readability of critical information. We recommend moving the net quantity statement to the lower left corner to improve readability of net quantity, and removing [redacted] (b) (4) since it is not specific to this drug product.

3. As currently presented, the first number of the temperature ranges is missing a temperature unit. Inconsistent reference to storage temperature may lead to drug deterioration errors. Revise storage statement to include a temperature unit after each temperature numerical value. For example, "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]" and ensure this storage statement is consistent with the storage information in the Prescribing Information.

4. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date 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 hyphen or forward slash to separate the portions of the expiration date. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)*.

5. The product identifier is missing. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers 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. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)*. If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the container labels.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Inluriyo received on October 31, 2024 from Eli Lilly and Company.

Table 2. Relevant Product Information for Inluriyo	
Initial Approval Date	N/A
Active Ingredient	Imlunestrant
Indication	INLURIYO is indicated for the treatment of adults with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, *estrogen receptor-1* (*ESR1*)-mutated advanced or metastatic breast cancer previously treated with an endocrine-based regimen.
Dosage Form	tablet
Strength	200 mg
Route of Administration	Oral
Dose and Frequency	The recommended dosage of INLURIYO is 400 mg (two 200 mg tablets) taken orally, once daily, at approximately the same time. Dose modification for adverse reactions: Decrease the dose by 200 mg. Discontinue INLURIYO for patients unable to tolerate 200 mg once daily. Dose modification for moderate or severe hepatic impairment: 200 mg once daily. Dose modification for strong CYP3A Inducer: 600 mg once daily
How Supplied	INLURIYO 200 mg tablets are supplied in either a 28-count or 56-count bottle configuration.
Storage	Store at 20°C to 25°C (68°F to 77°F). Excursions between 15°C to 30°C (59°F to 86°F) are permitted.
Container Closure	HDPE bottles with aluminum foil seal liner and (b) (4) .

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Inluriyo labels and labeling submitted by Eli Lilly and Company.

- Prescribing Information received on October 31, 2024, available from \\CDSESUB1\EVSPROD\nda218881\0001\m1\us\proposed-uspi-clean.docx
- Patient Package Insert received on October 31, 2024, available from \\CDSESUB1\EVSPROD\nda218881\0001\m1\us\proposed-ppi-clean.docx
- Container label(s) received on October 31, 2024

B.2 Container Label(s) Images

Container Label(s):

28 tablets

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

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

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