

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218881Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

Inluriyo (implunestrant)

NDA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number(s)	218881
Priority or Standard	Standard
Submit Date(s)	October 31, 2024
Received Date(s)	October 31, 2024
PDUFA Goal Date	October 31, 2025
Division/Office	DO1/OOD/OND/CDER
Review Completion Date	<i>Electronic Stamp Date</i>
Established Name	Implunestrant
(Proposed) Trade Name	INLURIYO
Pharmacologic Class	Estrogen receptor antagonist
Code name	LY3484356
Applicant	Eli Lilly and Company
Formulation(s)	200 mg tablets
Dosing Regimen	400 mg orally once daily, without food (at least 2 hours before food, or 1 hour after food)
Applicant Proposed Indication(s)/Population(s)	Implunestrant (INLURIYO) is an estrogen receptor antagonist indicated for treatment of adults with ER-positive, HER2-negative, <i>ESR1-mutated</i> advanced or metastatic breast cancer, previously treated with an endocrine-based regimen.
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	Implunestrant (INLURIYO) is indicated for the treatment of adults with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, <i>estrogen receptor-1 (ESR1)</i> -mutated advanced or metastatic breast cancer with

Inluriyo (imlunestrant)

	disease progression following at least one line of endocrine therapy.
--	---

Table of Contents

Reviewers of Multi-Disciplinary Review and Evaluation	12
Additional Reviewers of Application	12
Glossary	14
1 Executive Summary.....	17
1.1 Product Introduction.....	17
1.2 Conclusions on the Substantial Evidence of Effectiveness.....	17
1.3 Benefit-Risk Assessment (BRA).....	20
1.4 Patient Experience Data	27
2 Therapeutic Context	29
2.1 Analysis of Condition.....	29
2.2 Analysis of Current Treatment Options	29
3 Regulatory Background.....	32
3.1 U.S. Regulatory Actions and Marketing History	32
3.2 Summary of Presubmission/Submission Regulatory Activity	32
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety	35
4.1 Office of Scientific Investigations (OSI)	35
4.2 Product Quality	37
4.3 Clinical Microbiology	37
4.4 Devices and Companion Diagnostic Issues	37
5 Nonclinical Pharmacology/Toxicology	39
5.1 Executive Summary	39
5.2 Referenced NDAs, BLAs, DMFs.....	42
5.3 Pharmacology	42
5.4 Absorption, Distribution, Metabolism, Excretion/Pharmacokinetics	46
5.5 Toxicology	49

Inluriyo (implunestrant)

5.5.1	General Toxicology	49
5.5.2	Genetic Toxicology.....	68
5.5.3	Carcinogenicity	69
5.5.4	Reproductive and Developmental Toxicology	69
5.5.5	Other Toxicology Studies	78
6	Clinical Pharmacology	83
6.1	Executive Summary	83
6.2	Summary of Clinical Pharmacology Assessment	85
6.2.1	Pharmacology and Clinical Pharmacokinetics.....	85
6.2.2	General Dosing and Therapeutic Individualization	87
6.3	Comprehensive Clinical Pharmacology Review.....	91
6.3.1	General Pharmacology and Pharmacokinetic Characteristics	91
6.3.2	Clinical Pharmacology Questions.....	92
7	Sources of Clinical Data	104
7.1	Table of Clinical Studies	104
8	Statistical and Clinical Evaluation.....	106
8.1	Review of Relevant Individual Trials Used to Support Efficacy.....	106
8.1.1	EMBER-3: A Phase 3, Randomized, Open-Label Study of Imlunestrant, Investigator’s Choice of Endocrine Therapy, and Imlunestrant plus Abemaciclib in Patients with ER+, HER2- Locally Advanced or Metastatic Breast Cancer Previously Treated with Endocrine Therapy	106
8.1.2	Study Results	124
8.1.3	Integrated Review of Effectiveness	164
8.1.4	Assessment of Efficacy Across Trials	166
8.1.5	Integrated Assessment of Effectiveness.....	167
8.2	Review of Safety	167
8.2.1	Safety Review Approach	169
8.2.2	Review of the Safety Database	172
8.2.3	Adequacy of Applicant’s Clinical Safety Assessments	176
8.2.4	Safety Results.....	177

Inluriyo (implunestrant)

8.2.5	Analysis of Submission-Specific Safety Issues	200
8.2.6	Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability ..	204
8.2.7	Safety Analyses by Demographic Subgroups.....	204
8.2.8	Specific Safety Studies/Clinical Trials	205
8.2.9	Additional Safety Explorations.....	206
8.2.10	Safety in the Postmarket Setting	207
8.2.11	Integrated Assessment of Safety	208
8.3	Statistical Issues	210
8.4	Conclusions and Recommendations.....	211
8.4.1	Approach to Substantial Evidence of Effectiveness	211
9	Advisory Committee Meeting and Other External Consultations.....	214
10	Pediatrics	215
11	Labeling Recommendations	216
12	Risk Evaluation and Mitigation Strategies (REMS).....	225
13	Postmarketing Requirements and Commitment.....	226
14	Division Director (DHOT) (NME ONLY).....	227
15	Division Director (OCP).....	228
16	Division Director (OB).....	229
17	Division Director (Clinical).....	230
18	Office Director (or designated signatory authority)	231
19	Appendices	232
19.1	References	232
19.2	Financial Disclosure	234
19.3	Nonclinical Pharmacology/Toxicology	235
19.4	OCP Appendices (Technical documents supporting OCP recommendations)	235
19.4.1	Population PK Analysis	235

19.4.2	Exposure-Response Analysis	247
19.4.3	Bioanalytical Methods	261
19.5	Additional Safety Analyses Conducted by FDA	267

Table of Tables

Table 3.1: Key U.S. Regulatory Interactions Related to the Development of Implunestrant.....	32
Table 5.1: Summary of toxicokinetic data on Day 4 in female rats	81
Table 6.1: Key Clinical Pharmacology Review Issues, Recommendations, and Comments	84
Table 6.2: ORR by Implunestrant Monotherapy Dose Level in EMBER	88
Table 6.3: The effect hepatic impairment on Implunestrant PK based on Child-Pugh Classification	95
Table 6.4: Frequency of <i>ESR1</i> Mutations in the <i>ESR1</i> m-Detected Population in EMBER-3 trial	96
Table 6.5: Subgroup Analysis of Progression-free Survival – <i>ESR1</i> m-detected Biomarker Subpopulations in EMBER-3	97
Table 6.6: Summary of Dose-Normalized C _{max} and AUC ₀₋₂₄ by <i>UGT1A1</i> Genotype – Studies JZLA and JZLD	98
Table 6.7: The effect of CYP3A inhibitors (itraconazole, 200 mg for multiple days) on Implunestrant PK	99
Table 6.8: The effect of CYP3A inducers (carbamazepine, 300 mg for multiple days) on Implunestrant PK	100
Table 6.9: The Effect of Implunestrant on PK of P-gp Substrates (Digoxin, 0.25 mg)	101
Table 6.10: The Effect of Implunestrant on PK of BCRP Substrates (Rosuvastatin, 10 mg)	101
Table 7.1: Listing of Completed and Ongoing Clinical Studies	104
Table 8.1: Study Interventions Administered	108
Table 8.2: Key Primary and Secondary Objectives	113
Table 8.3: Timing of OS Analyses in the ITT Population	118
Table 8.4: Timing of OS Analyses in the <i>ESR1</i> m-Detected Population.....	119
Table 8.5: Summary of Protocol Amendments.....	121
Table 8.6: EMBER-3 SAP Version History	122
Table 8.7: Summary of Patient Disposition in the ITT Population	126
Table 8.8: Summary of Patient Disposition in the <i>ESR1</i> m-detected Population.....	128
Table 8.9: Summary of Important Protocol Deviations for <i>ESR1</i> m-detected and ITT Population	130

Inluriyo (imlunestrant)

Table 8.10: Patient Deviations for Eligibility Criteria 3	131
Table 8.11: Summary of Patient Demographics	133
Table 8.12. Summary of Key Baseline Disease Characteristics	135
Table 8.13. Disease Characteristics in Select Regions	137
Table 8.14. Categories of Selected Concomitant Therapy in the Safety Population	138
Table 8.15 Subsequent Anticancer Therapies in the <i>ESR/m</i> Population	139
Table 8.16. INV-Assessed PFS <i>ESR/m</i> -detected Population Imlunestrant versus SOC	140
Table 8.17. BIRC-Assessed PFS Imlunestrant versus SOC <i>ESR/m</i> Population	142
Table 8.18: Prespecified Sensitivity Analyses for PFS <i>ESR/m</i> -detected Population Imlunestrant versus SOC	143
Table 8.19: Investigator-Assessed PFS in the ITT Population the <i>ESR/m</i> -nd Population (Imlunestrant versus TPC)	146
Table 8.20: Discordance Analysis for PFS per Investigator Assessment vs PFS per BIRC Assessment.....	148
Table 8.21: Discordance Analysis for PFS per Investigator Assessment vs PFS per BIRC Assessment.....	149
Table 8.22: Sensitivity Analyses of Investigator-assessed PFS to Assess the Impact of Palliative Radiation Therapy in the <i>ESR/m</i> -detected Population (Imlunestrant versus TPC)	150
Table 8.23: Overall Survival <i>ESR/m</i> -detected Population Imlunestrant versus SOC.....	153
Table 8.24: Summary of Secondary Endpoints <i>ESR/m</i> -detected Population Imlunestrant versus SOC	155
Table 8.25 Overall Survival Events by Time Interval in the <i>ESR/m</i> -detected Population (Imlunestrant versus TPC)	156
Table 8.26: Overall Survival in the ITT Population and the <i>ESR/m</i> -nd Population (Imlunestrant versus TPC).....	157
Table 8.27: Sensitivity Analyses of OS in the <i>ESR/m</i> -detected Population (Imlunestrant versus TPC).....	160
Table 8.28: Summary of Exposure for the <i>ESR/m</i> - Detected and Overall Safety Populations	173
Table 8.29: Summary of Deaths <i>ESR/m</i> -detected and Overall Safety Population Imlunestrant versus SOC	178

Inluriyo (implunestrant)

Table 8.30: Summary of TE-SAEs Occurring in ≥ 2 Patients in Either Treatment Arm by Decreasing Frequency in the Implunestrant Arm ESR1m-detected and Overall Safety Population Implunestrant versus SOC	185
Table 8.31: Overview of Adverse Events <i>ESR1m</i> -detected and Overall Safety Population Implunestrant versus SOC	189
Table 8.32: Summary of TEAEs by Maximum CTCAE Grade Occurring in 5% of Patients in Either Treatment Arm, Preferred Term by Decreasing Frequency in the Implunestrant Arm ESR1m-Detected and Overall Safety Population Implunestrant versus SOC	190
Table 8.33: Adverse Reactions ($\geq 10\%$) in Patients Who Received INLURIYO in EMBER-3 .	194
Table 8.34: Summary of Treatment-Emergent Maximum Postbaseline CTCAE Laboratory Toxicities for ALT and AST ESR1m-detected and Overall Safety Population Implunestrant versus SOC	195
Table 8.35: Select Laboratory Abnormalities ($\geq 10\%$) That Worsened from Baseline in Patients Who Received INLURIYO in EMBER-3	197
Table 8.36: Treatment-Emergent Elevated Transaminases by Decreasing Frequency Safety Population; Implunestrant versus SOC	200
Table 8.37: Summary of Characteristics of Treatment-Emergent Elevated Transaminase Adverse Events Safety Population Implunestrant versus SOC	202
Table 19.1: Summary of Baseline Patient Characteristics for the popPK Analysis	239
Table 19.2: PK and Covariate Parameters in popPK Model	241
Table 19.3: Parameter Estimates from Time-to-Event Model for PFS	250
Table 19.4: Parameter Estimates from Logistic Regression Model for CBR.....	250
Table 19.5: Parameter Estimates from Logistic Regression Models for Safety	259
Table 19.6: Summary of Bioanalytical Validation Used for Quantitation of Implunestrant in Human Plasma	262
Table 19.7: Summary of Bioanalytical Validation Used for Quantification of Implunestrant in Human K2EDTA Plasma.....	266

Table of Figures

Figure 5.1: Anti-tumor activity of implunestrant in MCF-fluc brain orthotopic model.	44
Figure 5.2: Summary of body weight	72
Figure 8.1: EMBER-3 study schema.	108
Figure 8.2: Initial graphical representation of the testing scheme.	117
Figure 8.3: Patient disposition.	125
Figure 8.4: Kaplan-Meier plot of INV-assessed PFS <i>ESR/m</i> -detected population Implunestrant versus SOC.	142
Figure 8.5: Kaplan-Meier Plot for Investigator-Assessed PFS in the ITT Population (Implunestrant versus TPC).....	147
Figure 8.6: Kaplan-Meier Plot for Investigator-Assessed PFS in the <i>ESR/m</i> -nd Population (Implunestrant versus TPC)	147
Figure 8.7: Tipping-point Analysis for Early Censoring on Investigator-assessed PFS in the <i>ESR/m</i> -detected Population (Implunestrant versus TPC)	149
Figure 8.8: Investigator-assessed PFS Subgroup Analyses in the <i>ESR/m</i> -detected Population (Implunestrant versus TPC)	151
Figure 8.9: Kaplan-Meier plot of overall survival, <i>ESR/m</i> -detected population implunestrant versus SOC.	154
Figure 8.10: Kaplan-Meier Plot for Overall Survival in the ITT Population (Implunestrant versus TPC).....	157
Figure 8.11: Kaplan-Meier Plot for Overall Survival in the <i>ESR/m</i> -nd* Population (Implunestrant versus TPC).....	158
Figure 8.12: OS Subgroup Analyses in the <i>ESR/m</i> -detected Population (Implunestrant versus TPC).....	158
Figure 8.13: Tipping-point Analysis for Withdrawal of Consent on OS in the <i>ESR/m</i> Population (Implunestrant versus TPC)	160
Figure 19.1: Implunestrant popPK final model goodness-of-fit plots.	243
Figure 19.2: Visual predictive check of the popPK model for implunestrant stratified by study population.....	244
Figure 19.3: Simulated PK profiles at 400 mg QD for patients with body weights that are 5th, 50th, and 95th percentiles of observed patient characteristics in the pooled analysis population.....	245

Inluriyo (imlunestrant)

Figure 19.4: Simulated imlunestrant PK profiles at 400 mg QD for patients and healthy participants in the pooled analysis population.	246
Figure 19.5: Visual predictive check graphs for time-to-event model of PFS. Clockwise from top-left: average concentrations below/above median, presence/absence of abemaciclib, prior/no prior CDK4/6i therapy, presence/absence of visceral metastases.	252
Figure 19.6: Logistic regression model for CBR.....	253
Figure 19.5 (addendum): Visual predictive check graphs for time-to-event model of PFS. Clockwise from top-left: average concentrations below/above median, presence/absence of abemaciclib, prior/no prior CDK4/6i therapy, presence/absence of visceral metastases	255
Figure 19.6 (addendum): Exposure-Response plot of PFS against average imlunestrant concentration.....	256
Figure 19.7: Exposure-response relationships for safety endpoints using the average concentration of imlunestrant up to the day of TEAE for participants in monotherapy arms of Studies JZLA (EMBER) and JZLC (EMBER-3).	260

Regulatory Project Manager	Ja’Kaya Wilson, MS
Pharmacology/Toxicology Reviewer(s)	Wilmolnut Manheng, PhD
Pharmacology/Toxicology Team Leader(s)	Nikolett Biel, PhD
Office of Clinical Pharmacology Reviewer(s)	Banu Zolnik, PhD (OCP/DCPI), Fang Li, PhD (OCP/DPM) Tien Troung, PharmD, PhD (OCP/DTPM)
Office of Clinical Pharmacology Team Leader(s)	Lauren Price, PharmD (OCP/DCPII), Jingyu (Jerry) Yu, PhD (OCP/DPM), Jeffrey Kraft, PhD (OCP/DTPM)

Inluriyo (imlunestrant)

Clinical Reviewer	Joshua Donaldson, MD, PhD (Efficacy) Maria Garcia-Jimenez, MD, MHS (Safety)
Clinical Team Leader	Preeti Narayan, MD
Safety Analyst (if applicable)	Ilynn Bulatao, MD, PhD
Safety Associate Director	Oladimeji (Ladi) Akinboro, MD
Safety Regulatory Project Manager	Meredith Hillig, MS
Associate Director for Patient Outcomes	Vishal Bhatnagar, MD
Statistical Reviewer	Hui Zhang, PhD
Statistical Team Leader	Xin (Cindy) Gao, PhD
Associate Director for Labeling (ADL)	William Pierce, PharmD, MPH
Cross-Disciplinary Team Leader	Preeti Narayan, MD
Acting Deputy Division Director (DHOT)	Tiffany Ricks, PhD
Division Director (OCP)	Nam Atiqur Rahman, PhD
Division Director (OB)	Shenghui Tang, PhD
Division Director (OOD)	Laleh Amiri-Kordestani, MD
Office Director (or designated signatory authority)	R. Angelo de Claro, MD

Reviewers of Multi-Disciplinary Review and Evaluation

Additional Reviewers of Application

OPQ	RPM: Utkarsh Desai DP/DS: Olen Stephens, Raymond Frankewich, Xing Wang, Haripada Sarker, David Claffey
------------	---

Inluriyo (imlunestrant)

	Facilities: Ann-Marie Afrifa, Christine Falabella Biopharmaceuticals: Min (Sammie) Kang, Anitha Govada Senior Quality Assessor: Xing Wang
Microbiology	N/A
OPDP	Courtney Leach, Rachael Conklin
OSI	Min Lu, Leigh Marcus
DPV	Afrouz Nayernamae
OSE/DEPI	Steven Bird
OSE/DMEPA	Sali Mahmoud, Tingting Gao
OSE/DRISK	Naomi Boston
CDRH	Liuya Tang, Shyam Kalavar, Anand Pathak, Yu Han, Soma Ghosh
Other	N/A

OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

Glossary

ABC	advanced breast cancer (locally advanced breast cancer not amenable to curative treatment or metastatic breast cancer)
AE	adverse event
AESI	adverse event of special interest
AI	aromatase inhibitor
AKT	protein kinase B
ALT	alanine aminotransferase
ASCO-CAP	American Society of Clinical Oncology and the College of American Pathologists
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC_{(0-\infty)}$	area under the concentration versus time curve from time zero to infinity
$AUC_{(0-\infty),u}$	unbound area under the concentration versus time curve from time zero to infinity
BCRP	breast cancer-resistance protein
BIRC	blinded independent review committee
CBR	clinical benefit rate
CDK4/6	cyclin-dependent kinase 4/6
CDK4/6i	cyclin-dependent kinase 4/6 inhibitor
CI	confidence interval
C_{max}	maximum observed drug concentration
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA

Inluriyo (imlunestrant)

CV	coefficient of variation
CYP	cytochrome P450
DoR	duration of response
EBC	early breast cancer
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEC	endometrioid endometrial cancer
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
ER	estrogen receptor
ER+	estrogen receptor positive
<i>ESR1</i>	estrogen receptor 1
<i>ESR1</i> m	estrogen receptor 1 mutation
ET	endocrine therapy
GCP	good clinical practice
GHS/QOL	global health status/quality of life
GnRH	gonadotropin hormone-releasing hormone agonist
HER2-	human epidermal growth factor receptor 2 negative
HR	hazard ratio
HR+	hormone receptor positive
ICH	International Council for Harmonisation
IM	intramuscular
imlun+abema	imlunestrant in combination with abemaciclib
ITT	intention to treat
MBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
mTOR	mammalian target of rapamycin

Inluriyo (imlunestrant)

NDA	new drug application
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	progressive disease
PDX	patient-derived xenograft
PFS	progression-free survival
P-gp	P-glycoprotein
PGR	progesterone receptor
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetics
PPK	population pharmacokinetics
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
QD	once daily
QTc	QT interval (corrected)
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SERD	selective estrogen receptor degrader
SERM	selective estrogen receptor modulator
SOC	standard of care
TE-SAE	treatment-emergent serious adverse event
TEAE	treatment-emergent adverse event
TEC ₈₀	therapeutic effective concentration required for 80% target inhibition
UGT1A1	uridine 5'-diphospho-glucuronosyltransferase 1A1

1 Executive Summary

1.1 Product Introduction

Imlunestrant is an orally bioavailable, estrogen receptor (ER) antagonist that binds to ER α . It is a new molecular entity. Imlunestrant currently has not been approved for any indication worldwide.

The Applicant proposed the following indication for NDA 218881:

Imlunestrant 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 indication for approval is:

Imlunestrant 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 with disease progression following at least one line of endocrine therapy.

The recommended dosage for imlunestrant is 400 mg orally once daily, without food (at least 2 hours before food, or 1 hour after food).

1.2 Conclusions on the Substantial Evidence of Effectiveness

The review team recommends granting regular approval for imlunestrant for the treatment of adults with ER-positive, HER2-negative, ESR1-mutated (ESR1m) advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy, in accordance with 21 Code of Federal Regulations (CFR) 314.126(a)(b).

Substantial evidence of effectiveness for this application is based on efficacy and safety results from the EMBER-3 trial, a multicenter, open label, active-control, 3-arm trial in 874 patients (323 with ESR1m disease) randomized to imlunestrant monotherapy, a treatment of physician's choice (TPC) arm of endocrine therapy of either fulvestrant or exemestane, or a third arm of imlunestrant plus abemaciclib, in patients with ER+, HER2- locally advanced or metastatic breast cancer previously treated with an AI, with or without a CDK4/6 inhibitor. Patients were excluded if they were eligible to receive a PARP inhibitor. The review for this NDA application was focused on the imlunestrant monotherapy arm vs. the TPC arm as these were the relevant arms for the proposed indication.

Inluriyo (imlunestrant)

The primary endpoints were investigator assessed progression free survival (PFS) in the *ESR1m* population and the ITT population (*ESR1m* and *ESR1m*-not detected). The secondary endpoints were overall survival (OS) in the *ESR1m* and ITT populations. Randomization was stratified by previous treatment with a CDK4/6 inhibitor (yes vs no), presence of visceral metastasis (yes vs no), and region (East Asia vs North America/Western Europe vs Others). *ESR1* mutational status was determined by blood circulating tumor deoxyribonucleic acid (ctDNA) using the Guardant360 CDx assay and was limited to specific *ESR1* mutations in the ligand binding domain.

EMBER-3 demonstrated a statistically significant and clinically meaningful improvement in PFS by investigator in the *ESR1m* population in this replacement trial. Median PFS was 5.5 months versus 3.8 months (HR 0.62, 95% CI: 0.46-0.82; p-value 0.0008). Results from the secondary endpoints of PFS by blinded independent review committee (BIRC), objective response rate (ORR) and duration of response (DoR) in the *ESR1m* population appeared to be supportive of the primary endpoint results. The PFS endpoint in the ITT population did not cross the prespecified significance alpha level and therefore was not statistically significant. The secondary OS endpoint in the *ESR1m* population was immature (31% maturity), and the interim analysis of OS at the time of final PFS analysis was not statistically significant. However, there was no evidence of detriment in the *ESR1m* population (HR 0.91, 95% CI: 0.56-1.47). OS could not be tested in the ITT population since PFS in the overall population failed to meet the prespecified threshold.

The FDA review team conducted an exploratory analysis of investigator-assessed PFS for the comparison of the imlunestrant arm and TPC arm in the *ESR1m*-not detected (*ESR1m*-nd) population and excluded 20 patients whose *ESR1* mutation status was failed or missing (n=385). The HR was 1.04 (95% CI: 0.82, 1.33). The observed median PFS was 5.6 (95% CI: 3.8, 7.3) months in the imlunestrant arm and 5.6 (95% CI: 5.5, 7.4) months in the TPC arm.

The Applicant removed ^{(b) (4)} before the trial started enrolling. ^{(b) (4)} patient demographics and baseline disease characteristics were generally well balanced between treatment arms in the *ESR1m* patient population. Additionally, prespecified sensitivity analysis using a multivariate Cox regression model adjusted for baseline covariates appeared to showed treatment benefit consistent with the primary analysis results.

While exploratory analyses by individual *ESR1* mutations may suggest some differential efficacy for imlunestrant, the subgroups were small and exploratory, and the evidence supports a consistent treatment benefit for patients with specific *ESR1* mutations.

Inluriyo (imlunestrant)

The majority of adverse reactions associated with imlunestrant in EMBER-3 were Grade 1-2 in severity, as would be anticipated with an endocrine therapy. However, notably GI toxicities were higher for imlunestrant compared to TPC, including diarrhea (22% vs. 12%), nausea (17% vs. 13%), constipation (10% vs. 6%), and abdominal pain (10% vs. 6%). Fatigue was also higher for imlunestrant compared to TPC (23% vs. 14%). The FDA review team also reviewed dyslipidemia as an adverse event of special interest, as this has been noted with another approved oral SERD. While the incidence was similar for increased triglycerides and increased cholesterol between the imlunestrant arm and the TPC arm, it was still notable to include these incidences in Section 6 of the US Prescribing information (USPI) for providers and patients to be aware to monitor for these during treatment.

Based on an overall favorable benefit:risk analysis, the review team recommends granting regular approval to imlunestrant in the *ESR1m* population. This indication was modified by FDA from the Applicant proposed indication to accurately reflect the patient population enrolled in the EMBER-3 trial. The indication for approval is:

Imlunestrant 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 with disease progression following at least one line of endocrine therapy.

A supplemental Pre-Market Approval (PMA) Application (sPMA P200010/S021) was submitted to CDRH for the Guardant360 CDx assay. The sPMA will receive contemporaneous approval with this NDA as a companion diagnostic device for imlunestrant.

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence.

Provide a description of the SEE that supported the regulatory action. If an application/submission is a CR due to lack of established SEE, below description is omitted.

Refer to Section 8.1 and 8.4.1 of this review for details.

Confirmatory evidence considered supportive for this NDA review included nonclinical pharmacology and toxicology studies, primary pharmacology data of binding affinity for *ESR1m*, PK/PD data for imlunestrant, and the first in human EMBER trial that evaluated initial dose finding for imlunestrant as a monotherapy.

1.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Breast cancer is the most common cancer in women worldwide. In the U.S., there are 316,950 new cases of breast cancer and 42,170 deaths from breast cancer estimated for 2025. Although rare (<1%), male patients can also develop breast cancer and may present at a higher stage than female patients.

Histopathological subtypes of breast cancer are defined by expression of the estrogen receptor (ER), progesterone receptor (PR), and/or human epidermal growth factor receptor 2 (HER2). Approximately 70% of patients with breast cancer will have ER-positive, HER2-negative disease. Although associated with a better prognosis than other breast cancer subtypes, if ER-positive, HER2-negative breast cancer is advanced and not surgically resectable, or metastatic, it is incurable and associated with a limited life expectancy.

The preferred first-line treatment for patients with ER-positive, HER2-negative advanced or metastatic breast cancer in the U.S. is a CDK4/6 inhibitor in combination with endocrine therapy (an AI or fulvestrant). At disease progression, FDA-approved options for second and later-line treatment options may include endocrine monotherapy with fulvestrant, an AI, or tamoxifen (if not received as first-line treatment); everolimus in combination with endocrine therapy; targeted therapy such as alpelisib in combination with fulvestrant in *PIK3CA*-mutated tumors, or capivasertib plus fulvestrant for *PIK3CA/AKT1/PTEN*-altered tumors, or PARP inhibitors for BRCA-mutated tumors; and chemotherapy such as capecitabine. Inavolisib with palbociclib and fulvestrant was approved in 2024 for adults with endocrine-resistant, *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.

Acquired resistance to endocrine therapy, particularly AIs, can occur due to activating missense mutations and in-frame deletions in

Inluriyo (imlunestrant)

the ligand-binding domain (LBD) of *ESR1*. It is estimated that approximately 10-50% of patients exposed to an AI for treatment of metastatic breast cancer will acquire tumor *ESR1* mutation(s). Elacestrant, an oral SERD, was approved in January 2023 for the treatment of postmenopausal women or adult men with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy. There remains an unmet need for additional therapies that may offer an additional option to improve clinical outcomes in all patients with ER-positive, HER2-negative advanced or metastatic breast cancer, including patients with *ESR1* mutations.

The efficacy and safety assessment for imlunestrant is primarily based on data from the EMBER-3 trial, a multicenter, active-controlled, open-label 3-arm trial in 874 patients (323 with *ESR1m* disease) randomized to imlunestrant monotherapy, a treatment of physician's choice (TPC) arm of endocrine therapy with either fulvestrant or exemestane, or a third arm with an additional investigational combination regimen, in patients with ER+, HER2- locally advanced or metastatic breast cancer previously treated with an AI, with or without a CDK4/6 inhibitor. The results from the combination arm are not part of this NDA review. Patients continued treatment until disease progression or unacceptable toxicity. The primary endpoints were investigator assessed PFS in the *ESR1m* population and the ITT population (*ESR1m* and *ESR1m*-not detected). The secondary endpoints were OS in the *ESR1m* and ITT populations. Approximately 67% of patients in the imlunestrant arm received prior CDK4/6 inhibitor in any setting vs. 72% of patients in the TPC arm in the *ESR1m* population.

EMBER-3 demonstrated a statistically significant and clinically meaningful improvement in PFS by investigator assessment in the *ESR1m* population. Median PFS was 5.5 months versus 3.8 months (HR 0.62, 95% CI: 0.46-0.82; p-value 0.0008). The PFS endpoint in the ITT population did not cross the prespecified significance alpha level and therefore was not statistically significant. The secondary OS endpoint in the *ESR1m* population was immature (31% maturity) and not statistically significant. However, there was no detriment in the *ESR1m* population (HR 0.55, 95% CI: 0.35-0.86). A postmarketing commitment (PMC) has been issued by the FDA and agreed to by the Applicant to obtain the next prespecified interim and final OS results for the *ESR1m* population. OS could not be tested in the ITT population since PFS in the overall population failed to meet the prespecified threshold.

Inluriyo (imlunestrant)

The safety profile of imlunestrant was generally reflective of an endocrine therapy, with mostly Grade 1-2 ARs. Fatal adverse reactions occurred in 1.8% of patients who received imlunestrant, including cardiac arrest, acute myocardial infarction, right ventricular failure, hypovolemic shock, and upper gastrointestinal hemorrhage (each 0.3%), plus an additional death thought to be unrelated (dengue fever). Fatal adverse reactions occurred in 0.9% of patients who received TPC, including cardiac arrest (0.6%) and abdominal infection (0.3%). Serious adverse reactions (SARs) occurred in 10% of patients who received imlunestrant and in 11% of patient who received TPC. SARs in > 1% of patients receiving imlunestrant included pleural effusion (1.2%) and in TPC included fracture (1.5%). The most common (incidence $\geq 10\%$) ARs, including laboratory abnormalities, were decreased hemoglobin, musculoskeletal pain, decreased calcium, decreased neutrophils, increased AST, fatigue, diarrhea, increased ALT, increased triglycerides, nausea, decreased platelets, constipation, increased cholesterol, and abdominal pain. Imlunestrant was associated with increased GI toxicity compared to TPC, including diarrhea (22% vs. 12%), nausea (17% vs. 13%), constipation (10% vs. 6%), and abdominal pain (10% vs. 6%). Dyslipidemia incidence was similar for increased triglycerides (21% vs. 22%) and increased cholesterol (10% vs. 12%) between the imlunestrant arm and the TPC arm, and given the trial was an active controlled trial, it was deemed reasonable to include these incidences in labeling for providers and patients to be aware of the need to monitor these during treatment with imlunestrant.

Male patients were eligible for enrollment on EMBER-3; however, none were enrolled in the *ESR/m* population. The FDA included male patients in the approved indication based on extrapolation from female patient data, supported by both biological rationale and regulatory precedent. The mechanism of action of imlunestrant, estrogen receptor antagonist, supports that it should work regardless of patient sex. The FDA's guidance on male breast cancer specifically supports this extrapolation approach, recognizing the practical impossibility of conducting adequately powered studies in this rare population while ensuring that male patients have access to effective treatments (FDA Guidance: Male Breast Cancer, 2020).

The FDA review team concluded that for patients in the *ESR/m* population, the benefit-risk assessment for imlunestrant was favorable given the statistically significant improvement in PFS, which was robust to multiple sensitivity analyses and supported by a positive OS HR trend (despite OS being immature). Although the magnitude of improvement in median PFS was small, it should be interpreted in the context of a replacement design and the fact that the HR result was robust. The toxicities were considered

acceptable given that clinical benefit was demonstrated.

At the time of the EMBER-3 trial design (early 2021), single-agent endocrine therapy represented an acceptable standard of care option for second line therapy. Elacestrant, another SERD, was approved in U.S. for ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer while this trial was enrolling; however, elacestrant was not available in most countries when the trial was enrolling. Subsequently, it has been noted in trials that fulvestrant monotherapy underperforms after progression on a CDK4/6i therapy. More than half of patients on this trial had prior CDK4/6i therapy. There is still an unmet medical need in this patient population despite the recent approvals and the FDA does not require comparative effectiveness studies against all available therapies for regular approval, and the chosen comparator was appropriate when the trial was initiated.

FDA also revised the Applicant proposed indication to reflect the patient population enrolled in EMBER-3 (i.e., disease progression following at least 1 line of endocrine therapy). Based on the overall benefit-risk assessment, the review team recommends regular approval for the following indication:

Imlunestrant 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 with disease progression following at least one line of endocrine therapy.

Patients should be selected for treatment using the Guardant360 CDx assay. The Guardant360 CDx assay is a qualitative next generation sequencing (NGS)-based in vitro diagnostic device which uses targeted high throughput hybridization-based capture technology for the detection of single nucleotide variants (SNVs) and insertions/deletions (indels) in 55 genes, copy number amplifications (CNAs) in 2 genes, and fusions in 4 genes. The sPMA P200010/S021 will receive contemporaneous approval with this NDA as a companion diagnostic device for imlunestrant. The specific *ESR1* mutations detected by Guardant360 CDx for the imlunestrant indication include: E380 mutations, V422 deletion, S463P/F, L469V, L536 mutations, Y537 mutations, and D538

Inluriyo (imlunestrant)

mutations.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Breast cancer is the most common cancer in women, with 316,950 new cases estimated and 42,170 deaths estimated from breast cancer in the U.S. in 2025. Although rare (<1%), breast cancer can also occur in males. - Approximately 70% of patients with breast cancer will have ER+HER2- disease. - Acquired <i>ESR1</i>-mutations are estimated to range anywhere from 10-50% in the advanced and metastatic setting after prior exposure to prior endocrine therapy, especially aromatase inhibitors. - Advanced or metastatic breast cancer is incurable.	ER-positive, HER2-negative (<i>ESR1</i>-mutated advanced or metastatic breast cancer is a serious and life-threatening condition.
Current Treatment Options	- Advanced or metastatic breast cancer remains incurable. Treatment is palliative, with the aims of reducing cancer-related symptoms, delaying disease progression, and prolonging survival. - Following treatment with a CDK4/6 inhibitor in combination with endocrine therapy, treatment options may include endocrine monotherapy with fulvestrant, an AI, or tamoxifen; everolimus in combination with endocrine therapy; targeted therapy such as alpelisib in combination with fulvestrant in	All treatment options are palliative. There is an unmet medical need to improve outcomes in patients with ER-positive, HER2-negative advanced or metastatic breast cancer with <i>ESR1</i>-mutated tumors.

Inluriyo (imlunestrant)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<i>PIK3CA</i>-mutated tumors, or capivasertib plus fulvestrant for <i>PIK3CA/AKT1/PTEN</i>-altered tumors, or PARP inhibitors for BRCA-mutated tumors; and chemotherapy such as capecitabine. • Elacestrant, on oral SERD, was approved January 2023 for treatment of postmenopausal women or adult men with ER-positive, HER2-negative, <i>ESR1</i>-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.	
<u>Benefit</u>	• The EMBER-3 trial enrolled 874 patients randomized to imlunestrant monotherapy, a treatment of physician's choice (TPC) arm of endocrine therapy of either fulvestrant or exemestane, or a third arm of an additional investigational combination regimen, in patients with ER+, HER2- locally advanced or metastatic breast cancer previously treated with an AI, with or without a CDK4/6 inhibitor. • There were 323 patients enrolled with <i>ESR1</i>m disease across all 3 arms, with 256 patients with <i>ESR1</i>m in total enrolled in the imlunestrant monotherapy arm and TPC arm. • In the <i>ESR1</i>m population, median PFS by investigator was 5.5 months versus 3.8 months (HR 0.62, 95% CI: 0.46-0.82; p-value 0.0008). • PFS by BICR results were supportive of the primary endpoint (HR 0.66, 95% CI: 0.47, 0.92).	For patients in the <i>ESR1</i>-mutated population, imlunestrant demonstrated a statistically significant and clinically meaningful improvement in PFS by investigator, which was supported by a favorable trend in OS and secondary endpoints such as PFS by BICR.

Inluriyo (imlunestrant)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	At the planned interim analysis for OS, the OS did not reach statistical significance (HR 0.55, 95% CI: 0.35-0.86).	
<u>Risk and Risk Management</u>	- Serious adverse reactions (SARs) occurred in 10% of patients who received imlunestrant and 11% in patients who received TPC. SARs in > 1% of patients receiving imlunestrant included pleural effusion (1.2%). - Fatal adverse reactions occurred in 1.8% of patients who received imlunestrant (cardiac arrest, acute myocardial infarction, right ventricular failure, hypovolemic shock, and upper gastrointestinal hemorrhage) and 0.9% of those receiving TPC (cardiac arrest and abdominal infection). - Imlunestrant was associated with increased GI toxicity compared to TPC, including diarrhea (22% vs. 12%), nausea (17% vs. 13%), constipation (10% vs. 6%), and abdominal pain (10% vs. 6%). - The most common (incidence $\geq 10\%$) adverse reactions, including laboratory abnormalities were hemoglobin decreased, musculoskeletal pain, calcium decreased, neutrophils decreased, AST increased, fatigue, diarrhea, ALT increased, triglycerides increased, nausea, platelets decreased, constipation, cholesterol increased, and abdominal pain.	Embryo-Fetal Toxicity was included under Warnings and Precautions. Safe use of imlunestrant in this population can be managed with labeling. There is no indication for a REMS.

Inluriyo (imlunestrant)

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:		Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as	Section 8.1.1, Section 8.2
		X Patient reported outcome (PRO)	
		☐ Observer reported outcome (ObsRO)	
		☐ Clinician reported outcome (ClinRO)	
		☐ Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify)	

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 218881

Inluriyo (imlunestrant)

☐	Patient experience data that was not submitted in the application, but was considered in this review.
--------------------------	---

X

Cross-Disciplinary Team Leader

Preeti Narayan, MD

2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:

It is estimated that 2.3 million new cases of breast cancer occurred worldwide in women in 2022 (Bray et al. 2024). Treatment options for patients with breast cancer are largely determined by ER and HER2 status (Waks and Winer 2019; Cardoso et al. 2024; NCCN 2024). ER-driven breast cancers remain the most frequent cancers among women and are a major cause of cancer-related deaths worldwide (Bray et al. 2024).

ER is expressed in more than two thirds of breast cancers, and advances in ET targeting the ER have reduced the risk of recurrence in EBC and prolonged survival in advanced or MBC, henceforth referred to as ABC. However, ER+ ABC is incurable with a median OS of 3 to 5 years (Hortobagyi et al. 2022; Meegdes et al. 2023; Cardoso et al. 2024), representing an unmet medical need to optimize ET options as monotherapy and in combination with targeted therapy.

The FDA's Assessment:

The FDA generally agrees with the Applicant's characterization of advanced and metastatic ER-positive (ER+), HER2-negative (HER2-) breast cancer. Advanced and metastatic ER+ breast cancer is incurable, and the goal of therapy is palliative.

2.2 Analysis of Current Treatment Options

The Applicant's Position:

Medicines that target ER, through inhibition of ligand (estrogen) synthesis, direct receptor antagonism, or receptor degradation, are the most crucial component of treatment (Patel et al. 2023; Jhaveri et al. 2024). For patients with ER+, HER2- ABC, standard of care (Cardoso et al. 2024; NCCN 2024) includes giving

- single-agent ET to inhibit ER signaling, such as
 - an AI (anastrozole, letrozole, exemestane)
 - a SERM (tamoxifen), or
 - a SERD (fulvestrant or elacestrant [for tumors harboring *ESR1* mutations]), or
- combinations of ET (with the exception of elacestrant) with
 - a CDK4/6i (abemaciclib, palbociclib, or ribociclib)
 - an mTOR inhibitor (everolimus)

Inluriyo (imlunestrant)

- a PI3K inhibitor (alpelisib, for tumors harboring *PIK3CA*-activating mutations)
- an AKT inhibitor (capivasertib, for tumors harboring *PIK3CA*- or *AKT1*-activating mutations or *PTEN* alterations), or
- a PARP inhibitor (olaparib or talazoparib, for tumors harboring germline *BRCA1* or *BRCA2* mutations).

Most patients receive an AI combined with a CDK4/6i or single-agent ET in the first-line setting. Subsequent treatment involves changing the ET backbone generally to IM SERD (fulvestrant) given alone or combined with targeted agents (alpelisib or capivasertib) based on presence of targetable tumor mutations or with everolimus in a biomarker-unselected population. However, per NCCN guidelines and current U.S. practice, some patients may receive ET monotherapy in the ABC setting (NCCN 2024).

Some patients may receive chemotherapy (Cardoso et al. 2024; NCCN 2024)

- as initial therapy based on (disease burden and clinical signs and symptoms suggesting visceral crisis) aggressiveness at initial presentation
- for endocrine refractory disease, involving the use of antibody-drug conjugates, or
- as salvage therapy following failure of ET-based interventions.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment of the current treatment landscape for advanced and metastatic ER+, HER2-, breast cancer. Endocrine therapy [an aromatase inhibitor (AI) or fulvestrant] in combination with a CDK4/6 inhibitor is the preferred first-line therapy with some combinations demonstrating an overall survival benefit versus placebo (Hortobaygi et al. 2022). CDK4/6 inhibitors are approved with fulvestrant following disease progression on endocrine therapy. Together this suggests that patients should receive a CDK4/6i with ET with or without a PI3K inhibitor in the first or second-line of therapy. The choice of therapy in later lines of ET depends on prior therapy and may include ET combinations (e.g., everolimus in combination with exemestane), and targeted therapy alone or in combinations (*ESR1* mutated, *PIK3CA* mutated, *AKT1* mutated, *PTEN* alteration, or *BRCA1* and *BRCA2* mutated), and endocrine monotherapy. The evidence for ET monotherapy is weaker but is indicated for a non-biomarker selected population.

Elacestrant was approved in the US on January 27, 2023, for patients with *ESR1* ABC based on the results of the EMERALD trial which had a control arm of fulvestrant or an aromatase inhibitor. The pivotal study for imlunestrant, EMBER-3, was still enrolling and therefore elacestrant would have been available therapy for patients in the US (Shah, et al. 2024). The ideal sequencing of therapies for patients eligible for multiple therapies is currently unknown.

While BRCA testing was not required for study eligibility, patients with a known or suspected deleterious BRCA mutation were excluded if they were enrolled in a region where PARP inhibitors were approved and available. Patients who were assessed to have visceral crisis or inflammatory breast cancer and therefore eligible for chemotherapy were similarly excluded.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant’s Position:

Imlunestrant is not currently registered or approved in the U.S. or in any other part of the world.

The FDA’s Assessment:

The FDA agrees with the Applicant’s assessment.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant’s Position:

Table 3.1 outlines the key U.S. regulatory actions and marketing history.

Table 3.1. Key U.S. Regulatory Interactions Related to the Development of Imlunestrant

Date	Details of Meeting or Submission
08 November 2019	Evaluation of imlunestrant was initiated with the opening of IND 145311, containing a first-in-human study, J2J-MC-JZLA, titled “EMBER: A Phase 1a/1b Study of LY3484356 Administered as Monotherapy and in Combination with Anticancer Therapies for Patients with ER+ Locally Advanced or Metastatic Breast Cancer and Other Select Non-Breast Cancers.” Study May Proceed letter for IND 145311 was received.
11 February 2021	Type B EOP1 meeting was held with FDA regarding the Phase 3 study “EMBER-3: 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.”
08 April 2021	A partial clinical hold was issued by the FDA with the following limitation for Study EMBER-3: “No more than 50 patients may be enrolled into your phase 3 clinical trial EMBER-3 until results of 3-month toxicity studies in a rodent and nonrodent species are available. You will need to submit, at a minimum, draft reports with signed histopathology reports.”
30 June 2021	Agreed iPSP was submitted to IND 145311 for metastatic breast cancer, requesting a waiver for pediatric requirements due to the mechanism of action and the condition not occurring in children. The FDA acknowledged the agreement on 26 July 2021.
11 October 2021	EMBER-3 Amendment (a) was submitted, adding a treatment arm to evaluate imlunestrant in combination with abemaciclib. Updated the title “EMBER-3: A Phase 3, Randomized, Open-Label Study of Imlunestrant, Investigator’s Choice of Endocrine Therapy, and Imlunestrant plus Abemaciclib in Patients with Estrogen Receptor-Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer Previously Treated with Endocrine Therapy.”

NDA/BLA Multi-disciplinary Review and Evaluation NDA 218881

Inluriyo (imlunestrant)

Date	Details of Meeting or Submission
09 November 2021	Fast track designation was granted for treatment of patients with ER+, HER2- locally advanced or metastatic breast cancer, previously treated with endocrine therapy.
16 November 2021	A complete response was submitted to the FDA to address the partial clinical hold for Study EMBER-3 issued on 08 April 2021, including the requested results from 3-month toxicity studies.
04 December 2021	Type C Written Responses Only was received regarding proposed environmental assessment studies to impact the environmental impact of imlunestrant. Aligned with FDA regarding proposed data package to support an environmental assessment, including for the preliminary screening studies and the definitive fish full life cycle study.
14 December 2021	Partial Clinical Hold for Study EMBER-3 was removed, along with the limitations imposed on enrollment.
16 June 2022	Type C Written Responses Only was received regarding the EMBER-3 SAP and its ability to evaluate (b) (4) potential indications supported by data from Study EMBER-3, namely imlunestrant (b) (4)
26 April 2023	Type B EOP CMC Only meeting was held to discuss drug product development proposals for planned NDA submissions. Lilly and the FDA aligned on matters related to starting material, drug substance manufacturing facility, and drug product primary stability.
27 June 2023	Type C Written Responses Only, pre-NDA administrative feedback was provided on the content and format of the proposed 2024 NDA.
23 September 2024	Type B pre-NDA meeting was held to review the results of EMBER-3 and attain agreement on the data package to support the filing of an NDA, including the content and format of the NDA

Abbreviations: CMC = chemistry, manufacturing, and controls; EOP = end-of-phase; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IND = investigational new drug (application); iPSP = initial pediatric study plan; NDA = new drug application; SAP = statistical analysis plan.

The FDA's Assessment:

The FDA generally agrees with the Applicant's review of key regulatory interactions with the following clarifications.

The Applicant originally proposed including (b) (4) in their pre-IND meeting package submitted December 23, 2020, to FDA. After receiving FDA preliminary responses, which included standard comments regarding the possible need for a companion diagnostic (CDx), the Applicant conveyed (b) (4)

At the Type B, EOP1 teleconference held on February 11, 2021, the FDA reiterated that the need for a CDx would depend on the results of the trial and encouraged the Applicant to make provisions if this were needed. (b) (4) FDA recommended prespecifying *ESR1* missense mutations that were considered activating, consideration in the trial design that not all *ESR1*m may be clinically equivalent, that multiple co-occurring *ESR1*m may influence

Inluriyo (imlunestrant)

efficacy, and that the effect of alternative splicing of *ESR1* should be considered. Despite this advice, ^{(b) (4)} when the protocol was submitted. The Applicant ultimately submitted a proposed indication for an *ESR1m* population when the NDA was submitted in October 2024.

On December 20, 2024, the FDA recommended against adding an interim analysis of OS after data unblinding as it would be considered exploratory only and may be data driven. The Applicant chose to add this interim OS analysis despite FDA's comments. See details in Section 8.1.1.

Regulatory feedback regarding Arm C was not reviewed as it is beyond the scope of the proposed indication for this NDA review.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

For clinical inspections, 3 clinical sites were selected in conjunction with OSI for FDA inspection based on being high enrolling sites for the EMBER-3 trial. In addition, the Applicant (Eli Lilly and Company), was also selected for inspection. The full report was completed by Dr. Leigh Marcus from FDA OSI and is summarized below. Overall, the inspection findings were acceptable and did not alter the conclusions from the NDA review.

1. Dr. Monica Lis Casalnuovo (Site #33334)

Buenos Aires, Argentina

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

This was the first FDA inspection for this clinical investigator. At this site, 15 patients were screened and 9 were enrolled to the trial (5 with tumors that were *ESR1-mut*). During the inspection, the primary efficacy endpoint data were verifiable. There was no underreporting of adverse events (AEs) or serious AEs (SAEs). It was noted that Informed consent Documents (ICDs) did not contain the required statement related to ClinicalTrials.gov in any of their versions of the main ICD document. 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.

Clinical Reviewer: The findings from this site did not alter the benefit: risk of this application.

2. Dr. Jose Angel Garcia Saenz (Site #74489)

Madrid, Spain

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

This was the first FDA inspection for this clinical investigator. At this site, 15 patients were screened and 12 were enrolled to the trial (4 with tumors that were *ESR1-mut*). 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

Inluriyo (imlunestrant)

interstitial lung disease]). The site 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.

Clinical Reviewer: The findings from this site did not alter the benefit: risk of this application. Late reported AEs were still captured and reviewed in the NDA with appropriate labeling.

3. Dr. Komal Jhaveri, (Site #99301)

New Jersey, United States

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

This investigator has been inspected previously for a different application in July 2024. Prior FDA inspection in 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 patient. For the current inspection, 21 patients were screened and 19 were enrolled to the trial (5 with tumors that were *ESR1-mut*). The primary efficacy endpoint data were verifiable. There was underreporting of one AE in 1 patient (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 patient (Subject # (b) (6)), and the site did not properly calculate the proper window of dates to obtain scans which resulted 2 patients having multiple “out of window (OOW)” +/- 3-day scans, 1 of whom with the *ESR1-mutation* (Subject # (b) (6)) in the indicated population. The underreported AE in Subject # (b) (6) was added into electronic data capture (EDC) by the 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 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.

Clinical Reviewer: The issues found regarding underreporting of an AE in one patient and use of outdated informed consent document did not alter the FDA review teams conclusion of the benefit: risk for this NDA review.

4. Eli Lilly and Company (Applicant)

Lilly Corporate Center
Indianapolis, Indiana United States

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

Inluriyo (imlunestrant)

This inspection covered the Sponsor's study conduct related to the EMBER-3 trial. The previous FDA inspection of this Applicant in September 2022 had no significant regulatory violations. The Applicant 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 by the Applicant due to prior noncompliance on a different trial not related to this NDA application.

No data discrepancies were identified for imaging reports. The primary efficacy endpoint of PFS was verified from the data listings provided. OSI concluded that the Applicant's oversight and monitoring for the EMBER-3 trial appears to have been conducted adequately.

Clinical Reviewer: Concur with FDA OSI findings that the Applicant monitoring for the EMBER-3 trial was adequate and did not alter the conclusions for this NDA review.

4.2 Product Quality

The FDA Product Quality Team recommended approval for imlunestrant. The review team assessed the drug substance, drug product, quality labeling, manufacturing, and biopharmaceutics for imlunestrant and concluded that the Applicant provided sufficient information to assure the identity, strength, purity, and quality of the proposed product. The review team also concluded that all associated manufacturing, testing, and packaging facilities were acceptable based on prior inspection history. The review team determined that approval of this application is not expected to have significant effects on the quality of the human environment and issued a finding of no significant impact (FONSI). There were no product quality PMRs or PMCs issued. For further detail see the Product Quality review.

4.3 Clinical Microbiology

Not applicable.

4.4 Devices and Companion Diagnostic Issues

CDRH received a supplemental PMA Application (sPMA P200010/S021) from Guardant Health, Inc. for the Guardant360 CDx assay. CDRH considers this sPMA approvable as a companion diagnostic device to aid in detecting specific *ESR1* mutations in patients with breast cancer for treatment with INLURIYO (imlunestrant).

Inluriyo (imlunestrant)

The Guardant360 CDx assay is a qualitative next generation sequencing (NGS)-based in vitro diagnostic device which uses targeted high throughput hybridization-based capture technology for the detection of single nucleotide variants (SNVs) and insertions/deletions (indels) in 55 genes, copy number amplifications (CNAs) in 2 genes, and fusions in 4 genes. The assay uses circulating cell-free DNA (cfDNA) from plasma of peripheral whole blood collected in Streck Cell-Free DNA Blood Collection Tubes (BCTs). This assay is already approved as a companion diagnostic for 5 other drugs:

- TAGRISSO (osimertinib) for NSCLC patients with EGFR exon 19 deletions, L858R, and T790M mutations
- RYBREVANT (amivantamab-vmjw) for NSCLC patients with EGFR exon 20 insertions
- ENHERTU (fam-trastuzumab deruxtecan-nxki) for NSCLC patients with *ERBB2*/HER2 activating mutations
- LUMAKRAS (sotorasib) for NSCLC patients with KRAS G12C mutations
- ORSERDU (elacestrant) for breast cancer patients with *ESR1* missense mutations between codons 310 and 547

The clinical validity of the Guardant360 CDx assay as a companion diagnostic device for INLURIYO (imlunestrant) is supported by a prospective analysis of plasma samples and clinical outcome data from the EMBER-3 clinical study (NCT04975308). Pre-treatment plasma samples from 630 of the primary EMBER-3 registration population subjects were tested with Guardant360 CDx. Of these, 254 patients (40.3%) had one or more *ESR1* mutation(s) detected. The specific *ESR1* mutations detected by Guardant360 CDx for the imlunestrant indication include: E380 mutations, V422 deletion, S463P/F, L469V, L536 mutations, Y537 mutations, and D538 mutations. The analytical performance of Guardant360 CDx for the detection of specific *ESR1* mutation(s) were assessed and deemed acceptable.

The CDRH review team concluded that both analytical and clinical validation data submitted supported the reasonable assurance of safety and effectiveness of Guardant360 CDx assay as a companion diagnostic device to aid in the selection of patients with breast cancer with detectable *ESR1* mutations in plasma for treatment with INLURIYO (imlunestrant). For details, refer to the Summary of Safety and Effectiveness Data (SSED) for the Guardant360 CDx device.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

Implunestrant (Inluriyo) is an estrogen receptor (ER) antagonist indicated for the treatment of adult patients with ER-positive, human epidermal growth factor receptor 2 (HER2)-negative, *ESR1*-mutated advanced or metastatic breast cancer, with disease progression following at least one line of endocrine therapy. The recommended dose of Inluriyo is 400 mg orally once daily. The nonclinical development program for implunestrant consisted of studies in mice, rats, and monkeys to evaluate the pharmacology (primary, secondary, safety), metabolism, general toxicity, embryo-fetal development, and genotoxicity. During the nonclinical development, implunestrant was referred to as LY3484356 tosylate, LSN3484356, and LSN3513322.

Estrogen receptors (ERs) consist of nuclear ERs, extra-nuclear ERs, and G protein-coupled ERs. Estrogen receptor-alpha (ER α) and estrogen receptor-beta (ER β) are located in the nucleus and are encoded by the *ESR1* and *ESR2* genes, respectively. ER α is expressed in breast, prostate, uterus, liver, and bone tissues. Mutations in the *ESR1* gene, such as Y537S/N and D538G, contribute to ER⁺HER2⁻ breast cancer resistance to endocrine therapy.

In primary pharmacology studies, implunestrant bound to wild-type ER α , mutant (Y537S) ER α , and wild-type ER β with Ki values of 0.6 nM, 2.8 nM, and 0.1 nM, respectively. Implunestrant induced degradation of ER α in breast cancer cell lines with wild-type and *ESR1*-mutated (Y537S/N) ER α and led to inhibition of ER-dependent gene transcription. In vitro, implunestrant inhibited the proliferation of both ER α wild-type and *ESR1*-mutated (Y537S/N) breast cancer cell lines (IC_{50s} 1.67 to 7 nM). In vivo, daily oral administration of implunestrant (3 to 30 mg/kg, 28 days) to mice bearing ER α wild-type and *ESR1*-mutated (Y537S) breast cancer xenografts led to $\leq 83\%$ tumor growth inhibition (TGI) compared to control.

In secondary pharmacology studies, the binding affinity of implunestrant to ER was at least 300-fold higher than other nuclear hormone receptors such as human glucocorticoid receptor, androgen receptor, mineralocorticoid receptor, or progesterone receptor (PR) suggesting unlikely off-target activity at clinical concentrations. The Applicant conducted a non-GLP study in immature female rats to evaluate the potential agonistic effects of implunestrant on ER α . Oral administration of implunestrant at doses up to 200 mg/kg for 4 days did not result in remarkable changes to uterine weight or the histopathology of uterus, cervix, and vagina when compared to control. On the other hand, positive controls estradiol and tamoxifen led to severely increased uterine weights and histopathology findings in female reproductive organs. The data suggests that implunestrant does not have agonistic effects on ER α .

Implunestrant had no remarkable effects on the central nervous and respiratory systems when administered orally once daily to rats up to 150 mg/kg/day for up to 6 months or on the

Inluriyo (implunestrant)

cardiovascular, central nervous, and respiratory systems when administered orally once daily to cynomolgus monkeys up to 600 mg/kg/day for up to 3 months.

In vitro, implunestrant demonstrated high plasma protein binding ($\geq 99\%$) in rat, dog, mouse, monkey, and human plasma. There were no unique human metabolites identified. In repeat dose toxicology studies, exposures ($C_{\max}$ and AUC_{0-24}) generally increased with increasing dose in a less than dose proportional manner in rats and approximately dose proportionally in monkeys. Animal to human exposure margins were calculated using the mean steady state clinical $C_{\max}$ (141 ng/mL) and AUC_{0-24} (2400 ng*h/mL) at the recommended dose.

Repeat-dose toxicity studies were conducted with implunestrant in rats (≤ 150 mg/kg/day) up to 6-months duration and monkeys (≤ 600 mg/kg/day) up to 3-months duration. Recovery groups were only included in the chronic rat study to assess the reversibility of effects following long-term implunestrant administration. Of note, a 6-month repeat-dose toxicity study is not warranted to support an NDA submission for an advanced cancer indication. In the 6-month repeat-dose toxicity study in rats, mortality occurred at 150 mg/kg/day in 2 females due to urinary obstruction with correlated histopathology findings in the urinary bladder that was likely implunestrant-related. In addition, early drug-induced mortalities occurred during the 1-month study in male rats at 300 mg/kg/day due to hepatocellular and/or muscular damage with accompanied increase in transaminase and creatine kinase levels. There were no early mortalities in the monkey studies. The major target organs of toxicity in the general rat and monkey toxicology studies were male and female reproductive organs, hematopoietic/lymphatic system, kidney, urinary bladder, and eye and were generally consistent across the short and long-term studies.

Hematologic changes were generally more pronounced in rats than monkeys and included increases in red and white blood cell parameters with microscopic correlates of increased hematopoietic cells in the bone marrow (rat) and macrophage vacuolation in various tissues including gastrointestinal organs. Increased liver enzymes were noted without adverse microscopic correlates in the liver. In rats, kidney tubular degeneration, transitional cell hyperplasia in the urinary bladder, granulosa cell hyperplasia in the ovary, and hyperplasia in the mammary gland were observed at all tested dose levels (≥ 4 times the human AUC at the recommended dose). Findings of hyperplasia were included in Section 13.2 of the label. Additionally, in the 6-month rat study, an increased trend in lens degeneration and corneal opacity was noted at 150 mg/kg/day; however, these findings with similar intensity but lower frequency were noted in the control group and were not observed at higher doses in shorter term studies. Adverse ocular effects were also not observed in patients. Toxicology findings were either fully or partially reversible where recovery groups were assessed.

A dedicated fertility study was not conducted with implunestrant in accordance with ICH S9 guidance and the intended advanced cancer indication. The Applicant assessed the effects of

Inluriyi (implunestrant)

implunestrant on reproductive organs in rats and monkeys as part of the GLP-compliant repeat dose toxicology studies. Daily oral administration of implunestrant resulted in follicular cysts in the ovary and atrophy in the vagina, cervix, and uterus at doses ≥ 10 mg/kg/day in female rats (≥ 4 times the human AUC at the recommended dose) and ≥ 15 mg/kg/day in female cynomolgus monkeys (≥ 1 times the human AUC at the recommended dose). Decreased sperm and cellular debris in the epididymis and spermatid retention in the testis were observed in male rats at ≥ 10 mg/kg/day. The effects of implunestrant on male and female reproductive organs were reversible in rats following a 3-month recovery period. Reversibility was not assessed in cynomolgus monkeys.

The Applicant conducted several GLP-compliant phototoxicity studies in BALB/c 3T3 mouse fibroblasts, and implunestrant was considered phototoxic. An additional study was conducted to determine the potential phototoxic effects of implunestrant on the eyes and skin of Long-Evans pigmented female rats, when administered implunestrant orally at doses up to 1000 mg/kg for 4 days. The results showed no ocular findings indicative of phototoxicity, but implunestrant caused grade 1 erythema of skin (up to 4/5 rats) following administration at 1000 mg/kg with UV light exposure (47 times human AUC at the recommended dose). There were no clinical adverse events reported suggestive of phototoxicity.

Implunestrant was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay. Implunestrant produced chromosomal damage (increase in the percent micronuclei) in the in vitro micronucleus assay in lymphoblastoid TK6 cells, but it did not cause chromosomal damage in the rat bone marrow micronucleus test or DNA strand breaks in the rat liver and duodenum comet assays in vivo when administered up to 2000 mg/kg. Thus, overall implunestrant is not considered genotoxic. Carcinogenicity studies were not conducted with implunestrant in accordance with ICH S9 guidance.

In the embryo-fetal developmental (EFD) study, daily oral administration of implunestrant (0.3, 3, 30 mg/kg) to pregnant rats during the period of organogenesis from gestation days 6 to 17 resulted in embryo-fetal mortality at ≥ 0.3 mg/kg and structural abnormalities at ≥ 3 mg/kg at maternal exposures that were below the human AUC₀₋₂₄ at the recommended dose.

The label advises females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of implunestrant based on the recommendations in the FDA guidance, "Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations". The guidance recommends a contraception period of 5 half-lives (implunestrant half-life = 30.1 hours after repeated dosing) after the last dose for nongenotoxic small molecules that cause teratogenicity or embryo-fetal lethality. Additionally, the label advises lactating women not to breastfeed during treatment and for 1 week (5 half-lives) after the last dose due to the potential for severe adverse reactions in a breastfed child.

Inluriyo (imlunestrant)

Recommendation:

The nonclinical data submitted to this NDA are adequate to support approval of Inluriyo for the proposed indication. The nonclinical recommendation is approval.

5.2 Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no other referenced NDAs, BLAs, or DMFs applicable to the nonclinical pharmacology or toxicology of imlunestrant.

To maintain consistency with the submitted modules and reports, doses of nonclinical pharmacology/toxicology studies are expressed as imlunestrant-free base.

5.3 Pharmacology

Primary pharmacology

Imlunestrant is a next-generation orally bioavailable, noncovalent, SERD and antagonist. Imlunestrant binds with high affinity to wild-type and mutant (Y537S) ER α and wild-type ER β ligand-binding domains with K_i values of 0.64 nM, 2.8 nM, and 0.11 nM, respectively.

Imlunestrant is a potent degrader of ER α wild-type and mutant (Y537N/S) proteins in ER+ breast cancer cell lines, with an IC₅₀ value of 3 nM in MCF7 *ESR1* wild-type cells. In MCF7 *ESR1* wild-type and Y537N mutant cells, imlunestrant potently inhibited ER-mediated PGR gene transcription (IC₅₀ 41 nM and 13 nM, respectively). Imlunestrant is a pure antagonist and has not shown agonist activity in MCF7 cells as measured by the absence of PGR expression induction. Imlunestrant potently inhibits cell proliferation in MCF7 and T47D *ESR1* wild-type and Y537N mutant breast cancer cell lines as well as an *ESR1*-Y537S mutant PDX-derived cell line. In a panel of breast cancer cell lines, 11 out of 12 ER+ breast cancer cell lines were sensitive to imlunestrant (IC₅₀ <100 nM), while all ER- cell lines tested were insensitive (IC₅₀ >2 μ M). In vitro combination of imlunestrant with abemaciclib displayed synergistic anti-proliferative activity in ER+ breast cancer cell lines.

Imlunestrant demonstrated dose- and time-dependent sustained in vivo target inhibition (>75% PGR gene expression inhibition up to 96 hours) in *ESR1* wild-type (MCF7) and *ESR1*-Y537S mutant (ST941/C) xenograft tumors in mice. Imlunestrant was well tolerated and induced significant tumor growth inhibition and tumor regressions in multiple ER+ breast cancer xenograft models, including an *ESR1*-Y537S mutant PDX model. Combination of imlunestrant with abemaciclib was well tolerated and exhibited enhanced antitumor activity in a T47D breast cancer xenograft model. In clinically relevant ER+ breast cancer PDX models, including models with *ESR1* mutations and palbociclib resistance, imlunestrant exhibited single-agent efficacy and

Inluriyo (imlunestrant)

enhanced combination activity with abemaciclib. Additionally, imlunestrant crosses the blood-brain barrier in mice and showed antitumor activity and improved OS in an intracranial ER⁺ breast cancer model. Consistent with its profile as a pure antagonist, imlunestrant displayed no uterotrophic effects or adverse microscopic findings in the uterus, cervix, or vagina of immature female rats.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's position. The data in combination with the CDK4/6 inhibitor were not reviewed for this NDA application since the proposed indication is for imlunestrant monotherapy.

The established pharmacologic class (EPC) for imlunestrant is estrogen receptor antagonist. In vitro, imlunestrant induced degradation of ER α , leading to inhibition of ER-dependent gene (i.e., PGR, PDZK1, AREG, RASGRP1, WISP2, and GREB1) transcription and cellular proliferation in ER⁺ breast cancer cells.

The Applicant states that imlunestrant showed anti-tumor activity in ER⁺ breast cancer PDX models including those that were resistant to palbociclib (b) (4)

, the Applicant did not provide direct evidence from in vitro or in vivo studies demonstrating anti-tumor activity following imlunestrant treatment in either palbociclib or other CDK4/6 inhibitor (abemaciclib) resistant models.

In an orthotopic brain model, daily oral administration of imlunestrant (≥ 10 mg/kg, 28 days) to mice implanted with luciferase expressing breast cancer cells (MCF7-fLuc) led to reduced tumor growth and increased animal life span compared to control. Exposure to imlunestrant was observed in the brain following oral administration to mice bearing ER α wild-type flank breast cancer xenografts. Although the nonclinical data suggests the ability of imlunestrant to penetrate the brain resulting in anti-tumor activity, there is insufficient clinical data to support anti-tumor activity on brain metastases from primary breast tumors.

A summary of the uterotrophic effects of imlunestrant are included in the Secondary Pharmacology section of the review.

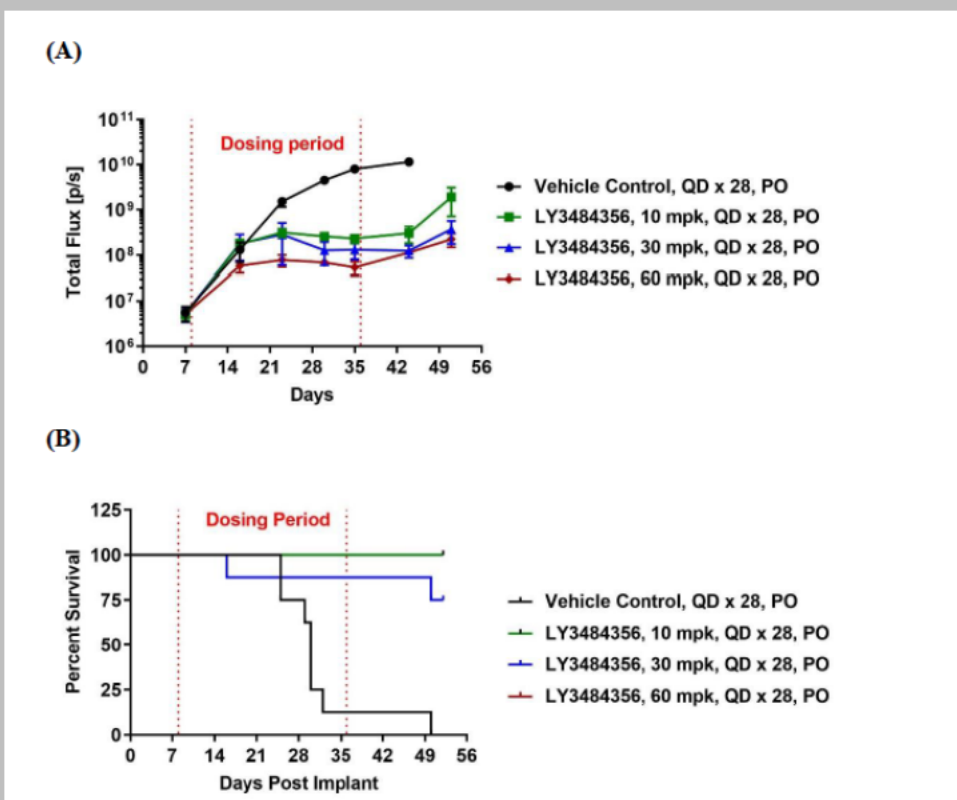
Additional data (presented by the FDA in **Figure 5.1**)

#ONCO167: The in vivo anti-tumor activity of imlunestrant was examined using MCF7-fLuc breast cancer cells implanted orthotopically in mouse brain. Luciferase labelled MCF7 (ESR1 wild type) ER⁺ breast cancer cells were implanted in the brain and tumor growth was followed using live imaging. Daily administration of 10 to 60 mg/kg imlunestrant orally once daily for 28 days increased animal life span compared to the control group (> 75% VS. 0% on Day 49). Additionally, imaging data showed that imlunestrant inhibited tumor cell growth in the brain

Inluriyo (imlunestrant)

(decreased tumor cell luciferase luminescence) suggesting imlunestrant penetrated the brain. Of note, based on current available clinical data there is insufficient clinical evidence of imlunestrant induced anti-tumor activity on brain metastases of patients with *ESR1*-mutated breast cancer.

Figure 5.1 Anti-tumor activity of imlunestrant in MCF-fluc brain orthotopic model.



(Excerpted from the Applicant's submission.)

Secondary pharmacology

The Applicant's Position:

Imlunestrant demonstrated high selectivity as an ER α antagonist with >1734-fold selectivity over other nuclear hormone receptors such as androgen receptor, glucocorticoid receptor, mineralocorticoid receptor, and PGR. Imlunestrant was highly selective against 33 kinases and 8 human G-protein coupled receptors relevant for human safety when tested in enzymatic assays in vitro. Imlunestrant displayed no uterotrophic effects or adverse microscopic findings in the uterus, cervix, or vagina of immature female rats, indicating no agonist activity in these tissues.

Inluriyo (implunestrant)

The FDA's Assessment:

The FDA agrees with the Applicant's position. Additional details from the uterine study are summarized below.

Data (presented by the FDA):

#8393708: This non-GLP study assessed the potential agonistic effects of implunestrant on ER α through effects on the uterus, cervix, and vagina. Immature female rats (19-21 days old) were administered either vehicle or 10, 30, 75, or 200 mg/kg implunestrant orally once daily for 4 days (n = 5 females/group). Positive controls were estradiol (0.01 mg/kg) and tamoxifen (10 mg/kg) administered orally once daily for 4 days. The toxicity parameters included organ weight and histopathology changes in uterus (endometrium, endometrial glands, and stroma), cervix (epithelium), and vagina (epithelium). When compared to the control group, there were no remarkable changes to the histopathology findings in uterus, cervix, and vagina of rats treated with implunestrant at doses up to 200 mg/kg. Findings were limited to a decrease in uterus weight relative to body weight when implunestrant was administered at 30 mg/kg (11%) and 75 mg/kg (32%) without remarkable change at 200 mg/kg compared to control. Both positive controls caused minimal to marked microscopic changes in endometrium (karyomegaly, hypertrophy, hyperplasia, increased mitotic figure), endometrial gland (severe hypertrophy), stroma (minimal to severe eosinophils infiltrates), and myometrium of uterus (severe hypertrophy), and showed histopathology changes in cervix (slight to moderate keratinization and hyperplasia epithelium) and vagina (minimal to severe keratinization and hyperplasia epithelium). A statistically significant increase in uterus weight was observed in rats administered estradiol (452%) and tamoxifen (247%) compared to control. Overall, the results indicate that implunestrant does not exhibit agonistic activity on ER α , while the positive controls demonstrated the expected agonistic effects.

Safety pharmacology

Implunestrant had no effect on the cardiovascular, central nervous, and respiratory systems of monkeys in 4-week or 3-month toxicology repeat-dose toxicology studies. Additionally, implunestrant did not demonstrate inhibitory activity, defined as 50% inhibition or greater, in a human ether-à-go-go-related gene (hERG) cardiac potassium channel assay. Safety pharmacology assessments were performed in compliance with good laboratory practice regulations and according to ICH S7 and ICH S9 guidelines.

The FDA's Assessment:

The FDA agrees with the Applicant's position. Additionally, implunestrant had no remarkable effects on the central nervous and respiratory systems of rats in the repeat dose toxicology studies based on clinical observations.

Data (presented by the FDA):

Inluriyo (imlunestrant)

190112.FMF: The in vitro data showed that imlunestrant inhibited hERG current by 4% at 0.3 μ M and 28% at 1 μ M versus 3% in the control group. No data was obtained at the 3 μ M tested concentration due to disruption of the giga-ohm seal required for successful patch clamp recordings. Therefore, the IC₅₀ for inhibitory effect of imlunestrant on hERG potassium current was not calculated.

5.4 Absorption, Distribution, Metabolism, Excretion/Pharmacokinetics

The Applicant's Position:

In single-dose PK and oral bioavailability studies in CD-1 mice and cynomolgus monkeys, imlunestrant oral bioavailability ranged from approximately 8% to 44%. In all species after single and multiple dose, imlunestrant was slowly absorbed. Following repeated dosing of imlunestrant in rats and in monkeys, systemic exposure (C_{max} and AUC) generally increased with increasing dose, but the increase was not consistently dose proportional. In both species, generally no accumulation and no sex difference in exposure were observed.

Across mouse, rat, dog, and monkey, imlunestrant is highly bound (greater than 99.8%) to plasma proteins. In mice, imlunestrant was found to cross the blood-brain barrier. Imlunestrant was widely distributed across tissues in rats.

The metabolism of imlunestrant was primarily mediated by direct phenol glucuronidation and sulfation of the parent, with minor contribution from oxidation. The major human metabolite (M1, direct glucuronide conjugate) is present in rat and monkey, with appropriate steady-state coverage.

The route of excretion of [¹⁴C]-imlunestrant-derived radioactivity was determined in rats and indicated that the major route of elimination was in feces (greater than 50% of administered dose).

The FDA's Assessment:

The FDA generally agrees with Applicant's position. See the clinical pharmacology Section 6 for information regarding human data and drug interaction studies.

Data (presented by the FDA):

Type of Study	Major Findings
Distribution	
Tissue distribution of imlunestrant following a single IV administration of 1 mg/kg or 2 mg/kg in CD-1 male mice (Study no. MTVE18_8396397)	Terminal blood samples and tissues (brain, liver, and spleen) were collected at 0.5 and 2 hours. Concentrations of imlunestrant in plasma and tissues were measured by LC-MS/MS. Unbound tissue partition (K _p , uu) values were determined in mice. Mean unbound brain to unbound plasma ratio (K _p , uu-brain) was approximately 0.1 and 0.2 at 0.5 and 2 hours, respectively, suggesting that imlunestrant crossed the blood-brain barrier.

Inluriyo (imlunestrant)

		Time (hours)	Matrix	LY3484356 concentrations (Mean ± SD)	Mean Kp, _m (Mean ± SD)
		0.5	Plasma (ng/mL)	161 ± 46.2	
			Brain (ng/g)	213 ± 27.2	
			Liver (ng/g)	5300 ± 188	
			Spleen (ng/g)	2200 ± 248	
			Brain: Plasma		0.117 ± 0.035
			Liver: Plasma		2.967 ± 1.1044
			Spleen: Plasma		1.28 ± 0.5393
		2	Plasma (ng/mL)	102 ± 12.8	
			Brain (ng/g)	249 ± 46.9	
			Liver (ng/g)	4000 ± 271	
			Spleen (ng/g)	2100 ± 240	
			Brain: Plasma		0.209 ± 0.068
			Liver: Plasma		3.333 ± 0.679
Spleen: Plasma			1.749 ± 0.3925		
TK data from general toxicology studies					
Toxicokinetic data from a GLP-compliant 6 month repeat-dose toxicity study in Sprague Dawley rats with a 3-month recovery period (n = 9/sex/group) (Study no. 8003353)		-No sex differences in systemic exposure to imlunestrant were observed. -Systemic exposure to imlunestrant increased with increasing dose across dose levels on Days 1 and 182. -Overall, the increase in AUC₀₋₂₄ was approximately less than dose proportional from 10 to 150 mg/kg. On Day 182, AUC₍₀₋₁₄₄₎ also increased in a less than dose proportional manner from 10 to 150 mg/kg. -Slight accumulation (~2-fold) was observed following repeated oral exposure of imlunestrant once daily for 182 days.			

	Males				Females			
	Dose level (mg/kg)							
Parameters	10	30	60	150	10	30	60	150
Day 1								
AUC _{0-24hr} (hr*ng/mL)	4010	9420	23900	38200	3900	10700	19600	32200
C _{max} (ng/mL)	342	611	2310	1850	267	701	1140	1920
T _{max} (hr)	4	2	4	8	8	8	8	8
Day 182								
AUC _{0-24hr} (hr*ng/mL)	9970	21000	45300	85500	9160	26900	39600	59400
AUC _{0-144hr} (hr*ng/mL)	13900	31700	70800	161000	12500	40300	60900	118000
C _{max} (ng/mL)	577	1230	2410	5230	634	1630	2440	3400
T _{max} (hr)	4	8	4	4	4	8	4	8

Inluriyo (imlunestrant)

Toxicokinetic data from a GLP-compliant 3 month repeat-dose toxicity study in cynomolgus monkeys (n=4/sex/group) (Study no. 8003147)	-Systemic exposure (C_{max} and AUC₀₋₂₄) increased with increasing dose for both males and females, but it was less than dose proportional between 15 and 100 mg/kg and approximately dose proportional between 100 and 600 mg/kg. -No remarkable sex difference in exposure was observed on Days 1 and 105. -Following repeated dosing, exposure generally increased on Day 105 relative to Day 1, with accumulation ratios ranging from 1.20 to 2.88 for 15 mg/kg, 1.01 to 3.28 for 100 mg/kg, and from 0.776 to 10.3 for 600 mg/kg.																																																																																		
<table><tr><td></td><td colspan="3">Males</td><td colspan="3">Females</td></tr><tr><td></td><td colspan="6">Dose level (mg/kg)</td></tr><tr><td>Parameters</td><td>15</td><td>100</td><td>600</td><td>15</td><td>100</td><td>600</td></tr><tr><td>Day 1</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>AUC_{0-24hr} (hr*ng/mL)</td><td>938</td><td>3590</td><td>10700</td><td>1210</td><td>3240</td><td>14900</td></tr><tr><td>C_{max} (ng/mL)</td><td>61.1</td><td>194</td><td>623</td><td>75.8</td><td>187</td><td>896</td></tr><tr><td>T_{max} (hr)</td><td>3.50</td><td>8.50</td><td>7.00</td><td>4.00</td><td>3.00</td><td>15.00</td></tr><tr><td>Day 105</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>AUC_{0-24hr} (hr*ng/mL)</td><td>1540</td><td>6950</td><td>28600</td><td>2060</td><td>6750</td><td>23000</td></tr><tr><td>C_{max} (ng/mL)</td><td>105</td><td>399</td><td>1660</td><td>130</td><td>381</td><td>1130</td></tr><tr><td>T_{max} (hr)</td><td>3.00</td><td>5.33</td><td>7.50</td><td>2.50</td><td>5.00</td><td>5.50</td></tr></table>								Males			Females				Dose level (mg/kg)						Parameters	15	100	600	15	100	600	Day 1							AUC _{0-24hr} (hr*ng/mL)	938	3590	10700	1210	3240	14900	C _{max} (ng/mL)	61.1	194	623	75.8	187	896	T _{max} (hr)	3.50	8.50	7.00	4.00	3.00	15.00	Day 105							AUC _{0-24hr} (hr*ng/mL)	1540	6950	28600	2060	6750	23000	C _{max} (ng/mL)	105	399	1660	130	381	1130	T _{max} (hr)	3.00	5.33	7.50	2.50	5.00	5.50
	Males			Females																																																																															
	Dose level (mg/kg)																																																																																		
Parameters	15	100	600	15	100	600																																																																													
Day 1																																																																																			
AUC _{0-24hr} (hr*ng/mL)	938	3590	10700	1210	3240	14900																																																																													
C _{max} (ng/mL)	61.1	194	623	75.8	187	896																																																																													
T _{max} (hr)	3.50	8.50	7.00	4.00	3.00	15.00																																																																													
Day 105																																																																																			
AUC _{0-24hr} (hr*ng/mL)	1540	6950	28600	2060	6750	23000																																																																													
C _{max} (ng/mL)	105	399	1660	130	381	1130																																																																													
T _{max} (hr)	3.00	5.33	7.50	2.50	5.00	5.50																																																																													
Toxicokinetic data from a GLP-compliant embryo-fetal development study of imlunestrant via oral gavage in rats (Study no. 9001840)	-Following once daily oral administration of imlunestrant from gestation Days 6 to 17, systemic exposure (C_{max} and AUC₀₋₂₄) increased proportionally with increasing dose from 0.3 to 30 mg/kg/day. -After repeated administration on gestation Day 17, systemic exposure (C_{max} and AUC₀₋₂₄) was higher in all dose levels relative to gestation Day 6.																																																																																		
<table><tr><td>Parameters</td><td colspan="3">Dose level (mg/kg)</td></tr><tr><td>Gestation Day 6</td><td>0.3</td><td>3</td><td>30</td></tr><tr><td>C_{max} (ng/mL)</td><td>6.42</td><td>66.9</td><td>709</td></tr><tr><td>AUC_{0-24hr} (hr*ng/mL)</td><td>96.3</td><td>977</td><td>11000</td></tr><tr><td>T_{max} (hr)</td><td>8</td><td>8</td><td>8</td></tr><tr><td>Gestation Day 17</td><td></td><td></td><td></td></tr><tr><td>C_{max} (ng/mL)</td><td>9.25</td><td>116</td><td>902</td></tr><tr><td>AUC_{0-24hr} (hr*ng/mL)</td><td>180</td><td>2180</td><td>15600</td></tr><tr><td>T_{max} (hr)</td><td>8</td><td>8</td><td>8</td></tr></table>							Parameters	Dose level (mg/kg)			Gestation Day 6	0.3	3	30	C _{max} (ng/mL)	6.42	66.9	709	AUC _{0-24hr} (hr*ng/mL)	96.3	977	11000	T _{max} (hr)	8	8	8	Gestation Day 17				C _{max} (ng/mL)	9.25	116	902	AUC _{0-24hr} (hr*ng/mL)	180	2180	15600	T _{max} (hr)	8	8	8																																									
Parameters	Dose level (mg/kg)																																																																																		
Gestation Day 6	0.3	3	30																																																																																
C _{max} (ng/mL)	6.42	66.9	709																																																																																
AUC _{0-24hr} (hr*ng/mL)	96.3	977	11000																																																																																
T _{max} (hr)	8	8	8																																																																																
Gestation Day 17																																																																																			
C _{max} (ng/mL)	9.25	116	902																																																																																
AUC _{0-24hr} (hr*ng/mL)	180	2180	15600																																																																																
T _{max} (hr)	8	8	8																																																																																

Inluriyo (implunestrant)

5.5 Toxicology

5.5.1 General Toxicology

The Applicant's Position:

The general toxicology profile across repeat-dose toxicity studies in rats and monkeys demonstrates that implunestrant was well tolerated at doses and exposures that exceeded the anticipated therapeutic levels in humans.

Single-dose toxicity studies

No single-dose toxicity studies of implunestrant were conducted. Single-dose studies are typically not conducted for modern drug development, as short pilot and range-finding studies generally provide equivalent or more information. In pilot and range-finding studies, single doses were well tolerated with no mortality or clinical observations indicating acute toxicity from Day 1 to Day 2.

Repeat-dose toxicity studies

Implunestrant has been administered by QD oral gavage to rats for up to 6 months and to monkeys for up to 3 months. Consistent with implunestrant pharmacology, the primary target organs in rat and monkey repeat-dose studies were female reproductive tissues. Microscopic findings included

- cysts in the ovaries of rats and monkeys
- hyperplasia of ovarian granulosa cells in rats
- atrophy of the epithelium of the uterus, cervix, and vagina of rats, as well as
- hypertrophy/hyperplasia of the female mammary glands.

Except for the mammary gland effects, these findings were generally correlated with organ weight changes, macroscopic changes, or both. Effects on male reproductive tissues were also apparent in longer-term rat studies. Reproductive tissue effects were collectively considered adverse in both sexes but their relevance for the intended patient population of implunestrant is minimal because men and pre/perimenopausal women treated with implunestrant will receive GnRH agonist and because the effects in animals were generally reversible.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. Additional target organs of toxicity included kidney and urinary bladder.

Inluriyo (implunestrant)

The 7-day dose range finding study in monkeys and 14-day dose range finding toxicity study in rats were not included in the review since the Applicant submitted GLP-compliant repeat dose toxicity studies up to 6 months in rats and up to 3 months in monkeys.

Data (presented by the FDA):

Study title: A 6-month toxicity and toxicokinetic study of LY3484356 tosylate (compound 3513322) by oral gavage daily to rats with a 3-month recovery period

Study no.:	8003353
Date of study initiation:	May 26, 2021
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Implunestrant (LY3484356 tosylate), lot# CR-C18071754-J21001, and 67.6% (free base) and 89.8% (salt) for potency/content

Key Study Findings

- Early mortality occurred at 150 mg/kg attributed to implunestrant-related urinary obstruction.
- The major target organs were male and female reproductive organs, kidney, urinary bladder, and hematopoietic/lymphatic systems. Changes in histopathology findings were either reversible or trending towards recovery.

Inluriyo (imlunestrant)

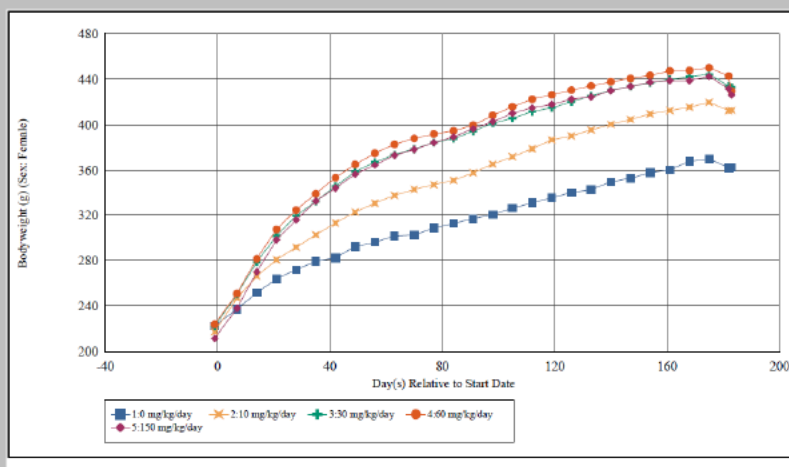
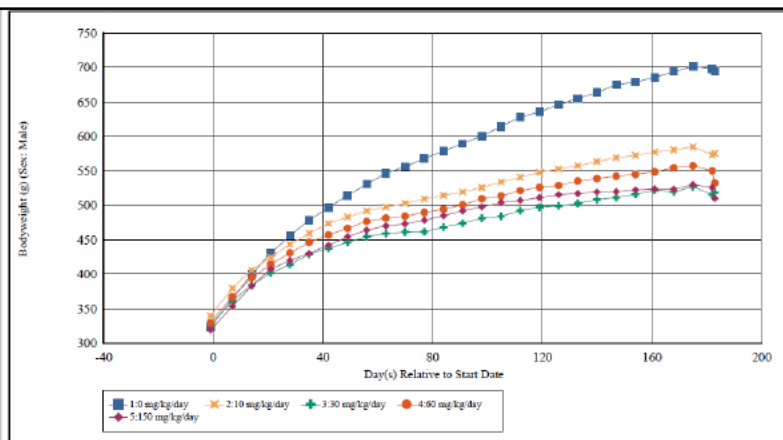
Methods

Doses:	0, 10, 30, 60, 150 mg/kg
Frequency of dosing:	Once daily
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	(b) (4) in ultra-pure water
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	15/sex/group (main study); 5/sex/group (recovery group for the VH, 60 mg/kg and 150 mg/kg)
Age:	6-8 weeks
Weight:	160 to 210 g (males)/ 140 to 180 g (females)
Satellite groups:	9/sex/group (toxicokinetic group, except VH was 3/sex/group); 5/sex/group (T-dependent antibody response [TDAR] testing group)
Unique study design:	None
Deviation from study protocol:	All deviations that occurred during the study did not impact the overall integrity of the study or the interpretation of the data.

Observations and Results

Parameters	Major findings
Mortality	-At 150 mg/kg, three rats were early moribund sacrificed between Days 82 and 176 of dosing phase. These animals showed decreases in body weight and activity, hunched posture, decreased vocalization, cold to touch, and shallow breathing. The cause of early moribund sacrifice was due to urinary obstruction (2 females at 150 mg/kg euthanized on Days 82 and 106) or a mass observed in the thymus (1 male at 150 mg/kg on Day 176). Urinary obstruction correlated with histopathology findings of marked bacterial pyelonephritis in the kidney (inflammation, pelvis) and moderate cystitis (inflammation) with hyperplasia of epithelium, dilation, and hemorrhage in the urinary bladder. Changes in the thymus may not be related to the administration of imlunestrant based on lack of correlating histopathology findings in the surviving main study animals.
Clinical Signs	Unremarkable
Body Weights	<u>Terminal Sacrifices (compared to VH control)</u>

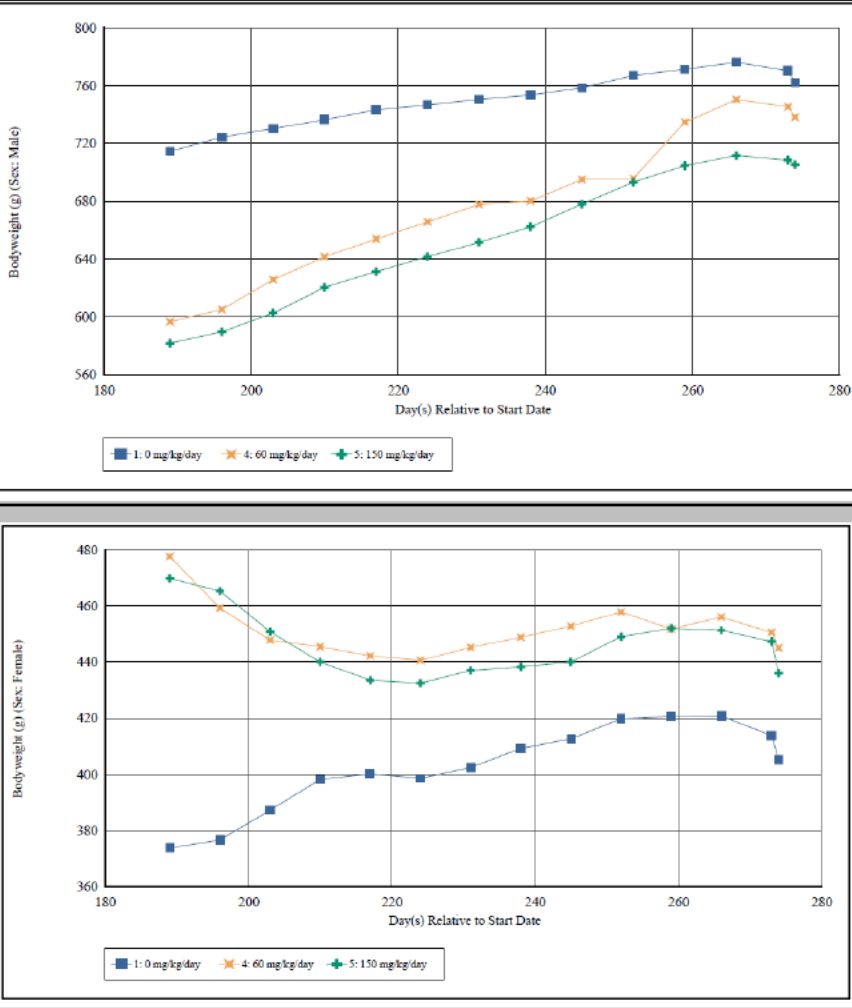
Inluriyo (imlunestrant)



(Excerpted from the Applicant's submission)

Recovery (compared to the VH control)

Inluriyo (imlunestrant)

	 (Excerpted from the Applicant's submission)
Feed consumption	<u>Terminal Sacrifices (compared to VH control)</u> - In male rats, a non-dose dependent decrease in food consumption (8-23%) was observed at all doses during Days 98 to 182. - In female rats, a non-dose dependent decrease in food consumption was observed at all doses only on Day 182 (17-20%). <u>Recovery (Day 274; compared to VH control)</u> - Food consumption normalized to control means at the end of recovery period.
Ophthalmoscopy	<u>Terminal Sacrifices (Week 26/27; compared to VH control)</u> Increased incidence of slight focal and central posterior cortical lens opacity was noted at 150 mg/kg (up to 5/21 in males and up to 5/20 females); an increase in incidence of minimal to mild lens degeneration was observed microscopically at ≥ 60 mg/kg.

Inluriyo (imlunestrant)

Recovery (Week 39; compared to VH control)

Animals dosed with imlunestrant at 60 mg/kg (1/4 males; 3/5 females) and 150 mg/kg (4/5 males; 4/5 females) still showed slight corneal opacity suggesting no recovery. However, both male (4/5) and female (3/5) control animals also showed very slight corneal opacity at the end of the recovery period.

Although an increased incidence in ophthalmoscopy finding was noted at 150 mg/kg, the relationship to imlunestrant treatment is unclear considering findings with the same severity were noted in recovery control animals and ocular findings were absent in the 1- and 3-month studies including higher doses of imlunestrant.

Hematology

Terminal sacrifices

Parameters	% Change from control at sacrifices (Day 183)							
Sex	Males				Females			
Dose levels (mg/kg)	10	30	60	150	10	30	60	150
Total number of animals	15	14 ^a	15	14 ^b	13 ^c	15	15	13 ^d
Absolute white blood cells	-23	-24	11	45**	22	20	33*	51**
Absolute neutrophils	-23	-19	-16	28		-22	-17	
Absolute lymphocytes	-22	-24	17	49**	29	30	45**	63**
Absolute monocytes	-24	-32		58**	13	11	20	57
Absolute red blood cells					23**	23**	17*	21**
Absolute hemoglobin					18**	15**	12	14**
%Hematocrit					20**	18**	13	17**
Absolute basophils	-22	-67	56	95	62	413**	320	546**
Absolute platelet		-14*	-13*					
Absolute reticulocytes	-15	-23**	-21**	-11			15	-24**

*p ≤ 0.05; **p ≤ 0.01

^{a, b} The blood sample in one male at dose 30 and 150 mg/kg mg/kg were clotted during analysis and were excluded from data analysis.

^c According to the Applicant, 2 females from the control group were excluded from the fold different calculation because they had anemia and lymphoma. However, the Applicant states that these changes in control animals had no impact on the totality of the data because it was not related to imlunestrant administration.

^d At 150 mg/kg dose level, one blood sample in a female at dose 150 mg/kg was clotted during sample analysis.

Inluriyo (imlunestrant)

	<u>Recovery (Day 274)</u> When compared to control group, all changes in hematological parameters were trending towards recovery; except an increase in the absolute basophils in males at dose 60 mg/kg (150% above control) and 150 mg/kg (400% above control).																																																																																																																																																																				
Coagulation	Unremarkable																																																																																																																																																																				
Clinical Chemistry	<u>Terminal sacrifices</u> <table><tr><th>Parameters</th><th colspan="8">% Change from control at sacrifices (Day 183)</th></tr><tr><th>Sex</th><th colspan="4">Males</th><th colspan="4">Females</th></tr><tr><th>Dose levels (mg/kg)</th><th>10</th><th>30</th><th>60</th><th>150</th><th>10</th><th>30</th><th>60</th><th>150</th></tr><tr><th>Total number of animals</th><td>15</td><td>15</td><td>15</td><td>15</td><td>15</td><td>14</td><td>15</td><td>14</td></tr><tr><td>Alkaline phosphatase (ALP)</td><td>11</td><td>33</td><td>18</td><td>43**</td><td>86**</td><td>89**</td><td>80**</td><td>157**</td></tr><tr><td>Alanine transferase (ALT)</td><td></td><td></td><td></td><td>30*</td><td></td><td></td><td></td><td>27*</td></tr><tr><td>Creatine kinase (CK)</td><td>-14</td><td>-20</td><td></td><td></td><td>30</td><td>27</td><td>45</td><td>79</td></tr><tr><td>Cholesterol</td><td>-57**</td><td>-56**</td><td>-53**</td><td>-51**</td><td>-61**</td><td>-60**</td><td>-53**</td><td>-55**</td></tr><tr><td>Albumin</td><td></td><td></td><td></td><td></td><td>-19*</td><td>-22**</td><td>-22**</td><td>-24**</td></tr><tr><td>Albumin: globulin ratio</td><td>10</td><td>15**</td><td>16**</td><td>14*</td><td>-16*</td><td>-20**</td><td>-20**</td><td>-25**</td></tr><tr><td>Glucose</td><td></td><td></td><td></td><td></td><td></td><td>33**</td><td>24*</td><td>15</td></tr><tr><td>Total protein</td><td></td><td></td><td></td><td></td><td>-15**</td><td>-16**</td><td>-17**</td><td>-17**</td></tr><tr><td>Potassium</td><td></td><td></td><td></td><td></td><td>14**</td><td>13**</td><td>16**</td><td>21**</td></tr></table> *p ≤ 0.05; **p ≤ 0.01 <u>Recovery (Day 274; only 60 mg/kg and 150 mg/kg compared to VH control)</u> <table><tr><th>Parameters</th><th colspan="4"></th></tr><tr><th>Sex</th><th colspan="2">Males</th><th colspan="2">Females</th></tr><tr><th>Dose levels (mg/kg)</th><th>60</th><th>150</th><th>60</th><th>150</th></tr><tr><th>Total number of animals</th><td>4^e</td><td>5</td><td>5</td><td>4</td></tr><tr><td>Glucose</td><td>20</td><td>34</td><td></td><td></td></tr><tr><td>Phosphorus</td><td>24</td><td>30</td><td></td><td></td></tr><tr><td>AST</td><td></td><td></td><td>58</td><td>222</td></tr><tr><td>ALT</td><td></td><td></td><td>79</td><td>120</td></tr></table>								Parameters	% Change from control at sacrifices (Day 183)								Sex	Males				Females				Dose levels (mg/kg)	10	30	60	150	10	30	60	150	Total number of animals	15	15	15	15	15	14	15	14	Alkaline phosphatase (ALP)	11	33	18	43**	86**	89**	80**	157**	Alanine transferase (ALT)				30*				27*	Creatine kinase (CK)	-14	-20			30	27	45	79	Cholesterol	-57**	-56**	-53**	-51**	-61**	-60**	-53**	-55**	Albumin					-19*	-22**	-22**	-24**	Albumin: globulin ratio	10	15**	16**	14*	-16*	-20**	-20**	-25**	Glucose						33**	24*	15	Total protein					-15**	-16**	-17**	-17**	Potassium					14**	13**	16**	21**	Parameters					Sex	Males		Females		Dose levels (mg/kg)	60	150	60	150	Total number of animals	4 ^e	5	5	4	Glucose	20	34			Phosphorus	24	30			AST			58	222	ALT			79	120
Parameters	% Change from control at sacrifices (Day 183)																																																																																																																																																																				
Sex	Males				Females																																																																																																																																																																
Dose levels (mg/kg)	10	30	60	150	10	30	60	150																																																																																																																																																													
Total number of animals	15	15	15	15	15	14	15	14																																																																																																																																																													
Alkaline phosphatase (ALP)	11	33	18	43**	86**	89**	80**	157**																																																																																																																																																													
Alanine transferase (ALT)				30*				27*																																																																																																																																																													
Creatine kinase (CK)	-14	-20			30	27	45	79																																																																																																																																																													
Cholesterol	-57**	-56**	-53**	-51**	-61**	-60**	-53**	-55**																																																																																																																																																													
Albumin					-19*	-22**	-22**	-24**																																																																																																																																																													
Albumin: globulin ratio	10	15**	16**	14*	-16*	-20**	-20**	-25**																																																																																																																																																													
Glucose						33**	24*	15																																																																																																																																																													
Total protein					-15**	-16**	-17**	-17**																																																																																																																																																													
Potassium					14**	13**	16**	21**																																																																																																																																																													
Parameters																																																																																																																																																																					
Sex	Males		Females																																																																																																																																																																		
Dose levels (mg/kg)	60	150	60	150																																																																																																																																																																	
Total number of animals	4 ^e	5	5	4																																																																																																																																																																	
Glucose	20	34																																																																																																																																																																			
Phosphorus	24	30																																																																																																																																																																			
AST			58	222																																																																																																																																																																	
ALT			79	120																																																																																																																																																																	

Inluriyo (imlunestrant)

		ALP			47	80				
		Gamma-glutamyl transferase (GGT)				108				
		CK				13				
		Total bilirubin			44	84				
		Urea nitrogen				20				
		Globulin				20*				
		Albumin: globulin				-28*				
		*p ≤ 0.05								
		* One male at dose 60 mg/kg level was early moribund sacrificed on Day 258; however, the cause of moribundity was not related to imlunestrant exposure.								
Urinalysis	Unremarkable									
Gross Pathology										
<u>Terminal sacrifices (excluded unscheduled death animals)</u>										
	Males					Females				
Dose levels (mg/kg)	0	10	30	60	150	0	10	30	60	150
Total number of animals	15	15	15	15	15	15	15	15	15	14
Cervix										
Small										1
Prostate gland										
Focus dark			1		1					
Kidney										
Enlargement					1					
Lung										
Focus, pale					1					
Lymph node										
Discoloration, dark					1					
Lymph node, mesenteric										
Focus, dark					1					
Ovary										
Focus, dark							4	7	3	4
Mass							1	1		
Small intestine, jejunum										
Diverticulum										1
Stomach										
Thick					1					
Urinary bladder										
Thick			1							1

Inluriyo (imlunestrant)

Recovery (only at 60 mg/kg and 150 mg/kg)

All gross pathology findings were reversible at the end of recovery period, except findings in prostate gland (pale and dark focus in males at 60 mg/kg (1/4) and 150 mg/kg (1/5)), thyroid gland (small; 1/4 females at 150 mg/kg), stomach (thick; 2/5 males at 150 mg/kg).

Organ WeightsTerminal sacrifices (organ weight relative to body weight)

Parameters	% Change from control at sacrifices (Day 183)							
Sex	Males				Females			
Dose levels (mg/kg)	10	30	60	150	10	30	60	150
Total number of animals	15	15	15	15	15	15	15	14
Brain	15	30**	27**	31**	-11**	-14**	-14**	-11**
Epididymis		25**	23**	27**	-	-	-	-
Adrenal gland				16	-53**	-47**	-48**	-45**
Pituitary gland					-63**	-61**	-62**	-59**
Heart		11**	17**	23**				
Kidney	11	21**	22**	29**				
Spleen				15	-59	-60	-55	-53
Testis	20*	30**	37**	39**	-	-	-	-
Thymus	22			10	-34	-43	-43	-50
Ovary	-	-	-	-	287**	203**	179**	258**
Uterus	-	-	-	-	-70**	-74**	-74**	-74**

**p ≤ 0.01

Recovery (Day 274; organ weight relative to body weight; compared to control)

All changes in organ weight relative to body weight were trending towards recovery, except a statistical increase in thymus weight relative to body weight (108%).

Histopathology

Adequate battery:
Yes

Peer review: No

Terminal sacrifices (excluded unscheduled death animals)

Inluriyo (imlunestrant)

	Males					Females				
Dose levels (mg/kg)	0	10	30	60	150	0	10	30	60	150
Total number of animals	15	15	15	15	15	15	15	15	15	14 ^g
Bone marrow Cellularity, increased; hematopoietic										
Minimal		1	2	4			1		1	7
Cervix Atrophy										
Minimal								7	12	1
Mild										7
Moderate										6
Epididymis Cellular debris, lumen										
Minimal			1	2						
Mild		1			1					
Vacuolation; epithelial										
Minimal			5	13	6					
Mild					8					
Cellularity, decreased; sperm; lumen										
Minimal				2	1					
Marked		2								
Severe			1							
Eye Degeneration; lens										
Minimal		6	5	3	6	3	5	3	6	9
Mild					2				1	1
Atrophy; retina										
Minimal						1	1			
Mild					1				1	
Adrenal gland Vacuolation, cortical										
Minimal			1		1					
Gland, mammary Hypertrophy/ Hyperplasia, alveolus/duct, lobule										
Minimal							4	3	5	2
Mild							6	3	2	4
Moderate							1	4	2	6
Gland, pituitary Hypertrophy, cellular, pars distalis										
Minimal							7	9	7	10
Cyst, pars distalis										
Minimal			1	1	1					1
Kidney Hyperplasia, transitional epithelium										
Minimal										1
Moderate			1							

NDA/BLA Multi-disciplinary Review and Evaluation NDA 218881

Inluriyo (imlunestrant)

Inflammation, pelvis Minimal Mild							1	1	3 1	4	
Degeneration/ regeneration, tubular Minimal Mild Moderate Marked		5	6	5	3 1 7 2		1	4	5	3 3	
Dilation, tubular Minimal Glomerulopathy Minimal				1	1					1	
Lung Hemorrhage Minimal			1		1			1	1		
Lymph node, mesenteric Erythrocytosis, sinus Minimal Mild		3		3	3 1		2		1	4	
Vacuolation, macrophage Minimal Mild Moderate		2	6 2	6 8	1 9 5			7 1	10 2	1 10 1	
Ovary Hyperplasia; granulosa cell Minimal Mild Moderate Marked Severe Pigment Minimal Mild Cyst; follicular/luteal Minimal Mild Moderate Marked Severe							1 1 1 1 1	2 2 2 1 6	1 1 3 3 5	2 2 3 3 5	
						2					1 4
							5 10	2 3 10	2 6 7	3 9 2	
Small intestine, ileum Vacuolation, macrophage, lamina propria Minimal Mild					12 1				1	11	
Small intestine, jejunum Vacuolation, macrophage, lamina propria											

Inluriyo (imlunestrant)

Minimal Mild Diverticulum					4 11				3	3 9	
Mild										1	
Testis Spermatid retention											
Minimal Mild		2 1	5	2 2	3						
Urinary bladder Hyperplasia, transitional epithelium											
Minimal Mild				6	6		1	2	3	4 1	
Uterus Atrophy											
Minimal Mild Moderate							12	2 13	4 11	4 10	
Vagina Atrophy											
Minimal Mild Moderate							10	12	10 3	1 6 7	

^g One female at dose 150 mg/kg was early moribund sacrificed on Day 105, but the cause of moribundity was not related to imlunestrant administration.

Recovery

Sex	Males			Females		
Dose levels (mg/kg)	0	60	150	0	60	150
Total number of animals	5	4	5	5	5	4 ^f
Eye Degeneration, lens						
Minimal	1	1	3		1	3
Rosette, retina						
Minimal				1		
Mild			1			
Heart Metaplasia, osseous						
Minimal			1			
Joint, femorotibial Degeneration joint disease						
Minimal			2			
Kidney Inflammation, pelvis						
Minimal			1		1	1
Degeneration/ Regeneration, tubular						
Minimal		2	1			1
Mild			2			

Inluriyo (imlunestrant)

	Accumulation, hyaline droplets Minimal Mild			1 1			
	Infiltration, mononuclear cell, interstitial Minimal			1			
	Large intestine, colon Parasitism, lumen			1			
	Liver Hypertrophy; Kupffer cell Minimal Focus of cellular alteration, eosinophils Minimal					2 1	
	Lymph node, mandibular Cellularity, increased, lymphoid Mild			1			
	Lymph node, mesenteric Vacuolation, macrophage Minimal Mild Moderate		4	4 1		2 3 1	3
	Ovary Cyst; follicular/luteal Minimal Mild Hyperplasia, granulosa cell Minimal Moderate Pigment Minimal Mild					2 3 2 2 2 2	2 2 1 2 2 1
	Testis Spermatid retention Minimal Degeneration/atrophy, seminiferous tubule Minimal		1	1 1			
	Urinary bladder Hyperplasia, transitional epithelium Minimal					1 1	
	Immunophenotyping analysis	On Day 183 (end of dosing), the Applicant evaluated changes for total lymphocytes for all treatment groups in blood, spleen, and thymus. Other parameters, including total T lymphocytes, helper T lymphocytes, cytotoxic T lymphocyte, B lymphocyte, NK cells,					

Inluriyo (imlunestrant)

	and helper T cells: cytotoxic T cells ratio, were assessed at ≤ 30 mg/kg (blood) and ≤ 60 mg/kg (spleen, thymus). Reversibility was assessed on Day 274 at ≥ 60 mg/kg. Over all imlunestrant showed dose-dependent increases in various lymphocyte populations (especially T lymphocytes), with effects being more pronounced in females during the end of dosing period and in males during the recovery period only at the highest dose level. Changes in the immunophenotyping analysis in blood and spleen of females were reversible at the end of the recovery period. <u>Terminal Sacrifices (Day 183)</u> At the end of the dosing period in females, imlunestrant showed dose-dependent increases in various cell types including total lymphocytes (39-77% in blood and 18-84% in spleen from 10-150 mg/kg), absolute cytotoxic T lymphocyte (19-61% in thymus from 10-60 mg/kg), absolute T lymphocytes in spleen (18-43% from 10-60 mg/kg), absolute NK cells (29-43% from 10-60 mg/kg) when compared to the VH control. These changes were reversible in females at the end of the recovery period. <u>Recovery period (Day 274)</u> For immunophenotyping findings in thymus of females compared to VH control at the end of Day 274, changes were primarily observed at the 150 mg/kg including total lymphocyte count (33%), absolute total T lymphocytes (45%), absolute helper T lymphocytes (39%), absolute cytotoxic T lymphocytes (54%), total lymphocyte count/thymus (33%), absolute thymocyte subsets at different maturation stages (CD3⁺/CD4⁺/CD8a⁺; 54%), absolute thymocyte subsets at different stages (CD3⁻CD4CD8a⁺; 30%). For immunophenotyping in the spleen of males, changes observed were primarily in males at the 150 mg/kg at the end of Day 274 including total lymphocytes (61% in spleen and 122% in thymus), absolute T lymphocytes (63% in spleen), Total lymphocytes (126% in thymus), absolute helper T lymphocyte (77% in spleen and 135% in thymus), and cytotoxicity T lymphocytes (45% in spleen and 117% in thymus), total spleen cell count (61%), and absolute B lymphocytes (91%), total lymphocyte count/thymus (122%), absolute thymocyte subsets at different maturation stages (CD3⁺/CD4⁺/CD8a⁺; 115%), absolute thymocyte subsets at different stages (CD3⁻CD4CD8a⁺; 123%).
T-cell dependent antibody response	

Inluriyo (imlunestrant)

T-cell dependent antibody response (anti-KLH IgM)

- Compared to the vehicle control, changes were not dose-dependent, except a dose-dependent increase in anti-KLH IgM in the second challenge on Days 176 and 183 in males administered 30 to 150 mg/kg imlunestrant. Although it was not dose-dependent, a decrease in the primary anti-KLH IgM response was noted 7 to 14 days after the first KLH injection, but increased during Day 21 post-KLH administration. However, the magnitude of changes in T-cell dependent antibody response did not correlate with histopathology findings. Overall, imlunestrant had no effect on the primary immune response to KLH challenge.

T-cell dependent antibody response (anti-KLH IgG)

- Changes were not dose-dependent when compared to the VH control; except a dose-dependent increase in anti-KLH IgG in the second challenge on Days 176 and 183 in males administered 10-150 mg/kg imlunestrant. Changes in anti-KLH IgG responses also decreased at 7 to 14 days after the initial KLH injection, though this effect was not dose-dependent. However, the magnitude of changes in T-cell dependent antibody response did not correlate with histopathology findings. Overall, imlunestrant had no effect on the humoral immune response to KLH challenge.

Dosing solution analysis

Formulations met the concentration acceptance criteria ($\pm \frac{(b)}{(4)}$ % of the nominal concentration). Formulation met the homogeneity acceptance criteria (the mean relative standard deviation (RSD) of concentration was $\leq \frac{(b)}{(4)}$ %).

General toxicology, additional studies in rats:

GLP-compliant 4-week and 3-month daily oral repeat dose toxicology studies were conducted in rats. These studies were reviewed under IND 145311. The main findings including target organs of toxicity generally reflected those observed in the GLP-compliant 6-month study. Additional findings are noted below.

3-month study (#8003221/GLP compliant): Rats were administered daily oral imlunestrant (LY3484356; lot# CR-C18071754-J21001, 89.8% purity) at doses of 0, 10, 30, and 150 mg/kg/day for 3 months followed by a 6-week recovery period (n = 10/sex/group [main], 5/sex/group [recovery for only control and high dose groups]).

- No early deaths. Clinical observations of salivation and abnormal liquid/soft/mucoid feces were observed at ≥ 10 mg/kg in both males and females, and minimal nerve fiber degeneration in the optic nerve in a female administered 150 mg/kg.

4-week study (#8002568/GLP compliant): Rats were administered daily oral imlunestrant (lot# JR-C18071754-J19001, 92.7% purity) at doses of 0, 30, 100, and 300 mg/kg for 4 weeks followed by a 2-week recovery period (n = 10/sex/group [main], 5/sex/group [recovery for only control and high dose groups]).

- Early deaths (n=3 males) occurred at 300 mg/kg due to imlunestrant related hepatocellular and/or muscular damage, toxicities that were not observed in the 3- and 6-month studies up to 150 mg/kg.

Inluriyo (imlunestrant)

Study title/number: A 3-month toxicity and toxicokinetic study of LY3484356 tosylate (compound 3513322) given daily by oral gavage to Cynomolgus monkeys/ 8003147

Methods: Monkeys received daily oral imlunestrant (LY3484356; lot# CR-C18071754-J21001, 89.8% purity) at 0, 15, 100, and 600 mg/kg for 3 months (n = 4/sex/group).

Key Study Findings:

- The major target organs were the hematopoietic/lymphatic systems, female reproductive organs, gastrointestinal tract, liver, and kidneys with similar severity to those observed in the one-month repeat-dose toxicity study.

Observations and Results

Parameters	Major findings
Mortality	All animals survived to the end of the study.
Clinical Signs	At 600 mg/kg, imlunestrant-related clinical signs included vomitus during Days 5-102 in both males and females, salivation in males between Days 95-105, abdominal distension in females during Days 30-35. Abnormal feces (pale, soft, liquid) were observed at 600 mg/kg in both males and females during Days 4-106.
Body Weights	Unremarkable
Feed consumption	Unremarkable
Respiratory rate	Unremarkable
Neurological examination	Unremarkable
Body temperature	Unremarkable
Ophthalmoscopy	Unremarkable
ECG parameters	Unremarkable
Hematology	Unremarkable.
Coagulation	Unremarkable
Clinical Chemistry	An increase in alanine transaminase (ALT) was observed in both males (96% above control) and females (50% above control) at the high dose level of 600 mg/kg on Week 15.
Urinalysis	Unremarkable
Gross Pathology	<u>Terminal sacrifices</u>

Inluriyo (imlunestrant)

	Dose levels (mg/kg)	Males				Females			
		0	15	100	600	0	15	100	600
Total number of animals		4	4	4	4	4	4	4	4
Large intestine, cecum Abnormal content; watery									1
Large intestine, colon Abnormal content; watery									1
Large intestine, rectum Abnormal content; watery									1
Liver Discoloration, dark Focus, pale Adhesion			1	1	1		4		1
Lymph node Discoloration, dark Enlargement					1				1
Lymph node, mesenteric Discoloration, dark									1
Ovary Cyst, pale Mass							1 3	4	2 3
Small intestine, ileum Abnormal content, watery									1
Small intestine, jejunum Abnormal content, watery Mass					1				1
Stomach Focus, dark			1				1		1
Organ Weights	<u>Terminal sacrifices (organ weight relative to body weight)</u>								

Inluriyo (imlunestrant)

		Parameters	% Change from control at sacrifices (Week 15)					
		Sex	Males			Females		
		Dose levels (mg/kg)	15	100	600	15	100	600
		Total number of animals	4	4	4	4	4	4
		Epididymis	-14	-26	-39	-	-	-
		Pituitary gland	16		19		-10	-13
		Prostate gland	11		-31	-	-	-
		Spleen	-33	-17	-21	-12		-32
		Testis	48	16	-21	-	-	-
		Thymus	-17		-54		92	-72
		Heart				11	13	26**
		Thyroid/parathyroid				108	102	50
		Ovary				1597	3552*	3442*
		*p ≤ 0.01; **p≥ 0.05						

Histopathology Adequate battery: Yes Peer review: No	<u>Terminal sacrifices</u>								
		Males				Females			
	Dose levels (mg/kg)	0	15	100	600	0	15	100	600
	Total number of animals	4	4	4	4	4	4	4	4
	Bone marrow Hematopoietic cells, decreased Minimal				2		1	1	4
	Adipose tissue Cyst Moderate				1				
	Cervix Atrophy Minimal Mild						3	4	4
	Adrenal gland Atrophy; cortical Minimal								2
	Kidneys Basophilia; tubular Minimal Mild				1 1				
	Liver Pigment; Kupffer cell								

Inluriyo (imlunestrant)

	Minimal Mild Tension, lipidosis Minimal				1 1 1		1		2 1
	Lymph node Erythrocytosis, sinus Minimal Mild Cellularity, increased, lymphoid Minimal				1 1				1
	Lymph node, mandibular Erythrocytosis, sinus Minimal				1				
	Lymph node, mesenteric Vacuolation, macrophage, sinus Minimal Mild	1			2		1 1	2	3 1
	Ovary Cyst Mild Moderate Marked Severe						1 2 1	1 3	1 3
	Small intestine, duodenum Vacuolation, macrophage, lamina propria Minimal				1				2
	Small intestine, ileum Vacuolation, macrophage, lamina propria Minimal Mild				2 1				2 1
	Small intestine, jejunum Vacuolation, macrophage, lamina propria Mild Cyst Moderate				4 1				4
	Spleen Pigment; macrophage Mild Cellularity, decreased, lymphoid Minimal Mild	2	2		3			2	2 1

Inluriyo (imlunestrant)

	Stomach Granuloma Minimal				1				
	Thymus Cyst Minimal			1					
	Hemorrhage Minimal								
	Cellularity, decreased, lymphoid Minimal	1			2				4
	Marked Minimal				2				3 1
	Uterus Atrophy Minimal						2	4	4
	Vagina Atrophy Minimal						4	4	4
Immunophenotyping analysis	The Applicant conducted additional endpoints to evaluate immunophenotyping analysis (quantification of the T, B, and NK cells subsets using flow cytometry analysis. Compared to control and baseline, changes were unremarkable.								
T-cell dependent antibody response (TDAR) against keyhole limpet hemocyanin (KLH)	Overall, changes were unremarkable when compared to the vehicle control group.								

LD: low dose; MD: mid dose; HD: high dose; M: male; F: female

General toxicology, additional studies in monkeys:

A GLP-compliant 4-week daily oral repeat dose toxicology study was conducted in monkeys. This study was reviewed under IND145311. The main findings including target organs of toxicity generally reflected those observed in the GLP-compliant 3-month study. Additional findings are noted below.

4-week study (#8002569/GLP compliant): Monkeys were administered daily oral imlunestrant (LY3484356; lot# CR-C18071754-J19001, 89.8% purity) at doses of 0, 30, 150, and 600 mg/kg (n = 3/sex/group).

- No deaths or significant weight loss occurred at the high dose of 600 mg/kg during the 4-week toxicity study. Treatment-related clinical chemistry changes at doses $\geq$ 30 mg/kg included increases in alanine aminotransferase (up to 2X above control), creatine kinase (up to 3X above control), total bilirubin (up to 41%) and a dose-dependent decrease in globulin (11-18%).

5.5.2 Genetic ToxicologyThe Applicant's Position:

Inluriyo (implunestrant)

Implunestrant does not pose a biologically relevant genotoxic risk. Implunestrant was not mutagenic in the Ames bacterial reverse mutation assay. Implunestrant produced chromosomal damage in the in vitro micronucleus assay but did not cause chromosomal damage or DNA strand breaks in vivo when tested up to 2000 mg/kg in the rat comet and bone marrow micronucleus assays.

The FDA's Assessment:

The FDA agrees with the Applicant's position that implunestrant is not considered genotoxic.

5.5.3 Carcinogenicity

The Applicant's Position:

Carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer. Carcinogenicity studies have not been conducted to support the advanced cancer indication for implunestrant but are ongoing to support other indications.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

5.5.4 Reproductive and Developmental Toxicology

The Applicant's Position:

Based on its intended pharmacologic mechanism of action as a SERD and findings in animal studies, implunestrant could cause harm to a fetus and may impair fertility.

In repeat-dose toxicity studies, implunestrant was associated with reversible cessation of estrous cycling and generally reversible anatomic effects on the female reproductive tract. Anatomic effects on the male reproductive tract were observed in rats and were reversible.

In an embryo-fetal development study of pregnant rats administered 0, 0.3, 3, or 30 mg/kg/day oral implunestrant during the period of organogenesis from Gestation Days 6 to 17, implunestrant caused gross pathological changes in

- maternal reproductive tissues
- embryo lethality
- fetal malformations
- variations, and
- effects on fetal growth.

Inluriyo (implunestrant)

Adverse maternal and embryo-fetal effects were observed at doses based on body surface area and exposures less than or equal to those in clinical trials, and a no-observed-adverse-effect level for maternal and embryo-fetal toxicity was not established.

The FDA's Assessment:

The FDA agrees with the Applicant's position. Implunestrant caused embryo-fetal mortality at ≥ 0.3 mg/kg/day, approximately 0.1 times the human AUC at the recommended dose. Implunestrant related fetal malformations and fetal variations were observed at ≥ 3 mg/kg (1 times the human AUC at the recommended dose of 400 mg once daily).

Data (presented by the FDA):

Study title: An enhanced pilot embryo-fetal development study of LY3484356 tosylate (compound 3513322) via oral gavage in rats

Study no.:	9001840
Date of study initiation:	June 09, 2021
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Implunestrant (LY3484356 tosylate; compound 3513322), lot# CR-C18071754-J21001, 67.6% potency

Key Study Findings

- Decreases in maternal body weight, body weight gain, and gravid uterus were observed at ≥ 3 mg/kg.
- Embryo-fetal mortality occurred at ≥ 0.3 mg/kg/day and structural abnormalities at ≥ 3 mg/kg.

Methods

Doses:	0, 0.3, 3.0, 30 mg/kg/day
Frequency of dosing:	Once daily
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) in ultra pure water
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	10 pregnant females/group (main study)
Satellite groups:	12 pregnant females/group (toxicokinetic group) except VH group was 4/sex/group

Inluriyo (imlunestrant)

Study design: Pregnant rats were administered imlunestrant by daily oral gavage during gestational Days 6 through 17.

Deviation from study protocol: None of the deviations were considered to have impacted the overall integrity of the study

Observations and Results**Clinical Signs****Day 6 to 17**

Dose level (mg/kg)	No. of animals	Clinical signs	Day of observation
0.3	2/22	Fur, staining, ventral aspect generalized	13-14
3	1/22		13-14
30	1/22		13-14
0.3	1/22	Discharge, color, vagina	15-15
3	2/22		15-16
30	2/22		15-16
0.3	1/22	Discharge, consistency, vagina	15-15
3	2/22		15-16
30	2/22		15-16
30	2/22	Pinna, missing, left	8-17

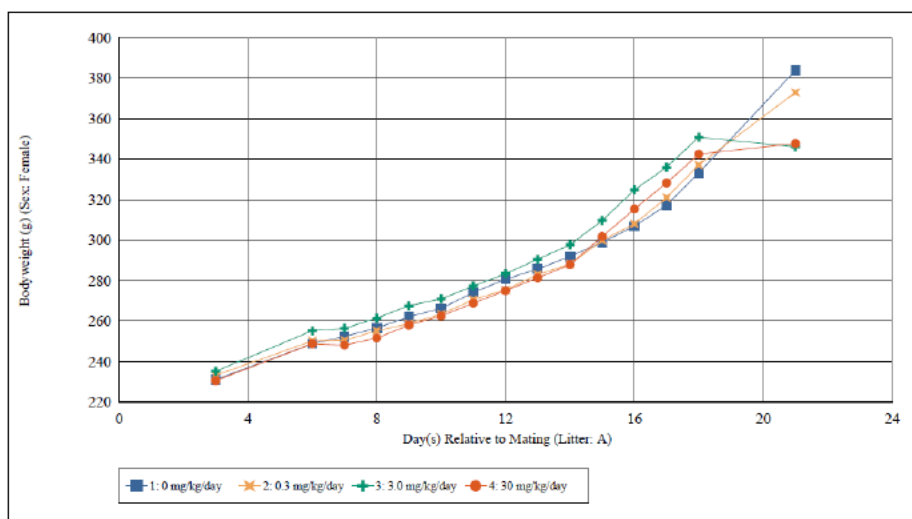
Day 18 to 21

Dose level (mg/kg)	No. of animals	Clinical signs	Day of observation
30	3/22	Discharge, color, vagina	21
30	3/22	Discharge, consistency, vagina	21
30	2/22	Pinna, missing, left	18-21

Body Weight

Inluriyo (imlunestrant)

Figure 5.2 Summary of body weight



(Excerpted from the Applicant's submission)

Feed Consumption

- When compared to the VH control, a decrease in maternal food consumption was observed starting on Days 16 through 21 in females administered 3 mg/kg (9-45%) and 30 mg/kg (15-43%) imlunestrant.

Gravid Uterus adjusted body weights:

- When compared to the VH control, a decrease in gravid uterus weight was observed in females administered 3 mg/kg (22%) and 30 mg/kg (18%) imlunestrant.
- There were no remarkable changes on the corrected body weight on Day 21 in females at all dose levels of imlunestrant when compared to the VH control. However, the corrected body weight changes on Day 21 relative to Day 6 were decreased in females at all dose levels of imlunestrant (32% at 0.3 mg/kg, 60% at 3 mg/kg, and 54% at 30 mg/kg).

Toxicokinetics

Data were presented in the pharmacokinetic section 5.4 of this NDA review.

Dosing Solution Analysis

- Mean dose formulation sample concentration results were within $\pm \frac{(b)}{(4)}\%$ of theoretical concentration, individual sample concentration results were within $\pm \frac{(b)}{(4)}\%$, and the mean relative standard deviation (RSD) was less than $\frac{(b)}{(4)}\%$. For homogeneity, the relative standard deviation (RSD) of concentrations was $\leq \frac{(b)}{(4)}\%$ for each group.

Gross pathology

Inluriyo (imlunestrant)

	Females			
Dose level (mg/kg)	0	0.3	3	30
Total number of animals	10	10	10	10
Lymph node				
Discoloration, dark			1	
Enlargement			1	1
Ovary				
Cyst, pale				9
Uterus				
Enlargement		1	4	3
Discoloration, pale			5	3
Abnormal appearance, deformity				1
Fluid accumulation, pale			5	7
Thick			7	9
Fluid accumulation, dark			2	
Focus, dark			1	1

Ovarian and uterine findings

- Pre-implantation loss (16.9%) at 30 mg/kg/day was statistically significantly increased compared to controls; however, according to the Applicant, this was within the Test Facility's historical control data (HCD) range (3.3-19.2%).
- Increased number of total resorptions, early resorptions, % post-implantation loss, and decreased number of live fetuses were observed at ≥ 0.3 mg/kg/day. To note, these differences from controls remained similar whether the data from 1 female (No. 3506) with total resorption of its litter (10 early and 1 late resorptions at 11 implantation sites; 100% post implantation loss) were included or excluded from the analysis. Table below summarizes the data with all the animals included.
- Although not observed at 30 mg/kg, early delivery (GD 21) occurred in 40% at 3 mg/kg, which was out of the HCD range (6-12%).
- Overall, the findings suggest imlunestrant treatment leads to embryo-fetal mortality.

Summary of ovarian and uterine examinations and litter observation: including animal with total resorption

	Number of incidences (% Changes from control)			
Dose level	0	0.3	3	30

Inluriyo (implunestrant)

(mg/kg)				
Findings				
Number of females with live fetuses	10	10	9	10
% Total	100	100	90	100
Mean number of corpora lutea	13.8	14.7 (7)	15 (9)	15.9 (15)
Mean % pre-implantation loss	5.95	8.09 (36)	7.76 (30)	16.9* (184)
Mean total number of resorption	0.2	1.9 (850)	6.4** (3100)	6.7** (3250)
Mean number of early resorption	0.2	1.2 (500)	3.3** (1150)	1.3* (550)
Mean % post-implantation loss	1.39	15.94 (1043)	52.17** (3642)	50.38 (3513)
Mean number of fetuses	12.8	11.6 (-9)	7.4** (-42)	6.4** (-50)
Mean number of live male fetuses	6	5.7 (-5)	3.1* (-48)	3.8 (-37)
Mean % live male fetus/litter	47.39	51.83 (9)	45.9 (-3)	54.08 (14)
Mean number of live female fetuses	6.8	5.8 (-15)	3.3* (-52)	2.6** (-62)

*p ≤ 0.05; **p ≤ 0.01

Fetal weights

- A decrease in fetal weight >10% was observed in both male and female fetuses when pregnant females were treated at ≥ 3 mg/kg; however, these changes were within the historical control range. The observed changes were similar across both male and female; thus, the data were presented as a combined analysis of both sexes.

Least square mean and group mean fetal weight (g) with differences from control means

Group (mg/kg/day)	Least square mean/mean of fetal weight (No. of animals)
	Combined sexes
HCD (Min-Max)	5.23-6.26 g
0	6.26/ 5.99 g (10)
0.3	5.83/ 5.66 g (10)
% Change from control	-7
3	5.23**/ 5.43 g (9)
% Change from control	-16
30	5.32**/ 5.57 g (10)
% Changes from control	-15

**p ≤ 0.01

Fetal malformations

Statistically significant increase in fetuses with malformations including small jaw (mandible, maxilla), protruding tongue, malrotated and hyperextended hindlimb were observed at ≥ 3 mg/kg when compared to litters in the control group.

Fetal external and visceral variations

Inluriyo (imlunestrant)

- When compared to VH control, there was an imlunestrant-related increase in the overall incidences of litters and fetuses with variations in external and visceral examinations at 3 and 30 mg/kg/day, indicative of a teratogenic effect of imlunestrant.

Fetal skeletal variations

- No statistically significant difference was observed in the overall incidence of skeletal variations among fetuses compared to litters in the control group.

Fetal abnormalities by classification

		Dose level (mg/kg)			
		0	0.3	3	30
	Number of fetuses evaluated	128	116	68	64
	Number of litters evaluated	10	10	9	10
Exam type					
External	<i>Variation</i>				
	Number of fetuses	1	1	14	15
	Litter % of fetus	0.7	1	23	24**
	Number of litters	1	1	6	9
	<i>Malformation</i>				
	Number of fetuses	0	0	34	24
	Litter % of fetus	0	0	57**	34**
	Number of litters				
	<i>All classifications</i>				
	Number of fetuses	1	1	37	32
	Litter % of fetus	0.7	1	61**	48**
	Number of litters	1	1	9	9
Fixed head	<i>Variation</i>				
	Number of fetuses	0	0	8	9
	Litter % of fetus	0	0	25*	24
	Number of litters	0	0	5	4
	<i>Malformation</i>				
	Number of fetuses	0	0	2	0
	Litter % of fetus	0	0	5	0
	Number of litters	0	0	2	0
	<i>All classifications</i>				
	Number of fetuses	0	0	9	9
	Litter % of fetus	0	0	29*	24
	Number of litters	0	0	5	4
Fresh visceral body abdominal	<i>Variation</i>				
	Number of fetuses	1	5	4	7
	Litter % of fetus	2	9	17	19

Inluriyo (imlunestrant)

	Number of litters	3	3	3	5
	<i>All classifications</i>				
	Number of fetuses	1	5	4	7
	Litter % of fetus	2	9	17	19
	Number of litters	1	3	3	5
Skeletal	<i>Variation</i>				
	Number of fetuses	48	49	20	22
	Litter % of fetus	72	84	63	69
	Number of litters	10	10	8	9
	<i>Malformation</i>				
	Number of fetuses	0	0	4	1
	Litter % of fetus	0	0	11	3
	Number of litters	0	0	3	1
	<i>All classifications</i>				
	Number of fetuses	48	49	21	22
	Litter % of fetus	72	84	68	70
	Number of litters	10	10	9	9

*p ≤ 0.05; **p ≤ 0.01

Summary of fetal abnormalities by finding with incidence, and affected fetuses

	No. of fetuses (% total)/ No. of litters (% total)			
Dose level (mg/kg/day)	0	0.3	3	30
Number of fetuses evaluated	128	116	68	64
Number of litters evaluated	10	10	9	10
Malformation types				
External				
<i>Face</i>				
Jaw, lower (mandible), small-malformation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	7**/ 5 (10%/ 56%)	1/ 1 (2%/ 10%)
Jaw, upper (maxilla), small-malformation	0/0 (0%/0%)	0/0 (0%/0%)	10**/6 (15%/ 67%)	1/1 (2%/ 10%)
<i>General</i>				
Entire subcutis, edema-malformation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	3/ 3 (6%/ 33%)	2/ 2 (4%/ 20%)
Localized subcutis, edema-variation	1/ 1 (1%/ 10%)	1/ 1 (1%/ 10%)	14*/ 6 (23%/ 67%)	15**/ 9 (24%/ 90%)
<i>Head/ neck</i>				
Head, domed-malformation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	2/ 2 (3%/ 20%)
<i>Limb</i>				
Forelimb, short-malformation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	1/ 1 (1%/ 10%)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 218881

Inluriyo (imlunestrant)

Hindlimb, hyperextension-malformation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	6*/ 4 (11%/ 44%)	4/ 3 (6%/ 30%)
Hindlimb, malrotated-malformation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	16**/ 6 (27%/ 67%)	11*/ 7 (15%/ 70%)
<i>Mouth</i>				
Tongue, protruding-malformation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	11**/ 6 (19%/ 67%)	2/ 2 (3%/ 20%)
<i>Tail</i>				
Tail, bent-malformation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	1/ 1 (1%/ 11%)	1/1 (2%/10%)
Tail, curled tail-malformation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	5/ 4 (9%/ 44%)	8/ 4 (11%/ 40%)
Fixed head				
<i>Brain</i>				
Perimeningeal space, large-malformation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	1/ 1 (4%/ 11%)	0/ 0 (0%/ 0%)
Perimeningeal space, red material-variation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	8*/ 5 (25%/ 56%)	9/4 (24%/ 44%)
Fresh visceral body abdominal				
<i>Kidney</i>				
<i>Ureter</i>				
Ureter, convoluted-variation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	2/ 2 (8%, 22%)
Ureter, dilation, moderate-variation	1/ 1 (2%, 10%)	4/ 2 (7%/ 20%)	1/ 1 (6%/ 11%)	3/ 3 (8%/ 33%)
Ureter, dilation, severe-variation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	1/ 1 (6%/ 11%)	3/ 2 (9%, 22%)
<i>Pelvic girdle</i>				
Pubis, incomplete ossification-variation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	1/ 1 (3%, 10%)
<i>Rib</i>				
Rib, nodule-variation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	4/ 2 (9%/ 20%)
Rib, incomplete ossification-variation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	1/ 1 (3%/ 10%)
Rib, wavy rib-variation	0/ 0 (0%/ 0%)	1/ 1 (2%/ 10%)	0/ 0 (0%/ 0%)	4/ 2 (10%/ 20%)
<i>Skull</i>				
Frontal, incomplete ossification-variation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	3/ 3 (11%, 33%)	3/ 2 (8%/ 20%)
Frontal, misshapen-malformation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	2/ 1 (3%, 11%)	1/ 1 (3%/ 10%)
Mandible, small-malformation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	2/ 2 (8%/ 22%)	2/ 0 (20%/ 0%)
Maxilla, small-malformation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	2/ 2 (8%/ 22%)	0/ 0 (0%/ 0%)

Inluriyo (imlunestrant)

Nasal, incomplete ossification-variation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	1/ 1 (3%/ 10%)
Parietal, incomplete ossification-variation	1/ 1 (1%/ 10%)	1/ 1 (2%/ 10%)	2/ 2 (7%/ 22%)	5/ 3 (12%/ 30%)
Supraoccipital, incomplete ossification-variation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	1/ 0 (11%/ 0%)	3/1 (8%/ 10%)
Zygomatic arch, incomplete ossification-variation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	1/ 1 (3%/ 10%)
<i>Sternebra</i>				
<i>Vertebra</i>				
Cervical arch, isolated ossification site-variation	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	0/ 0 (0%/ 0%)	1/ 1 (3%/ 10%)

*p ≤ 0.05; **p ≤ 0.01

5.5.5 Other Toxicology Studies

The Applicant's Position:

Impurities

Acceptance criteria for impurities in imlunestrant drug substance that are specified (b) (4) the ICH Q3A qualification threshold (b) (4) are toxicologically supported by the principles of ICH M7 and ICH S9, qualification in the 1-month rat qualification study or the 3-month repeat-dose monkey toxicology study, and genetic toxicity assessments consisting of an Ames assay, an in vitro micronucleus assay, or both.

Limits for ICH M7 Class 2 or 3 impurities are conservatively set based on an exposure of (b) (4) µg/day (b) (4) ppm) and a dosing duration of (b) (4) years, which maintains an excess cancer incidence of no more than 1 in 100,000 for the indicated advanced cancer population.

Consistent with the recommendations of ICH S9 and ICH M7, a limit of up to (b) (4) % of an impurity in drug substance may be justified based on the advanced cancer patient population as well as manufacturing considerations. The Ames-positive (b) (4) impurity (b) (4) can form at trace levels above (b) (4) of imlunestrant but has been consistently measured at below (b) (4) ppm (b) (4) % in imlunestrant tosylate. Due to manufacturing considerations, a limit of (b) (4) % is proposed for (b) (4).

The FDA's Assessment:

The FDA agrees that the proposed specification of (b) (4) % for (b) (4) is consistent with the recommendations of ICH S9 and ICH Q3B and is acceptable from a nonclinical perspective.

Version date: March 1, 2024 (ALL NDA/BLA reviews)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Inluriyo (imlunestrant)

The Applicant conducted genetic toxicology studies, bacterial reverse mutation assays (Ames) and/or in vitro micronucleus assays using human lymphoblastoid TK6 cells, on several impurities. The proposed specification limits of the following impurities (Table below) are the ICH Q3A/B guidelines, and some showed genotoxic potential. The proposed specification limits of the listed impurities in the drug substance and drug product were qualified by the GLP compliant 28-day or the 3-month repeat-dose toxicity study in rats. There are no concerns from a nonclinical perspective with these impurity specifications for the proposed advanced cancer indication.

Summary selected genotoxicity data for impurities (b) (4) **ICH Q3A/B levels**

Drug Substance (DS) and Drug Product (DP) Impurity	Proposed Specification Limit	Genetic Toxicology Assay and Results
(b) (4) (DS)	(b) (4)	Ames - negative
		In vitro micronucleus – positive
(DS)		In vitro micronucleus – positive
(DS)		In vitro micronucleus – negative
(DS)		In vitro micronucleus – negative
(DS)		Ames – negative
(b) (4) (DS)		In vitro micronucleus – negative
(DS)		In vitro micronucleus – negative
(DP)		In vitro micronucleus – negative
(DP)		In vitro micronucleus – negative

Data (presented by FDA):

In the 28-day toxicity study, rats were given imlunestrant lot# ALL-D00218-026 at 100 mg/kg (600 mg/m² Human Equivalent Dose [HED]) orally once daily for 28 days without any early mortalities. In the 3-month toxicity study, rats were given imlunestrant lot # CR-C18071754-J21001 at doses up to 150 mg/kg (900 mg/m² HED) without any early mortalities. Based on body surface area (mg/m²) in rats at the dose level that did not result in severe toxicities, these impurities were administered at higher levels than would be administered to patients receiving the recommended clinical dose of 400 mg (two 200 mg tablets) taken orally, once daily (400 mg/60 kg x (b) (4) mg/m²) at the proposed specification limits for these impurities in the imlunestrant drug substance and drug product and are considered qualified.

Inluriyo (implunestrant)

Phototoxicity

Implunestrant was positive for phototoxic potential in an in vitro study using BALB/c 3T3 mouse fibroblasts. In a rat phototoxicity study, implunestrant was mildly phototoxic to the skin, producing barely perceptible dermal redness following UV radiation exposure, with no evidence of ocular phototoxicity. The risk of clinically relevant phototoxicity is low because the dermal effects observed in rats were minimal at C_{max} exposures exceeding those at the human therapeutic dose by 36-fold.

The FDA's Assessment:

The FDA agrees with the Applicant's position that implunestrant showed phototoxic potential in vitro and was phototoxic to the skin in vivo.

The in vitro phototoxicity study and other toxicity studies to determine the potential ocular and skin irritancy were reviewed under IND 145311 and are summarized below.

20183318: The Applicant conducted a GLP-compliant study to evaluate the phototoxic potential of implunestrant as measured by the relative reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to implunestrant (0.032-100 $\mu\text{g/mL}$) in the presence or absence of ultraviolet radiation. Implunestrant showed mean photo effect (MPE) $> 0.15\%$ (0.495-0.823%); thus, it was considered phototoxic in the in vitro phototoxicity study in BALB/c 3T3 mouse fibroblasts.

19AD29.3500055: The bovine corneal opacity and permeability assay was used to assess the potential ocular irritancy of implunestrant to isolated bovine corneas. Three corneas were incubated in the presence of implunestrant (20% w/v) at 32°C for 4 hours. An in vitro score was determined for the test article based on the induction of opacity and permeability (to fluorescein) in the isolated bovine corneas. Based on in vitro score, implunestrant was not predicted to be an irritant.

#20183102: The Applicant conducted a GLP-compliant study to evaluate acute toxicity and irritant potential of implunestrant when administered by dermal route to Sprague Dawley rats as a single dose of 2000 mg/kg. The test article was administered dermally to approximately 10% of the body surface area. Rats were monitored for mortality, clinical signs, dermal observation, and body weight for 14 days post-dose. No mortality occurred during the study and no implunestrant-related clinical signs. No effects on body weight or gross pathology findings. Minimal implunestrant-related dermal irritation was noted in 1 male (Grade 1 erythema on Days 1 and 2) and all 5 females (Grade 1 erythema, flaking skin, and eschar on Days 1 to 12).

Additional in vivo phototoxicity study in female rats was reviewed and summarized below.

Study title/number: A GLP repeated dosage phototoxicity study to determine the effects of

Inluriyo (implunestrant)

oral administration of LY3484356 tosylate (implunestrant) on eyes and skin in pigmented rats/ 20405711

Methods: The objective of this GLP-compliant study was to determine the potential phototoxic effects of implunestrant on the eyes and skin of Long-Evans pigmented female rats when administered by oral gavage. Rats were administered 0, 5, 60, and 1000 mg/kg orally once daily for 4 days, followed by exposure to ultraviolet B, ultraviolet A, and visible light from a xenon lamp. This study also included rats administered implunestrant at 1000 mg/kg dose level without UV light exposure. The following parameters and endpoints were evaluated in this study; viability, clinical observations, dermal scoring, body weights and body weight gains, ophthalmology, bioanalysis, and toxicokinetic evaluation, and macroscopic and microscopic examinations.

Results:

- Clinical signs of toxicity related to implunestrant administration were observed during Days 4-7 in 4-5 out of 5 rats at 1000 mg/kg including hunched posture and thin appearance.
- At high dose of 1000 mg/kg following UV exposure, grade 1 erythema (light and dark pigment and red color skin) was observed in 3/5 rats on Days 5-7 at site 1 and 4/5 rats on Days 5-6 at site 2. Based on these results, implunestrant was phototoxic at a dose level of 1000 mg/kg.
- Compared to the VH control, there were no implunestrant-related ocular findings indicative of phototoxicity.
- A decrease in body weight was only observed in rats administered the highest dose of 1000 mg/kg during Days 5-7 (17-19% with UV light exposure and 13-16% without UV light exposure).
- Systemic exposure to implunestrant increased with increasing dose on Day 4. The increase in mean C_{max} and AUC_{0-8h} was less than dose proportional at 5, 60, and 1000 mg/kg on Day 4.

Table 5.1 Summary of toxicokinetic data on Day 4 in female rats

Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (hours)	$AUC_{0-8 hr}$ (h*ng/mL)
5	151	2	901
60	1540	2	9620
1000	5100	4	37600

At the clinical recommended dose of 400 mg once daily, the steady state C_{max} and AUC_{0-24} were 141 ng/mL (45% CV) and 2400 ng*h/mL (46% CV), respectively. Based on the toxicokinetic data from the in vivo phototoxicity study in female pigmented rats administered 1000 mg/kg

Inluriyo (imlunestrant)

imlunestrant orally once daily for 4 days, the exposure (AUC_{0-8hr}) was 37600 h*ng/mL (or 112800 h*ng/mL for AUC_{0-24hr}). Thus, exposure to 1000 mg/kg imlunestrant caused phototoxicity in rats at doses that were approximately 47 times the human AUC_{0-24} .

X

X

Wimolnut Manheng
Primary Reviewer

Nikolett Biel
Acting Team Lead

6 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:

The Applicant is seeking approval of imlunestrant 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 with disease progression following at least one line of endocrine therapy.

The clinical pharmacology review focused on the following key review issues:

1. Recommended dosage for the general population: 400 mg taken orally (PO), once daily (QD) taken on empty stomach, at least 2 hours before or 1 hour after food. The recommended dosage was selected based on safety, activity, pharmacokinetic (PK), and pharmacodynamic (PD) data from Studies EMBER and EMBER-2 and supportive exposure-response (E-R) analyses for safety and efficacy. Safety and efficacy of the recommended dosage in the intended patient population was demonstrated in EMBER-3. The recommendation for administration under fasting conditions is based on the positive food effect observed when imlunestrant was administered with a low-fat meal and the food conditions used in all three studies (i.e., imlunestrant at least 2 hours before or 1 hour after food).
2. Recommended dosage for patients with hepatic impairment (HI): 200 mg QD for patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. No dosage modification is recommended for patients with mild hepatic impairment (Child-Pugh A). Imlunestrant is hepatically metabolized, and data were available from population PK analysis (PopPK) and a dedicated HI study to support dosage recommendations for patients with HI.
3. Dosage modifications for patients receiving concomitant strong CYP3A inhibitors or inducers with imlunestrant (a substrate of CYP3A): Avoid concomitant use of imlunestrant with strong CYP3A inhibitors or inducers. However, if concomitant use cannot be avoided, reduce imlunestrant dosage to 200 mg QD when used with strong CYP3A inhibitors, or increase imlunestrant dosage to 600 mg QD when used with strong CYP3A inducers.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 218881. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and/or comments are summarized in **Table 6.1**.

Inluriyo (imlunestrant)

Table 6.1: Key Clinical Pharmacology Review Issues, Recommendations, and Comments	
Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of efficacy and safety comes from the randomized Phase 3 Study EMBER-3. In patients with ER+, HER2-, ESR1-mutated locally advanced or metastatic breast cancer, imlunestrant 400 mg QD resulted in an improvement in progression-free survival (PFS) as compared to the control arm (fulvestrant or exemestane) with hazard ratio for PFS of 0.62 and median PFS of 5.5 months in the imlunestrant arm compared to 3.8 months in the control arm. See Section 8 for details.
General dosing instructions	The recommended dosage is 400 mg PO QD, on an empty stomach (at least 2 hrs before or 1 hr after food).
Dosing in patient subgroups	• HI: The recommended dosage of imlunestrant for patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) HI is 200 mg QD. No dosage modification is recommended in patients with mild (Child-Pugh Class A) HI. • Renal impairment (RI): No dosage modification is recommended for patients with mild to moderate RI. The effect of severe renal impairment is unknown; however, renal clearance of imlunestrant is low. • ESR1 Mutations: No dosage modification is recommended based on ESR1 mutations. • Other Intrinsic Factors: No dosage modification is recommended based on age, sex, body weight, race, ethnicity, or UGT1A1 polymorphisms (e.g., UGT1A1*1/*28 or UGT1A1*28/*28).
Drug-Drug Interactions	• Imlunestrant as an Object: Imlunestrant is a CYP3A substrate. ○ Avoid concomitant use with strong CYP3A inhibitors. If concomitant use cannot be avoided, decrease the imlunestrant dosage to 200 mg QD. ○ Avoid concomitant use with strong CYP3A inducers. If concomitant use cannot be avoided, increase the imlunestrant dosage to 600 mg QD. • Imlunestrant as a Precipitant: ○ Imlunestrant inhibits P-gp and BCRP. Avoid concomitant use unless otherwise recommended in the Prescribing Information for P-gp or BCRP substrates where minimal concentration changes may lead to serious adverse reactions.
Labeling	Proposed labeling language was reviewed, corrected, and updated according to applicable FDA guidances. Overall, the proposed labeling language in the clinical pharmacology pertinent sections is generally acceptable upon the Applicant's agreement to the FDA revisions.

Inluriyo (imlunestrant)

Post-Marketing Requirements (PMRs) and Commitments (PMCs)	No clinical pharmacology PMRs or PMCs will be issued.
--	---

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Data:

Imlunestrant has been administered orally at doses ranging from

- 200 to 1200 mg QD in patients with ER+ locally advanced or MBC and ER+ recurrent, persistent, or metastatic EEC, and
- 200 to 800 mg QD in healthy participants.

Exposures of imlunestrant increased proportionally across the 200 mg to 1200-mg dose range.

Patients with ER+, HER2- locally advanced or MBC in the EMBER-3 Phase 3 pivotal study were administered 400 mg QD imlunestrant. The $C_{max,ss}$, $C_{min,ss}$, and $AUC_{0-24,ss}$ were 141 ng/mL (45% CV), 71.2 ng/mL (54% CV), and 2400 ng*h/mL (46% CV), respectively.

Absorption

- The absolute oral bioavailability of imlunestrant was 10.5%.
- Maximal plasma concentrations of imlunestrant were reached approximately 4 hours postdose with an elimination half-life of approximately 30 hours.

Distribution

- The mean apparent oral volume of distribution for imlunestrant was (b) (4) L in patients with locally advanced or MBC.
- The percent of imlunestrant bound in human plasma was greater than 99.9%.

Metabolism

- The primary clearance pathways involved in imlunestrant metabolism are sulfation, glucuronidation, and CYP3A4-mediated oxidation.

Elimination

- Following a single 400 mg (100 µCi) oral dose of [¹⁴C]-imlunestrant, the primary elimination route of imlunestrant-related radioactivity was via the feces with a mean

Inluriyo (implunestrant)

recovery of 97.3%. Negligible amounts were found in urine with a mean recovery of 0.3%.

- Implunestrant was the predominant component in feces, accounting for a mean of 61.8% of the radioactive dose.
- The mean apparent oral clearance of implunestrant was 166 L/h, and the mean elimination $t_{1/2}$ was estimated to be 30 hours in patients with locally advanced or MBC.

Exposure-response relationships

- Implunestrant exposure was a significant predictor of PFS. In the monotherapy setting, compared to the mean average exposure at 400 mg QD, patients with 2-fold higher exposures had approximately 5 months longer median PFS and patients with 2-fold lower exposures had approximately 2 months shorter median PFS.
- Increase in implunestrant exposures were not associated with increases in treatment-emergent AEs (SAEs, nausea, diarrhea, and fatigue).
- In the Phase 1 EMBER (Study J2J-MC-JZLA), implunestrant concentrations across the 200 mg to 1200 mg dose range had no clinically meaningful effect on QTc interval, with the upper bound of the 90% CI of the mean delta QTc at C_{max} of 400 mg equal to 3.87 msec (90% CI: -0.43, 3.87).

The Applicant's Position:

Overall, the clinical pharmacology profile of implunestrant is considered supportive of the proposed 400 mg QD dose.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the pharmacology and clinical pharmacokinetics of implunestrant with the following exception:

FDA disagrees with the exposure-PFS relationship conclusions that implunestrant exposure was a significant predictor of PFS.

During the review, the Applicant identified an error in the description of the exposure-PFS analysis data presented in the EMBER-3 Population PK/PD report. The dataset for the exposure-PFS analysis used an incorrect unit conversion. Correction of this error resulted in a change in interpretation of the exposure-PFS analysis results. Using the corrected dataset, there is no exposure-PFS relationship based on data from EMBER-3. Variations in implunestrant exposure among patients enrolled in the EMBER-3 trial who received implunestrant 400 mg QD do not affect PFS.

In addition, the exposure-PFS relationship was deemed not fully characterized as the E-R analysis for efficacy only includes data from one dose level.

The E-R analyses for safety were not impacted by the error. See **Section 19.4.2** for details.

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

Data:

Please see Section 6.2.1.

The Applicant's Position:

The recommended Phase 2 dose of 400 mg QD was established in the Phase 1 EMBER study based on PK, safety, and antitumor activity data. This study did not reach the maximum tolerated dose at the highest dose level of 1200 mg. An optimum biologically active dose of 400 mg was chosen based on PK data and EMBER-2 PD data for Phase 3 studies.

Based on the popPK analysis, after 400 mg QD doses, 87% of patients are predicted to exceed TEC_{80} over the entire dosing interval at steady state, indicating that biologically efficacious concentrations are achieved and sustained at this dose in the majority of patients. After 200 mg QD doses, 45% of patients are predicted to exceed TEC_{80} over the entire dosing interval at steady state.

The 400 mg QD dose in EMBER demonstrated a manageable safety profile with a lower incidence of nausea and diarrhea compared with higher doses. Finally, among the imlunestrant monotherapy cohorts, 4 out of 6 partial responses were observed at the 400-mg dose level indicating clinical activity.

In parallel with EMBER-3, the EMBER-2 window-of-opportunity study (Neven et al. 2024) evaluated the on-target PD effect of imlunestrant at 3 dose levels (200 to 800 mg QD) in postmenopausal women with early-stage breast cancer. Though similar on-target effects with substantial ER degradation were observed across all doses, the 200 mg QD dose had the lowest rate of complete cell cycle arrest and the 800 mg QD dose had the highest incidence of nausea and diarrhea. Thus, the EMBER-2 data supported the ongoing enrollment in EMBER-3 with 400 mg QD and the dose reduction strategy of 200 mg QD.

Exposure-response analyses identified a wide therapeutic window for imlunestrant in patients with ABC. Exposures up to 2.5-fold above and 2-fold below those achieved with 400 mg QD retain both safety and efficacy. The 400-mg dose allows

1. flexibility to accommodate a wide range of intrinsic or extrinsic patient factors, such as mild hepatic impairment, and
2. dose reductions for safety while still providing therapeutic benefit.

The FDA's Assessment:

Inluriyo (imlunestrant)

FDA agrees that the proposed recommended imlunestrant dosage of 400 mg PO QD on an empty stomach is appropriate for the indicated population.

In EMBER-3, the proposed recommended dosage demonstrated a favorable benefit-risk profile compared to the control arm (fulvestrant or exemestane) in patients with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer. Imlunestrant improved median PFS by 1.7 months (5.5 months for imlunestrant vs 3.9 months for control arm with HR of 0.62) in the proposed patient population with an acceptable safety profile. In EMBER-3, permanent discontinuation, dosage interruption, and dosage reduction of imlunestrant due to an AE occurred in 4.6%, 10%, and 2.4% of patients, respectively. Refer to **Section 1.3** for additional assessment of the benefit-risk.

With regard to safety, the MTD was not reached at up to 1,200 mg QD in EMBER and there were no apparent E-R relationships for safety of imlunestrant. Higher rates of nausea and diarrhea were observed for 800 mg QD compared to 200 and 400 mg QD in EMBER-2, despite the lack of E-R relationships for safety, which contributed to the selection of 400 mg QD for further evaluation.

With regard to activity, there was no apparent dose-response relationship for ORR in patients treated with imlunestrant monotherapy in EMBER (**Table 6.2**), similar ER degradation was observed across 200 mg to 800 mg QD dosages in EMBER-2, and there was no apparent E-R relationship for PFS among patients treated with 400 mg QD in EMBER-3.

Table 6.2: ORR by Imlunestrant Monotherapy Dose Level in EMBER

	200 mg (n=14)	400 mg (n=14)	600 mg (n=12)	800 mg (n=14)	1,200 mg (n=2)	Total (n=56)
	n (%)					
Complete Response	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Partial Response	0 (0)	3 (21.4)	0 (0)	0 (0)	1 (50)	4(7.1)

Source: Table 8.158 in J2J-MC-JZLA-04 EMBER Clinical Study Report

The proposed administration of imlunestrant without food is appropriate given that administration of imlunestrant 400 mg with a low-fat meal increased C_{max} 3.6-fold and AUC_{0-inf} 2-fold as compared to administration under fasting conditions (Refer to **Section 6.3.2.4** for details). In addition, all three studies were conducted using the proposed food conditions (i.e., imlunestrant at least 2 hrs before or 1 hr after food); therefore, the observed safety and efficacy in EMBER-3 is representative of the recommended dosage and administration instructions.

6.2.2.2 Therapeutic Individualization

Data:

Intrinsic factors

Inluriyo (implunestrant)

In a hepatic impairment (determined by Child-Pugh classification) clinical pharmacology study (Study J2J-MC-JZLG), mild hepatic impairment did not have a significant effect on implunestrant exposures. Moderate hepatic impairment increased the $AUC_{(0-\infty)}$ by 122% and $AUC_{(0-\infty),u}$ by 82% with no significant difference on C_{max} . Severe hepatic impairment increased the dose-normalized $AUC_{(0-\infty)}$ by 206% and dose-normalized $AUC_{(0-\infty),u}$ by 133% with no significant difference on dose-normalized C_{max} . Dose reductions to 200 mg QD in patients with moderate and severe hepatic impairment are recommended, since these chronic conditions may lead to increased accumulation of implunestrant. Moreover, the exposure increase in severe hepatic patients is beyond the range of exposures over which the exposure-safety analyses were conducted.

Following a single radiolabeled 400-mg dose of implunestrant to healthy participants, approximately 97.3% of the dose was recovered in feces (19.8% unchanged) and 0.3% in urine, suggesting implunestrant is not cleared renally. Based on a popPK analysis, mild and moderate renal impairment does not affect implunestrant PK. There were insufficient patient numbers to draw clear conclusions regarding the effect of severe renal impairment and moderate and severe hepatic impairment on the PK of implunestrant.

Based on a popPK analysis, implunestrant disposition is not affected by

- serum albumin (range: 22.0 to 55.0 g/L)
- age (range: 28 to 95 years)
- ethnicity (180 Hispanic [17%], 777 non-Hispanic [74%])
- race (667 White [64%], 50 Black or African American [5%], 240 Asian [23%], 93 others/missing [9%])
- mild and moderate renal impairment (448 normal [43%], 482 mild [46%] 108 moderate [10%], 2 severe [$<1\%$]) classified by estimated glomerular filtration rate, and
- mild hepatic impairment (842 normal [81%], 201 mild [19%]).

Based on a popPK analysis, implunestrant disposition is statistically significantly affected by

- body weight (range: 36 to 145 kg), and
- study population (MBC: N = 914 [87%], EEC: N = 72 [6.9%], healthy participants: N = 64 [6.1%]).

However, PK simulations performed for a range of body weights and between patients and healthy participants showed a large degree of overlap between the PK profiles, illustrating the minimal impact body weight or study population have on the PK profile when considering the degree of natural PK variability (CL/F interindividual variability = 51%) in the analysis population.

Inluriyo (implunestrant)

In a retrospective analysis examining the effect of UGT1A1 polymorphism on implunestrant PK, results showed that UGT1A1 genetic polymorphisms with reduced function did not affect implunestrant exposures.

The primary clearance pathways involved in implunestrant metabolism are sulfation, glucuronidation, and CYP3A4-mediated oxidation. There are no clinically relevant genetic polymorphisms of cytosolic sulfotransferases or CYP3A4.

Extrinsic factors

Based on a popPK analysis, implunestrant disposition is not affected by formulation or the presence of abemaciclib or omeprazole.

In Study J2J-MC-JZLD, a strong CYP3A4 inhibitor (itraconazole) increased implunestrant $AUC_{(0-\infty)}$ by 111%, and a strong CYP3A4 inducer (carbamazepine) decreased implunestrant $AUC_{(0-\infty)}$ by 42.2%. In Study J2J-MC-JZLI, a statistically significant decrease in the $AUC_{(0-\infty)}$ of implunestrant of 13.1% was observed when implunestrant was dosed in the presence of quinidine (P-gp inhibitor). This decrease in implunestrant exposure was not considered clinically meaningful.

Statistically significant increases in $AUC_{(0-t_{last})}$, $AUC_{(0-\infty)}$, and C_{max} of implunestrant of 99%, 104%, and 255%, respectively, were observed following a single oral dose of 400 mg implunestrant in the fed state (low-fat meal) compared to in the fasted state. The increase in C_{max} observed in the presence of a low-fat meal was beyond the exposure range studied in the clinical development of implunestrant. Therefore, implunestrant should be dosed in the fasted state.

The Applicant's Position:

Intrinsic factors requiring dose modification or adjustment

Implunestrant dose reduction by 200 mg is recommended in moderate and severe hepatic impairment.

Extrinsic factors requiring dose modification or adjustment

Strong CYP3A inhibitors should be (b) (4). Strong CYP3A inducers should be avoided, and alternative agents considered when coadministered with implunestrant. If concomitant use is unavoidable, implunestrant dose should be increased by 200 mg QD since there was a positive exposure-efficacy relationship.

Implunestrant should be dosed in the fasted state. Patients should not eat at least (b) (4) before and at least (b) (4) after taking implunestrant, which are the conditions under which EMBER, EMBER-2, and EMBER-3 were carried out.

Inluriyo (implunestrant)

The FDA's Assessment:

FDA agrees with the Applicant regarding therapeutic individualization with the following exceptions:

Avoid concomitant use with strong CYP3A inhibitors. If concomitant use cannot be avoided, decrease the implunestrant dosage to 200 mg QD.

Implunestrant inhibits both P-gp and BCRP which may result in increased exposure and increased adverse reactions of the substrates of these transporters. Avoid concomitant use of P-gp and BCRP substrates unless prescribing information for P-gp and BCRP substrates recommends specific dosage modifications.

Additional drug-drug interaction (DDI) studies supported lack of clinically significant interaction for implunestrant as a precipitant with substrates of CYP2C8, CYP2C19, CYP2D6, and CYP3A.

No clinically significant differences in the pharmacokinetics of implunestrant were observed when used concomitantly with omeprazole (gastric acid-reducing agent) or quinidine (P-gp inhibitor).

For additional information, refer to **Section 6.3.2.3** for intrinsic patient factors, **Section 6.3.2.4** for food effect and DDIs, and **Section 19.4.1** for PopPK analysis.

6.2.2.3 Outstanding Issues

The Applicant's Position:

There are no known outstanding issues.

The FDA's Assessment:

FDA agrees with the Applicant that there are no outstanding clinical pharmacology issues.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Data:

Please see Section 6.2.1.

The Applicant's Position:

Implunestrant clinical pharmacology has been well characterized in a series of clinical studies in healthy participants and in patients with HR+, HER2- ABC or MBC to support the appropriateness of the proposed implunestrant dose regimen.

Exposure-response analyses to evaluate the range of safe and efficacious exposures of implunestrant in patients with locally advanced or MBC identified a wide therapeutic window for

Inluriyo (imlunestrant)

imlunestrant. Changes in exposure from 400 mg QD that increase imlunestrant exposure by 2.5-fold or decrease exposure by 2-fold are not expected to have a major impact on safety or efficacy. This allows flexibility for the physician/patient in accommodating a wide range of intrinsic/extrinsic patient factors as well as allowing the proposed dose reductions for safety while still allowing some treatment benefit.

Imlunestrant can be coadministered with weak and moderate CYP3A inhibitors, weak and moderate CYP3A inducers, P-gp inhibitors and agents that modify gastric pH (for example, proton-pump inhibitors) without dose modification. Imlunestrant can also be coadministered with CYP2C8, CYP2C19, and CYP3A substrates. Intrinsic and extrinsic factors requiring imlunestrant dose adjustments or modifications are discussed in Section 6.2.2.2. (b) (4), BCRP, and P-gp substrates for which a small increase in concentration could lead to significant AEs.

The FDA's Assessment:

FDA agrees that imlunestrant clinical pharmacology has been well characterized. As described in Section 6.2.1, no significant E-R relationships for efficacy were identified in the indicated patient population; however, these results should be interpreted with caution.

FDA disagrees with the recommendation that (b) (4)

(b) (4). Imlunestrant inhibits P-gp and BCRP which may result in increased exposure and increased adverse reactions of the substrates of these transporters. Avoid concomitant use of P-gp and BCRP substrates with imlunestrant unless prescribing information for these substrates recommends specific dosage modifications.

The FDA recommended (b) (4)

(b) (4). A small increase in dextromethorphan exposure (a sensitive CYP2D6 substrate) was observed in a clinical DDI study. However, given the magnitude of dextromethorphan exposure change and the higher sensitivity of dextromethorphan compared to other CYP2D6 substrates, inhibition of CYP2D6 is unlikely to be clinically significant for other CYP2D6 substrates.

See Section 6.3.2 and Section 19.4 for additional information.

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

The evidence of effectiveness for EMBER-3 is also discussed in Section 8.

Inluriyo (imlunestrant)

The Applicant's Position:

Yes.

Results from popPK and exposure-response analyses showed that the proposed dose and dose intensity of imlunestrant lead to an efficacy benefit in the proposed label population. AEs can be managed through dose interruptions and dose reductions as outlined in the proposed labeling. Therefore, imlunestrant has a positive benefit-risk ratio at the proposed daily dose regimen.

The FDA's Assessment:

Refer to Section 8.1 for assessment of the evidence of effectiveness for imlunestrant. FDA agrees that the totality of data support the proposed dosage of imlunestrant 400 mg QD for the indicated patient population. As described in **Section 19.4.2**, the corrected E-R analysis for efficacy did not demonstrate a relationship between imlunestrant exposure and PFS.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

Please see Section 6.2.2 and Section 6.2.2.1.

The Applicant's Position:

Yes.

The proposed 400 mg QD dose is effective and generally well tolerated in the proposed patient population with no dosing difference based on demographic characteristics. No new safety findings were identified in Phase 3 clinical development with AEs being effectively managed through dose interruption or reduction, or standard clinical practice. Safety data were consistent across clinical trials and with the mechanism of action. AEs were transient and reversible upon imlunestrant discontinuation. See Section 8.2.

The FDA's Assessment:

FDA agrees that imlunestrant 400 mg PO QD without food (taking imlunestrant at least 2 hours before food, or 1 hour after food) is an acceptable dosage for the indicated patient population. See **Section 6.2.2.1** for additional information.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:

Please see Section 6.2.2, Section 6.2.2.1, and Section 8.

Inluriyo (imlunestrant)

The Applicant's Position:

Yes.

Dose adjustment of imlunestrant to 200 mg QD is recommended in moderate and severe hepatic impairment.

The FDA's Assessment:

I. Age, Race/Ethnicity, Body Weight

FDA agrees that no clinically significant differences in the pharmacokinetics of imlunestrant were observed based on age (28 to 95 years), race (64% White, 23% Asian, and 5% Black or African American), ethnicity (74% non-Hispanic or Latino, 17% Hispanic or Latino), body weight (36 to 145 kg), or UGT1A1 genetic polymorphisms (e.g., UGT1A1*1/*28 or UGT1A1*28/*28; see below for additional information).

Based on a popPK analysis, body weight (range 36 to 145 kg) showed statistically significant impact on clearance and volume parameters through allometric relationships. Patients at the 95th percentile weight (100.4 kg) had 40% higher clearance versus median weight (68.2 kg), while 5th percentile patients (48.5 kg) had 26% lower clearance. However, this impact is not considered clinically significant given the flat E-R relationships for efficacy and safety. See the FDA's Assessment in **Section 19.4.1** for details.

II. Patients with Renal Impairment

Based on PopPK analysis, there are no clinically significant differences in pharmacokinetics of imlunestrant in patients with mild to moderate (eGFR 30 – 89 mL/min calculated based on CKD-EPI equation) RI as compared to patients with normal renal function (eGFR $\geq$ 90 mL/min). The effect of severe (eGFR 15- 29 mL/min) RI and patients on dialysis on imlunestrant pharmacokinetics is unknown. However, urinary elimination of imlunestrant was 0.3% of the total radioactivity excreted indicating limited renal clearance. Therefore, a dedicated study in subjects with severe RI is not warranted.

III. Patients with Hepatic Impairment

There were no clinically significant differences in the pharmacokinetics of imlunestrant in subjects with mild hepatic impairment (Child-Pugh A) based on the popPK analysis.

Imlunestrant AUC_{0-inf} increased 2.2-fold in subjects with moderate hepatic impairment (Child-Pugh B) and dose-normalized AUC increased 3.1-fold in subjects with severe hepatic impairment (Child-Pugh C) compared to subjects with normal hepatic function; see **Table 6.3**.

FDA agrees that the recommended imlunestrant dosage of 200 mg QD is appropriate for patients with moderate or severe HI and that no dosage modification is recommended for patients with mild HI. Based on the observed increase in imlunestrant exposure, the recommended dosage of 200 mg QD is likely to result in higher imlunestrant exposure in patients with severe HI

Inluriyo (imlunestrant)

compared to patients with normal hepatic function who receive 400 mg QD. Based on the available safety data from imlunestrant dosages up to 1,200 mg QD and the E-R safety analyses, the increase in exposure in patients with severe HI is still expected to remain within the safety margins; however, FDA recommends monitoring for increased adverse reactions in patients with severe HI given the increased rates of GI toxicities (nausea and diarrhea) observed at imlunestrant 800 mg QD compared to imlunestrant 400 mg QD in EMBER-2.

Table 6.3: The effect hepatic impairment on Imlunestrant PK based on Child-Pugh Classification

Parameter (units)	Hepatic Function	n	Geometric Least Square Mean (GLSM)	Ratio of GLSM (Impairment: Normal), 90% C.I.
C _{max} (ng/mL)	Normal (Reference)	9	57.9	---
	Mild	6	74.8	1.29 (0.82 - 2.02)
	Moderate	6	87.6	1.51 (0.97 - 2.37)
AUC _∞ (ng·hr/mL)	Normal (Reference)	9	2,010	---
	Mild	6	2,470	1.23 (0.83 - 1.84)
	Moderate	6	4,460	2.22 (1.49 - 3.32)
Dose Normalized C _{max} (ng/mL/mg)	Normal (Reference)	9	0.14	---
	Severe	6	0.23	1.62 (0.97 - 2.70)
Dose Normalized AUC _∞ (ng·hr/mL/mg)	Normal (Reference)	9	5	---
	Severe	6	15.3	3.06 (1.9 - 4.91)

Source: JZLG study report, Table JZLG.5.3. Of note: The reviewer-calculated PK parameters are in agreement with Applicant's analysis.

IV. ESRI Mutations

In EMBER-3, circulating tumor DNA (ctDNA) was analyzed using the FDA-approved Guardant360 CDx to detect the presence of *ESR1* mutations at baseline prior to initiating study treatment. A total of 37.9% (323/853) of patients had an *ESR1* mutation detected. Among these patients, the four most common *ESR1* mutations detected were D538G (21.8%), Y537S (12.9%), Y537N (9.5%), and E380Q (7.7%) (**Table 6.4**). Some patients had more than one *ESR1* mutation

Inluriyo (imlunestrant)

detected. The prevalence of *ESR1* mutation detected and the type of mutations were generally balanced across treatment arms.

FDA conducted exploratory analyses assessing the impact of *ESR1* mutations on imlunestrant efficacy in the *ESR1* mutation-detected (*ESR1*m-detected) population. Hazard ratios for PFS of imlunestrant vs control treatment were estimated from Cox proportional hazards model. Participants carrying single *ESR1* mutations demonstrated greater treatment effects for imlunestrant compared to control than those carrying multiple *ESR1* mutations. Participants carrying the D538G and Y537N mutations showed the largest treatment effects [(D538G: HR=0.52, 95% CI: 0.31-0.90, p-value=0.0181) and (Y537N: HR=0.40, 95% CI: 0.09-1.73, p-value = 0.2213)], while participants carrying only the Y537S mutation showed the smallest treatment effect (HR=0.79, 95% CI: 0.40-1.56, p-value=0.4954). These results suggest that while the HR point estimates were < 1 across the evaluated *ESR1* mutations, the magnitude of benefit of imlunestrant compared to standard of care (SOC) may differ depending on the *ESR1* mutation profile (**Table 6.5**). There are several limitations to these subgroup analyses. First, the study was not designed to assess treatment effect within these subgroups, and these exploratory analyses were not stratified for other factors such as prior treatments or visceral metastasis. Second, the number of participants were small in some of these subgroups. Therefore, although these results suggest variable response based on *ESR1* mutations, a broad indication across different *ESR1* mutations is justified. Further exploration of these relationships with other *ESR1*-targeting drugs is warranted.

Table 6.4: Frequency of *ESR1* Mutations in the *ESR1*m-Detected Population in EMBER-3 trial

Mutation, n (%)	Arm A Imlunestrant N=318	Arm B TPC N=323	Arm C Imlun + Abema N=212	Total N=853
<i>ESR1</i> mutation detected	138 (43.4)	118 (36.5)	67 (31.6)	323 (37.9)
D538G	85 (26.7)	66 (20.4)	35 (16.5)	186 (21.8)
Y537S	41 (12.9)	46 (14.2)	23 (10.8)	110 (12.9)
Y537N	32 (10.1)	31 (9.6)	18 (8.5)	81 (9.5)
E380Q	27 (8.5)	20 (6.2)	19 (9.0)	66 (7.7)
L536H	6 (1.9)	11 (3.4)	7 (3.3)	24 (2.8)
Y537C	6 (1.9)	10 (3.1)	6 (2.8)	22 (2.6)
L536P	4 (1.3)	4 (1.2)	8 (3.8)	16 (1.9)
S463P	4 (1.3)	4 (1.2)	6 (2.8)	14 (1.6)
V422del	1 (0.3)	3 (0.9)	6 (2.8)	10 (1.2)
L536R	3 (0.9)	1 (0.3)	5 (2.4)	9 (1.1)
L536K	3 (0.9)	0	0	3(0.4)
L536Q	0	1 (0.3)	1 (0.5)	2 (0.2)

Inluriyo (imlunestrant)

Y537D	0	2 (0.6)	0	2 (0.2)
D538E	0	1 (0.3)	0	1 (0.1)
D538N	0	1 (0.3)	0	1 (0.1)
E380K	1 (0.3)	0	0	1 (0.1)
L469V	0	1 (0.3)	0	1 (0.1)

Source: FDA Reviewer exploratory analysis based on ADSL dataset. *ESR1* = estrogen receptor 1; *ESR1m* = estrogen receptor 1 mutation; TPC = the physician's choice of endocrine therapy of fulvestrant or exemestane; Imlun = imlunestrant; Abema = abemaciclib; N = Number of patients; n = number of patients in the specific category

Table 6.5: Subgroup Analysis of Progression-free Survival – *ESR1m*-detected Biomarker Subpopulations in EMBER-3

<i>ESR1m</i> subpopulation	Arm A Imlunestrant Events/N (%) Median PFS, months (95% CI)	Arm B TPC Events/N (%) Median PFS, months (95% CI)	HR (95% CI) p-value
Single <i>ESR1</i> mutation detected	72/95 (75.8) 5.59 (4.67, 9.26)	64/73 (87.7) 3.78 (2.76, 5.52)	0.57 (0.40, 0.80) p-value = 0.0012*
Multiple <i>ESR1</i> mutations detected	37/43 (86.0) 3.71 (1.91, 9.13)	38/45 (84.4) 4.83 (3.68, 6.64)	0.71 (0.43, 1.16) p-value = 0.1658
D538G detected only (single gene only)	37/48 (77.1) 5.59 (4.34, 10.38)	24/27 (88.9) 4.63 (1.97, 5.42)	0.52 (0.31, 0.90) p-value = 0.0181*
Y537S detected only (single gene only)	15/18 (83.3) 3.91 (1.77, 9.49)	21/25 (84.0) 3.71 (1.87, 5.55)	0.79 (0.40, 1.56) p-value = 0.4954
Y537N detected only (single gene only)	6/7 (85.7) 10.94 (1.87, 25.43)	5/5 (100.0) 6.70 (3.25, 9.10)	0.40 (0.09, 1.73) p-value = 0.2213
E380Q detected only (single gene only)	9/16 (56.3) 6.51 (3.65, NE)	8/9 (88.9) 3.71 (1.84, 17.58)	0.62 (0.23, 1.69) p-value = 0.3547

Source: FDA Reviewer exploratory analysis based on ADSL and ADTTE datasets. *ESR1* = estrogen receptor 1; *ESR1m* = estrogen receptor 1 mutation; TPC = the physician's choice of endocrine therapy of fulvestrant or exemestane; Imlun = imlunestrant; Abema = abemaciclib; N = Number of patients; n = number of patients in the specific category; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval

V. Impact of UGT1A1 polymorphisms

In vitro studies demonstrated that uridine 5'-diphospho-glucuronosyltransferase (UGT)1A1 is involved in the clearance of imlunestrant, however, the relative contribution of various UGT enzymes toward the overall clearance of imlunestrant remains undetermined. The sponsor performed a retrospective exploratory analysis to explore the association of *UGT1A1* polymorphisms with imlunestrant exposure using a subset of participants enrolled in EMBER-3 and healthy women of childbearing potential enrolled in Study J2J-MC-JZLD. Paired genetic and PK data were available for a total of 137 subjects. The following genotypes were observed: UGT1A1*1/*1, UGT1A1*1/*28, UGT1A1*28/*28, UGT1A1*36/*28, UGT1A1*1/*37, and

Inluriyo (imlunestrant)

UGT1A1*28/*37. Only reduced function haplotypes (*6, *28, *37) were included in the analysis. Individuals presenting with UGT1A1*36/*28 genotype were excluded from analysis because *36 is an increased function allele. Individuals with one reduced function haplotype were grouped together (UGT1A1*1/*37 was grouped with UGT1A1*1/*28) as intermediate metabolizers, and individuals with two reduced function haplotypes were grouped together (UGT1A1*28/*37 was grouped with UGT1A1*28/*28) as poor metabolizers.

Results showed that *UGT1A1* genotype does not have an apparent effect on dose-normalized exposure (i.e., C_{max} and AUC) (**Table 6.6**). Safety data suggested that the safety profiles for participants who were *UGT1A1* extensive metabolizers were comparable to participants who were intermediate and poor metabolizers, consistent with the findings that UGT1A1 polymorphisms did not affect imlunestrant exposure.

Table 6.6: Summary of Dose-Normalized C_{max} and AUC₀₋₂₄ by *UGT1A1* Genotype – Studies JZLA and JZLD

UGT1A1 Phenotype	N	Median (range)	Geometric Mean (CV%)	
		T _{max} (h)	Dose Normalized C _{max} (ng/mL/mg)	Dose Normalized Day 1 AUC ₀₋₂₄ (ng*h/mL/mg)
Extensive Metabolizer	56	4.00 (1.00-36.00)	0.152 (75)	2.10 (63)
Intermediate Metabolizer	61	4.00 (1.83-36.00)	0.152 (63)	2.08 (60)
Poor Metabolizer	18	4.02 (2.00-8.00)	0.126 (76)	1.80 (64)

Source: Applicant's data. Extensive metabolizer: an individual carrying two reference or wild-type alleles (e.g., *1/*1). Intermediate metabolizer: an individual carrying one reference function (*1) and one decreased function allele (*6, *28, *37). Poor metabolizer: an individual carrying two decreased function alleles (*6, *28, *37). Abbreviations: AUC₀₋₂₄ = area under the drug plasma concentration versus time curve from time zero to 24 hours postdose; C_{max} = maximum drug plasma concentration; CV = coefficient of variation; T_{max} = time to maximum concentration; N = number of patients; h = hour; ng = nanogram; mL = milliliters; mg = milligram

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

Please see Section 6.2.2.2.

The Applicant's Position:

Inluriyo (imlunestrant)

Yes.

Strong CYP3A4 inducers should be avoided, and alternative agents considered when coadministered with imlunestrant. If concomitant use is unavoidable, imlunestrant dose should be increased by 200 mg QD since there was a positive exposure-efficacy relationship.

Imlunestrant should be dosed in the fasted state. Patients should not eat at least (b) (4) before and at least (b) (4) after taking imlunestrant.

Strong CYP3A4 inhibitors should be (b) (4) BCRP, and P-gp substrates for which a small increase in concentration could lead to significant AEs.

The FDA's Assessment:

I. Food effect:

Administration of a single dose of imlunestrant 400 mg with a low-fat meal (approximately 475 calories with 13% fat, 16% protein, and 71% carbohydrates) increased imlunestrant C_{max} 3.6-fold and AUC_{0-inf} 2-fold as compared to administration under fasting conditions. Therefore, FDA agrees with the Applicant that imlunestrant should be administered in the fasted state (at least 2 hours before and at least 1 hour after food). In EMBER-3, patients were instructed to take imlunestrant at least 2 hours before or 1 hour after food (i.e., the recommended administration instructions) therefore, EMBER-3 evaluated safety of imlunestrant under the recommended administration instructions with regard to food.

II. Drug-Drug Interactions:

1. Effects of Other Drugs on Imlunestrant

- a) **Strong CYP3A Inhibitors:** Co-administration of imlunestrant with itraconazole 200 mg (strong CYP3A inhibitor) for multiple days, increased imlunestrant AUC_{0-inf} 2.1-fold and increased C_{max} 1.9-fold (**Table 6.7**). Therefore, FDA disagrees with the Applicant's proposal of (b) (4) when imlunestrant is administered with a strong CYP3A inhibitor. Dosage modification for concomitant use with strong CYP3A inhibitors should be included in the labeling with the recommendation to avoid concomitant use of strong CYP3A inhibitors and if concomitant use is unavoidable, decrease the imlunestrant dosage to 200 mg once daily.

Table 6.7: The effect of CYP3A inhibitors (itraconazole, 200 mg for multiple days) on Imlunestrant PK

Study JZDL Cohort 3
N=20

Inluriyo (implunestrant)

Least-Square Geometric Means, Ratio and 90% Confidence Intervals			
Parameter (units)	Implunestrant alone	Implunestrant + Itraconazole	Ratio (90% C.I.)
AUC _∞ (ng·hr/mL)	1,415	3,116	2.11 (1.77-2.53)
C _{max} (ng/mL)	30.3	56.7	1.87 (1.62-2.17)

Source: JZLD-04 study report, Table JZLD.5.12. Of note: The reviewer-calculated PK parameters are in agreement with Applicant's analysis.

- b) **Strong CYP3A inducers:** Co-administration of implunestrant with carbamazepine, (100 mg BID on Days 6-8, 200 mg BID on Days 9-11, 300 mg BID Days 12-22, 300 mg QD on Day 23) (strong CYP3A inducer) for multiple days decreased implunestrant AUC_{0-inf} by 42% and decreased C_{max} by 29% (**Table 6.8**). FDA agrees with the Applicant's position and labeling proposal to avoid concomitant use of strong CYP3A inducers and if concomitant use is unavoidable increase implunestrant dosage to 600 mg QD.

Table 6.8: The effect of CYP3A inducers (carbamazepine, 300 mg for multiple days) on Implunestrant PK

Effect of CYP3A inducers (carbamazepine, 300 mg for multiple days) on Implunestrant PK			
Study JZDL Cohort 4			
N=29			
Least-Square Geometric Means, Ratio and 90% Confidence Intervals			
Parameter (units)	Implunestrant alone	Implunestrant + Carbamazepine	Ratio(90% C.I.)
AUC _∞ (ng·hr/mL)	1,952	1,129	0.58 (0.49-0.69)
C _{max} (ng/mL)	49.6	35.2	0.71 (0.60-0.84)

Source: JZLD-04 study report, Table JZLD.5.19. Of note: The reviewer-calculated PK parameters are in agreement with Applicant's analysis.

- c) **Other Drugs:** No clinically significant differences in the pharmacokinetics of implunestrant were observed when used concomitantly with omeprazole (gastric acid-reducing agent) or quinidine (P-gp inhibitor). Additional studies with weak or

Inluriyo (imlunestrant)

moderate CYP3A inhibitors or inducers are not warranted as the magnitude of exposure change is expected to be less than that observed with strong CYP3A inhibitors/inducers and not clinically significant.

2. Effect of Imlunestrant on Other Drugs:

- a) **P-gp substrates:** Digoxin (P-gp substrate) AUC_{0-inf} increased 1.4-fold and C_{max} increased 1.6-fold following concomitant use of single dose imlunestrant 400 mg (**Table 6.9**).
- b) **BCRP substrates:** Rosuvastatin (BCRP substrate) AUC_{0-inf} increased 1.5-fold and C_{max} increased 1.7-fold following concomitant use of single dose imlunestrant 400 mg (**Table 6.10**).

FDA disagrees with the Applicant's proposal

(b) (4)

. Concomitant use of P-gp and BCRP substrates should be avoided unless otherwise recommended in the Prescribing Information of these substrates given that concomitant use with imlunestrant leads to an increase in exposure of these substrates which may increase the risk of adverse reactions related to substrate exposure.

Table 6.9: The Effect of Imlunestrant on PK of P-gp Substrates (Digoxin, 0.25 mg)

Study JZLI			
N=27			
Least-Square Geometric Means, Ratio and 90% Confidence Intervals			
Parameter (units)	Digoxin	Digoxin + Imlunestrant	Ratio 90% C.I.
AUC_{∞} (ng·hr/mL)	20.2	28	1.39 (1.22-1.59)
C_{max} (ng/mL)	1.17	1.88	1.6 (1.34-1.91)
C_{max} (ng/mL)	3.05	5.03	1.65 (1.28-2.13)

Source: JZLI-04 study report, Table JZLI.5.28. Of note: The reviewer-calculated PK parameters are in agreement with Applicant's analysis.

Table 6.10: The Effect of Imlunestrant on PK of BCRP Substrates (Rosuvastatin, 10 mg)

Study JZLI			
N=27			
Least-Square Geometric Means, Ratio and 90% Confidence Intervals			

Inluriyo (implunestrant)

Parameter (units)	Rosuvastatin	Rosuvastatin + Implunestrant	Ratio (90% C.I.)
AUC _∞ (ng·hr/mL)	29	43.4	1.49 (1.14 -1.97)
C _{max} (ng/mL)	3.05	5.03	1.65 (1.28-2.13)

Source: JZLI-04 study report, Table JZLI.5.27. Of note: The reviewer-calculated PK parameters are in agreement with Applicant's analysis.

- c) **CYP2D6 substrates:** Dextromethorphan (sensitive CYP2D6 substrate) AUC_{0-inf} increased 1.3-fold and C_{max} increased 1.4-fold following concomitant use of single dose of implunestrant 800 mg. Based on evaluation of DDI studies using dextromethorphan and other CYP2D6 substrates, dextromethorphan is a more sensitive substrate of CYP2D6 than other CYP2D6 substrates. Therefore, based on the observed increase in dextromethorphan exposure following concomitant use of implunestrant, implunestrant is unlikely to result in a clinically significant increase in exposure for CYP2D6 substrates. FDA recommended (b) (4)
- d) **Other Drugs:** There were no clinically significant differences in the pharmacokinetics of midazolam (CYP3A substrate) or repaglinide (CYP2C8 substrate) observed when used concomitantly with implunestrant 400 mg QD.
3. In vitro study findings:
- a) **CYP Enzymes:** Although implunestrant is an inhibitor of CYP2B6 and CYP2C9 in vitro, the extent of inhibition is not considered clinically significant given that the R values for CYP2B6 (1.042) and CYP2C9 (1.026) were similar to the R value for CYP2C8 (1.027) which demonstrated a lack of clinically significant in vivo inhibition. Implunestrant is not an inhibitor of CYP1A2. Implunestrant is not an inducer of CYP1A2, CYP2B6, or CYP2C9.
- b) **Transporter Systems:** Implunestrant is not a substrate of BCRP, OCT1, OATP1B1, or OATP1B3.

X

X

NDA/BLA Multi-disciplinary Review and Evaluation NDA 218881

Inluriyo (imlunestrant)

Primary Reviewers

Banu S. Zolnik, Ph.D.

Fang Li, Ph.D.

Tien Truong, Ph.D.

Team Leaders

Lauren Price, Pharm.D.

Jingyu (Jerry) Yu, Ph.D.

Jeffrey Kraft Ph.D.

7 Sources of Clinical Data

7.1 Table of Clinical Studies

Data:

Table 7.1 summarizes all completed and ongoing clinical studies within the imlunestrant development program. The planned NDA reflects the program's initial focus on evaluating imlunestrant monotherapy in patients with ER+ locally advanced or MBC. Additional details can be found in Module 5.2 Tabular Listing of All Clinical Studies.

Table 7.1. Listing of Completed and Ongoing Clinical Studies

Study Identifier	Protocol Title	Included in Planned NDA	Number of Participants	Status
Biopharmaceutic and clinical pharmacology studies				
J2J-MC-JZLD	Evaluation of the Effect of Food, Omeprazole, Itraconazole, and Carbamazepine on the Pharmacokinetics of LY3484356 in Healthy Females of Non-Child-Bearing Potential	Yes	82	Completed
J2J-MC-JZLE	An Open-label, Two-part Study of the Disposition and Absolute Bioavailability of [14C]-LY3484356 in Healthy Females of Non-Childbearing Potential	Yes	16	Completed
J2J-MC-JZLG	Pharmacokinetics of Imlunestrant in Participants with Hepatic Impairment	Yes	27	Completed
J2J-MC-JZLI	The Effect of Imlunestrant on CYP2C8, CYP2C19, CYP2D6, P-gp, and BCRP Activity and the Effect of P-gp Inhibition on Imlunestrant Pharmacokinetics in Healthy Women of Non-childbearing Potential	Yes	113	Completed
J2J-MC-JZLK	The Effect of Repeat Dosing of Imlunestrant on CYP3A Activity in Healthy Women of Non-childbearing Potential	Yes	20	Completed
Phase 1 clinical studies				
J2J-MC-JZLA (EMBER)	EMBER: A Phase 1a/1b Study of LY3484356 Administered as Monotherapy and in Combination with Anticancer Therapies for Patients with ER+ Locally Advanced or Metastatic Breast Cancer and Other Select Non-Breast Cancers	Yes	385	Completed

Inluriyo (imlunestrant)

Study Identifier	Protocol Title	Included in Planned NDA	Number of Participants	Status
J2J-MC-JZLB (EMBER-2)	EMBER-2: A Phase 1, Open-Label, Preoperative Window Study evaluating the Biological Effects of LY3484356 in Post-menopausal Women with Stage I-III Estrogen Receptor-Positive, HER2-Negative Breast Cancer	Yes	87	Completed
J2J-MC-JZLF	A Phase 1 Study of LY3484356 in Chinese Patients with Estrogen Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer	Yes	24	Completed
Phase 3 clinical studies				
J2J-OX-JZLC (EMBER-3)	EMBER-3: A Phase 3, Randomized, Open-Label Study of Imlunestrant, Investigator's Choice of Endocrine Therapy, and Imlunestrant plus Abemaciclib in Patients with Estrogen Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer Previously Treated with Endocrine Therapy	Yes (registration study)	874	Primary outcome 24 June 2024

Abbreviations: BCRP = breast cancer-resistance protein; CYP = cytochrome P450; ER+ = estrogen receptor positive; HER2- = human epidermal receptor 2 negative; NDA = new drug application; P-gp = P-glycoprotein.

The Applicant's Position:

The primary study supporting the evaluation of safety and efficacy in this NDA is EMBER-3. A detailed description of the results is provided in Section 8.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the trials for imlunestrant listed in Table 7.1. The FDA's evaluation of efficacy and safety is mainly based on results from Study J2J-OX-JZLC (EMBER-3), hereafter EMBER-3.

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

EMBER-3 is a global, open-label, Phase 3, randomized study in patients with ER+, HER2- locally ABC or MBC after disease progression on AI with or without a CDK4/6i. The design of this study was discussed with the FDA at the End-of-Phase 2 meeting, and the final SAP was reviewed by the Agency prior to locking the database.

8.1.1 EMBER-3: A Phase 3, Randomized, Open-Label Study of Imlunestrant, Investigator's Choice of Endocrine Therapy, and Imlunestrant plus Abemaciclib in Patients with ER+, HER2- Locally Advanced or Metastatic Breast Cancer Previously Treated with Endocrine Therapy

Trial Design

The Applicant's Description:

Design and methodology

Study J2J-OX-JZLC (EMBER-3) was a global, open-label, Phase 3, randomized study in patients with ER+, HER2- locally ABC or MBC after disease progression on AI with or without a CDK4/6i. Prior CDK4/6i treatment was expected if it was approved and reimbursed.

EMBER-3 had 3 treatment arms:

1. Arm A: Imlunestrant (hereinafter referred to as the **implunestrant** arm)
2. Arm B: Investigator's Choice of ET (fulvestrant or exemestane, **SOC** arm)
3. Arm C: Imlunestrant plus abemaciclib (**implun+abema** arm).

EMBER-3 enrolled 874 patients from October 2021 to November 2023. Initially, patients were randomly assigned 1:1 between the **implunestrant** arm and the **SOC** arm. **Implun+abema** arm was added in Amendment (a), which was approved in October 2021 prior to the first patient entering treatment. Enrollment to the **implun+abema** arm began in March 2022 at which point 122 patients had been randomly assigned across the **implunestrant** and **SOC** arms. All 3 arms remained open until the target enrollment for the **implunestrant** arm and the **SOC** arm was met. At the end of enrollment, 426 patients had been concurrently assigned at random between the **implunestrant** arm and the **implun+abema** arm.

This pivotal study evaluated 3 comparisons for investigator-assessed PFS (primary endpoint):

- In the ITT population, **implunestrant** (Arm A) versus **SOC** (Arm B)

Inluriyo (imlunestrant)

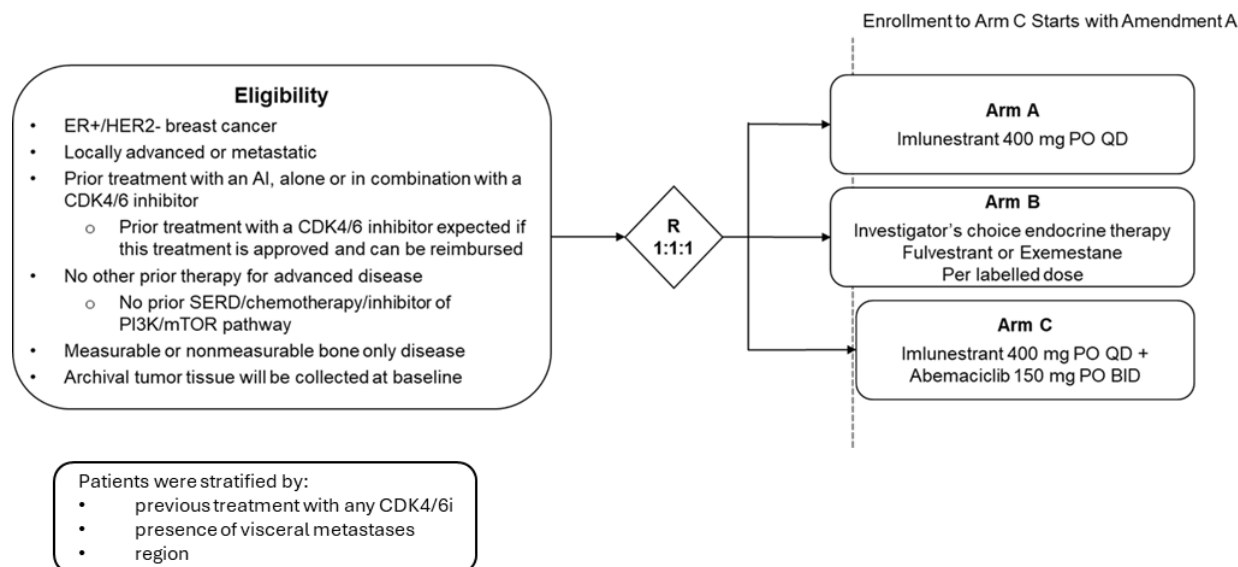
- In the *ESR/m* subpopulation, **imlunestrant** (Arm A) versus **SOC** (Arm B)
- In the ITT population, **imlun+abema** (Arm C) versus **imlunestrant** (Arm A).

Note: The efficacy analyses include only patients concurrently enrolled in Arms A and C. Safety analyses include all treated patients, whether concurrent or not.

Note: The analysis of **imlun+abema** arm versus **imlunestrant** arm was only conducted if the primary endpoints for PFS in the ITT population or in the *ESR/m* subpopulation were significant.

Participants were randomly assigned using the following stratification factors (Figure 8.1):

- previous treatment with any CDK4/6i (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).



Abbreviations: AI = aromatase inhibitor; BID = twice daily; CDK = cyclin-dependent kinase; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; mTOR = mammalian target of rapamycin; PI3K = phosphoinositide 3-kinase; PO = orally; QD = once daily; R = randomization; SERD = selective estrogen receptor degrader.

Inluriyo (imlunestrant)

Figure 8.1. EMBER-3 study schema.

Eligibility criteria

Eligible patients were required to be 18 years or older with a diagnosis of ER+, HER2- breast cancer per ASCO-CAP guidelines per local testing and either locally advanced or metastatic disease. In addition to postmenopausal women, men and premenopausal women with concomitant use of a GnRH agonist were also eligible. Patients were required to have 1 of the 3 scenarios given below:

- relapsed while on or within 12 months of completion of (neo)adjuvant AI, alone or in combination with a CDK4/6i, with no treatment for advanced disease
- relapsed after 12 months from completion of (neo)adjuvant ET (ET, tamoxifen, or AI), with subsequent progression on or after only 1 line of therapy with an AI, alone or in combination with a CDK4/6i, or
- 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 CDK4/6i.

Additionally, per RECIST v1.1, patients were required to have either measurable disease or non-measurable bone-only disease.

No chemotherapy for ABC was permitted. In addition, patients with prior use of fulvestrant, investigational SERDs, or other targeted agents except CDK4/6i were not allowed. Patients with inflammatory breast cancer, visceral crisis, symptomatic or untreated central nervous system metastasis, or carcinomatous meningitis were excluded.

Study treatment

Table 8.1 outlines the study interventions.

Table 8.1. Study Interventions Administered

	Imlunestrant (Arm A)	Investigator’s Choice Endocrine Therapy^a (Fulvestrant or Exemestane) (Arm B)		Imlunestrant + Abemaciclib (Arm C)	
Treatment	Imlunestrant	Fulvestrant	Exemestane	Imlunestrant	Abemaciclib
Dose	400 mg	500 mg	25 mg	400 mg	150 mg
Schedule	QD in 28-day continuous cycles	500 mg on C1D1 and C1D15 and then on Day 1 of a 28-day cycle starting at Cycle 2	QD in 28-day continuous cycles	QD in 28-day continuous cycles	BID in 28-day continuous cycles

Inluriyo (imlunestrant)

	Imlunestrant (Arm A)	Investigator's Choice Endocrine Therapy^a (Fulvestrant or Exemestane) (Arm B)		Imlunestrant + Abemaciclib (Arm C)	
Route	Oral ^b	Two 250 mg intramuscular injections	Oral	Oral ^b	Oral

Abbreviations: BID = twice daily; C1D1 = Cycle 1 Day 1; C1D15 = Cycle 1 Day 15; QD = once every day.

^a Per local label.

^b Patients were instructed not to consume any food at least 1 hour before and at least 2 hours after administration.

Source: Table JZLC.3.2

Planned measurements and timing of assessments

The protocol Schedule of Activities outlines the schedule, measurements, and collection methods of the efficacy, PK, safety, and biomarker assessments. Radiological imaging occurred at baseline and then at regular intervals thereafter until radiographic disease progression, death, start of a new anticancer therapy or study completion, whichever occurred first.

Patients who discontinued from the protocol treatment were required to enter a follow-up period. Following a short-term follow-up of approximately 30 days in which safety assessments were completed, patients continued in long-term follow-up for assessment of SAEs and OS (assessed every 12 weeks).

The protocol details the collection and assessment of safety information (evaluation, definitions, recording, and reporting of AEs, SAEs, and other reportable safety events).

Dose selection discussion

In the Phase 1 EMBER study, imlunestrant was administered at 5 dose levels (200 to 1200 mg QD). At the 200-mg dose, the trough concentrations of the majority of patients did not exceed the TEC₈₀ range (therapeutic effective concentration required for 80% target inhibition) and thereby did not have sustained biologically relevant concentrations over the entire dosing interval, which was also supported by the popPK study. This threshold has been associated with tumor regression in xenograft models, and therefore, considered a relevant benchmark. With doses at and above 400 mg, the TEC₈₀ range was exceeded throughout the dosing interval; 400 mg being the lowest dose that satisfied the desired PK requirements. In addition, there were notable differences in the frequency of low grade side effects (such as nausea) between 400 mg and higher doses, which could have potentially impacted long-term adherence to imlunestrant. Moreover, evidence of clinical activity was observed at the 400-mg dose, with 4 of 6 imlunestrant monotherapy partial responses observed across the study seen at the 400-mg dose level. Therefore, this was chosen as the registration dose for the EMBER-3 study.

At the same time, the EMBER-2 window-of-opportunity study evaluated 3 dose levels (200 mg, 400 mg, and 800 mg) to assess for effects on key biologically relevant PD biomarkers in

Inluriyo (imlunestrant)

postmenopausal women with EBC. Though similar on-target effects with substantial ER degradation were observed across all doses, the 200 mg QD dose had the lowest rate of complete cell cycle arrest and the 800 mg QD dose had the highest incidence of nausea and diarrhea. This further supported the ongoing EMBER-3 registration dose at 400 mg QD and a dose adjustment to 200 mg QD as needed.

Overall, the PK, safety, and initial clinical activity in EMBER supported the imlunestrant monotherapy starting registration dose at 400 mg QD in EMBER-3.

Choice of comparator discussion

Imlunestrant (Arm A) versus SOC (Arm B)

For the patients enrolled in EMBER-3, investigator's choice of SOC (Arm B), fulvestrant or exemestane, was an appropriate comparator for **imlunestrant** monotherapy (Arm A). Investigator's choice of SOC reflects the alternatives commonly used for ET-pretreated patients, is consistent with recommended options in treatment guidelines globally, and allows for physician and patient preferences between both agents.

Open-label design

EMBER-3 is an open-label study. Each participant in this study was aware of his or her own assigned treatment group. However, the open-label design was inevitable due to the route of administration for the study treatments:

- oral for imlunestrant and exemestane, and
- intramuscular for fulvestrant.

Although the participants and staff involved in treating and caring for participants were aware of participants' treatment assignments, the sponsor remained strictly blinded to the aggregate data prior to database lock.

The primary and secondary endpoints rely on objective measures, helping to control potential bias. Notably, the primary endpoint of investigator-assessed PFS was repeated by BIRC, both using RECIST v1.1, to

- assess any potential bias introduced through investigator assessments, and
- show consistency of treatment effect regardless of investigator or BIRC assessment.

Sensitivity analyses were prespecified to evaluate the robustness of the primary analysis.

Stratification factors discussion

Stratification factors are known prognostic factors with the potential to influence the primary PFS objective and were included to reduce potential bias.

ESR/m status was not a stratification factor. With the sample size of this EMBER-3 study and the known prevalence, up to 50% Bhav et al. 2024), of *ESR/m* incidence among patients

Inluriyo (imlunestrant)

receiving prior AI-based treatments, it was expected that the treatment arms would be balanced for *ESR1m*.

Prior CDK4/6i discussion

To reflect real-world clinical practice and global differences in CDK4/6i access in the advanced and metastatic setting, EMBER-3 also included patients who did not have previous CDK4/6i treatment.

The FDA's Assessment:

The FDA generally agrees with the Applicant's description of the EMBER-3 trial with the following comments and clarifications. Of note, throughout this review, FDA refers to the control arm in this trial as treatment of physician's choice (TPC), as the FDA believes this is more accurately reflective of the options in the EMBER-3 trial. The Applicant refers to this arm as standard of care (SOC).

Eligibility criteria

- Patients were required to have an ECOG performance status of 0 or 1 to be eligible for this trial. The FDA notes that men and women with an ECOG performance status of greater than 1 and ER-positive, HER2-negative advanced or metastatic breast cancer are routinely treated with endocrine monotherapy. Thus, the enrolled population is not representative of the whole US population that may receive imlunestrant.
- Patients who were eligible for PARPi therapy were excluded. It is not clear that these patients would not benefit from later lines of endocrine therapy; however, this was not adequately assessed in EMBER-3.

Prior CDK4/6i therapy

- The FDA cautioned the Applicant February 11, 2021, at a Type B, EOP1 meeting that most patients should have received prior CDK4/6i therapy to be representative of a US population. The Applicant submitted amendment (a) of the protocol to IND 145311 on October 11, 2021, that required prior CDK4/6i where available and reimbursed. On September 1, 2022, amendment (b) of the protocol was submitted which also allowed the Applicant to limit the number of patients enrolled that had not received prior CDK4/6i therapy.
- Although the study included both patients who did and did not receive prior CDK4/6i therapy, the prespecified analyses were not powered and are exploratory only.
- Practice patterns regarding the choice of CDK4/6i appear to be changing based on recent data that supports an overall survival benefit for some CDK4/6i given in a metastatic setting.

Stratification factors

Inluriyo (imlunestrant)

- The original design of the EMBER-3 trial included (b) (4), the prevalence of *ESR1*m was considered large enough (b) (4). See also FDA's review of Presubmission Regulatory Activities in Section 3.2 of this Assessment Aid review.
- The FDA also cautioned the Applicant that if differential activity was observed based on specific *ESR1* mutations (e.g., Y537S), the lack of stratification by specific mutations would be a review issue.

Detection of mutations, including *ESR1*

- Patients were required to provide blood samples of circulating tumor DNA analysis. Samples were analyzed using Oncoscreen520 Plus (Burning Rock - China) and Guardant360 (Guardant Health – rest of the world). Results were not required before randomization since this was not a stratification factor. As a result, some patients on EMBER-3 had an unknown *ESR1*m status. According to the Applicant's analyses patients were designated "*ESR1*m-detected" if either test showed a ligand binding domain mutation or "*ESR1*m-not detected" if no *ESR1* mutation(s) was detected, if the test did not detect ctDNA, or test results were missing.
- No tissue testing for *ESR1*m was performed.
- The Applicant clarified in an IR response on February 28, 2025, that patients and investigators were blinded to *ESR1*m status except for one patient (Subject ID: (b) (6)) who requested this information about 9 months after disease progression on treatment of physician's choice (TPC) treatment (fulvestrant). The Applicant does not have any data to show whether patients may have obtained information on *ESR1*m status outside of EMBER-3. Five patients with *ESR1* mutations received subsequent therapy with an oral SERD. Three were assigned to the TPC arm (Subject IDs: (b) (6)) and two were assigned to the imlunestrant arm (Subject IDs: (b) (6)).
- One patient (Subject ID: (b) (6)) enrolled in South Korea and randomized to the TPC arm had a *BRCA2* R2494* nonsense mutation with a VAF of 51%, indicating a germline mutation. This patient received saruparib after progression.

Open-label design

- The FDA agrees that the open-label design benefited patients on the trial by allowing them to forego a placebo injection. A prospectively planned sensitivity analysis of PFS by BIRC was also performed on all patients.

Control arm

At the time of that the EMBER-3 trial was designed, ET monotherapy was an acceptable comparator. However, since that time it has become clear that fulvestrant monotherapy underperforms as a standard of care therapy after prior CDK4/6i therapy. Additionally,

Inluriyo (imlunestrant)

elacestrant was approved in the US for patients with ER+, HER2- metastatic breast cancer and an *ESR1*m during the conduct of EMBER-3.

Concomitant therapy

- Patients were allowed to receive palliative radiotherapy on the trial if no other systemic or local therapy was effective to manage painful metastases. The Applicant provided sensitivity analyses to assess the impact of concomitant palliative radiotherapy on investigator assessed PFS.

The FDA did not review any study elements related to the combination (Arm C) as it is out of the scope of the proposed indication under this NDA.

Study Endpoints

The Applicant’s Description:

Choice of investigator-assessed PFS as the primary endpoint

Investigator-assessed PFS is an appropriate endpoint in MBC as demonstrated by recent pivotal studies supporting approvals in this setting (FDA 2019). Meta-analyses indicate that investigator-assessed PFS provides a reliable estimate of treatment effect (Amit et al. 2011; Dello Russo and Navarra 2022). Importantly, PFS as assessed by BIRC was a secondary endpoint to assess potential for bias in investigator assessments (Amit et al. 2011).

Table 8.2 details the key primary and secondary objectives.

Table 8.2. Key Primary and Secondary Objectives

Objectives	Endpoints
Primary	
• To compare the PFS of imlunestrant (Arm A) to the standard comparator of Investigator’s Choice Endocrine Therapy of either fulvestrant or exemestane (Arm B) in the ITT population. • To compare the PFS of Arm A to Arm B in the <i>ESR1</i>-mutation detected population. • To compare the PFS of imlunestrant plus abemaciclib (Arm C) to imlunestrant (Arm A) in the ITT population.	• Investigator-assessed PFS (between Arm A and Arm B) in the ITT population. • Investigator-assessed PFS (between Arm A and Arm B) in the <i>ESR1</i>-mutation detected population. • Investigator-assessed PFS (between Arm C and Arm A) in the ITT population.
Secondary	
• To compare OS of Arm A to Arm B in the ITT population. • To compare OS of Arm A to Arm B in the <i>ESR1</i>-mutation detected population. • To compare OS of Arm C to Arm A in the ITT population.	• OS between Arm A and Arm B in the ITT population (<i>key secondary endpoint</i>). • OS between Arm A and Arm B in the <i>ESR1</i>-mutation detected population (<i>key secondary endpoint</i>).

Inluriyo (imlunestrant)

Objectives	Endpoints
To compare other efficacy objectives of Arm A to Arm B, and Arm C to Arm A.	- OS between Arm C and Arm A in the ITT population (<i>key secondary endpoint</i>). - Investigator-assessed ORR, DoR, and CBR. - PFS by blinded independent review committee (BIRC).
To assess the safety and tolerability of each treatment arm.	Including, but not limited to, AEs, serious AEs, deaths, and clinical laboratory abnormalities per NCI CTCAE v5.0.
To evaluate the effectiveness of Arm A compared to Arm B and Arm C compared to Arm A based on PROs of pain using the Worst Pain NRS.	Time to sustained worsening of the “worst pain” as measured by Worst Pain NRS.
- To assess the PK of imlunestrant (Arm A and Arm C). - To assess the PK of abemaciclib and its metabolites (Arm C).	Plasma concentrations of imlunestrant and abemaciclib.
Exploratory	
To assess exploratory clinical parameters of Arm A compared to Arm B, and Arm C compared to Arm A.	- Time to progressive bone metastases. - Time to first SRE (defined as either pathological fracture, spinal cord compression, radiation to the bone, or surgery to the bone). - TTC - CFS - PFS2 (from randomization to disease progression on the next line of treatment or death). - Time to worsening of ECOG PS of ≥ 2.
To explore other PRO and HRQOL parameters of Arm A compared to Arm B, and Arm C compared to Arm A.	- Time to worsening of physical function as measured by the physical function score of EORTC IL 19. - Change from baseline as measured by EORTC-QLQ-C30 and EQ-5D-5L. - Incidence of AE using the PRO-CTCAE item for diarrhea. - Change from baseline as measured by the PGIS-Cancer Symptoms.
To compare clinical efficacy parameters of Arm C to Arm B.	- PFS. - OS.
To explore potential biomarkers related to the ER pathway and/or the pathogenesis of breast cancer.	Biomarker results and efficacy outcomes.

Inluriyo (imlunestrant)

Abbreviations: AE = adverse event; BIRC = blinded independent review committee; CBR = clinical benefit rate; CFS = chemotherapy-free survival; CTCAE = Common Terminology Criteria for Adverse Events; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC IL 19 = European Organization for Research and Treatment of Cancer Item Library 19; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L = 5-level-EuroQol; ER = estrogen receptor; *ESR1* = estrogen receptor 1; HRQOL = Health Related Quality of Life; ITT = intention to treat; NCI = National Cancer Institute; NRS = numeric rating scale; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PGIS = Patient's Global Impression of Symptoms; PK = pharmacokinetics; PROs = patient-reported outcomes; PS = performance status; SRE = skeletal-related event; TTC = time to chemotherapy.

Source: Table JZLC.1.1

The FDA's Assessment:

FDA generally agrees with the Applicant's description of study endpoints for the comparison of imlunestrant vs TPC in the overall population and in the *ESR1*-m-detected population. In general, PFS of appropriate magnitude is an acceptable endpoint to support traditional approval, when supported by other endpoints—such as blinded independent central review (BICR) and objective response rate (ORR)—and when results are consistent across subgroups.

The PRO-based time-to-event endpoint of time to sustained worsening of the “worst pain” as measured by Worst Pain NRS was challenging to interpret due to factors such as defining deterioration, accounting for intercurrent events, and potential missing data, as described in the literature.

The FDA did not review any study elements related to the combination (imlun+abema) as it is out of the scope of the proposed indication under this NDA.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Analysis of sample size

For **imlunestrant** treatment arm compared to patients enrolled in the **SOC** treatment arm in the ITT population, the sample size calculation assumed the median PFS of **SOC** arm to be 4.3 months, and the hazard ratio of 0.74 amounts to an approximate 1.5-month improvement in median PFS under the assumption of exponential survival distribution. The assumed median PFS of **SOC** arm was estimated based on an unpublished meta-analysis of historical controls. A total of 480 events yields at least 76% power to detect superiority of **imlunestrant** treatment arm over **SOC** treatment arm with the 1-sided log-rank test at the initial significance level of 0.005.

Inluriyo (imlunestrant)

For **imlunestrant** treatment arm compared to patients enrolled in the **SOC** treatment arm in the *ESR1m*-detected population, the sample size calculation assumed the median PFS of **SOC** arm in the subset is 3.6 months, the hazard ratio of 0.57 amounts to an approximate 2.7-month improvement in median PFS under the assumption of exponential survival distribution. A total of 192 events yields approximately 97% power to detect superiority of **imlunestrant** treatment arm over **SOC** treatment arm with the 1-sided log-rank test at the significance level of 0.02.

For **imlun+abema** treatment arm compared to **imlunestrant** treatment arm in the concurrent ITT population, if the median PFS of **imlunestrant** treatment arm is assumed to be 5.8 months (assuming the target HR for **imlunestrant** treatment arm compared to patients enrolled in the **SOC** treatment arm in the ITT population is met), the hazard ratio of 0.7 then amounts to an approximate 2.5-month improvement in median PFS under the assumption of exponential survival distribution. A total of 248 events yields at least 80% power to detect superiority of **imlun+abema** treatment arm over **imlunestrant** treatment arm with the 1-sided log-rank test at the significance level of 0.025.

Initially, patients were randomly assigned 1:1 between the **imlunestrant** arm and the **SOC** arm. Amendment (a) of the protocol, which added the **imlun+abema** arm, was approved before first patient visit, and the enrollment of this arm started approximately 6 months after recruitment into EMBER-3 began. After the addition of the **imlun+abema** arm, patients were randomly assigned 1:1:1 into each treatment arm. Under the enrollment assumptions, it is estimated that a total number of 860 participants were to be enrolled in this study. Specifically, approximately 320 participants were to be enrolled in the **imlunestrant** arm or the **SOC** treatment arms, and approximately 220 participants in the **imlun+abema** treatment arm.

EMBER-3 was appropriately powered for the 3 PFS comparisons.

Statistical analysis

The primary endpoints of PFS were evaluated in 3 comparisons:

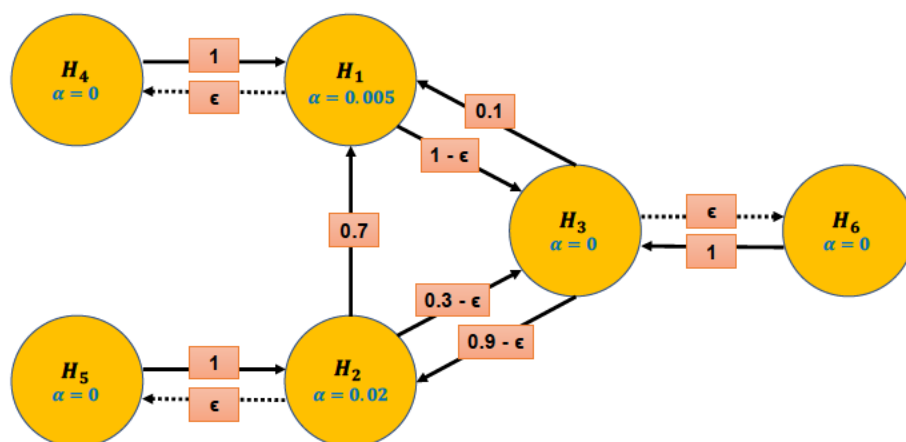
- compare **imlunestrant** treatment arm and the **SOC** treatment arm in the ITT population
- compare **imlunestrant** treatment arm and **SOC** treatment arm in the *ESR1m*-detected population, and
- compare **imlun+abema** treatment arm and **imlunestrant** treatment arm in the concurrent ITT population.

To adjust for multiplicity and control the overall type I error rate at 0.025 (1-sided), a graphical approach (Bretz et al. 2009; Maurer and Bretz 2013) was used to test the 3 PFS primary endpoints and the 3 key secondary OS endpoints. [Figure 8.2](#) represents the graph with initially allocated significance levels at each node and the associated weights for each directed edge from these respective nodes.

The graphical testing scheme ensured that H_3 (PFS between the **imlun+abema** arm and **imlunestrant** arm in the concurrent ITT population) would only be tested if at least 1 of the

Inluriyo (imlunestrant)

monotherapy comparisons (H_1 or H_2) was rejected, and the key secondary OS hypotheses (H_4 , H_5 , and H_6) would be tested only if the corresponding primary PFS hypotheses were rejected.



Abbreviations: *ESR1* = estrogen receptor 1; H_1 = PFS between Arm A and Arm B in the ITT population; H_2 = PFS between Arm A and Arm B in the *ESR1*-mutation-detected population; H_3 = PFS between Arm C and Arm A in the concurrent ITT population; H_4 = OS between Arm A and Arm B in the ITT population; H_5 = OS between Arm A and Arm B in the *ESR1*-mutation-detected population; H_6 = OS between Arm C and Arm A in the concurrent ITT population; imlun+abema = imlunestrant in combination with abemaciclib; ITT = intention to treat; OS = overall survival; PFS = progression-free survival; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Arm A = imlunestrant; Arm B = SOC; Arm C = imlun+abema.

Small edge weights are represented by dotted lines. ϵ denotes an infinitesimally small number ($\epsilon = 10^{-4}$).

Figure 8.2. Initial graphical representation of the testing scheme.

Analysis of the primary endpoints

The primary endpoint was investigator-assessed PFS. The Kaplan-Meier method (Kaplan and Meier 1958) was used to estimate the PFS curves. Median PFS and PFS rates at various time points with 95% CIs were estimated for each arm. The comparison of PFS curves between treatment arms was conducted by a stratified log-rank test as the primary analysis, stratified by the randomization strata (previous treatment with CDK4/6i, presence of visceral metastases, region). The treatment effect was estimated by hazard ratio with its corresponding 95% CIs using the stratified Cox proportional hazard model with treatment as the only covariate, stratified by the randomization strata.

Inluriyo (implunestrant)

PFS comparing **implunestrant** treatment arm and **SOC** treatment arm in the *ESR1m*-detected population was analyzed in the same way, except that region was excluded in the stratified analysis to reduce the number of strata.

Multiple sensitivity analyses were conducted to evaluate the robustness of the primary analysis.

Analysis of the key secondary endpoints

Overall survival between **implunestrant** treatment arm and the **SOC** treatment arm in the ITT population, OS between **implunestrant** treatment arm and **SOC** treatment arm in the *ESR1m*-detected population, and OS between **implun+abema** treatment arm and **implunestrant** treatment arm in the concurrent ITT population are the key secondary endpoints.

OS curves, median OS, and OS rates at 1 year and 2 years with 95% CI for each treatment arm were estimated using the Kaplan-Meier method. OS was compared between treatment arms using a log-rank test, stratified by the same factors as PFS. The corresponding hazard ratio between treatment arms was estimated using a stratified Cox regression model. The inferential analysis of OS was based on the stratified analyses.

Pre-specified interim analyses

For the primary endpoint of PFS between implunestrant treatment arm and the SOC treatment arm in the ITT population, one interim futility analysis was to be conducted when approximately 192 (40% information fraction) investigator-assessed events had occurred. No interim analysis was conducted for PFS comparing **implunestrant** treatment arm and the **SOC** treatment arm in the *ESR1m*-detected population.

For the key secondary endpoint of OS for **implunestrant** treatment arm and the **SOC** treatment arm in the ITT population, the interim and final analyses were planned at the number of events summarized in [Table 8.3](#).

Table 8.3. Timing of OS Analyses in the ITT Population

OS look 1	At the time of final analysis of PFS in the ITT population
OS look 2	Approximately 255 OS events
OS look 3	Approximately 330 OS events
Final OS	Approximately 390 events

Abbreviations: ITT = intent-to-treat population; OS = overall survival; PFS = progression-free survival.

For the OS comparing **implunestrant** treatment arm and the **SOC** treatment in the *ESR1*-detected population, the interim and final analyses are summarized in [Table 8.4](#).

Table 8.4. Timing of OS Analyses in the *ESR/m*-Detected Population

OS look 1	At the time of final analysis of PFS in the ITT population
OS look 2	At the time of OS look 2 in the ITT population
OS look 3	At the time of OS look 3 in the ITT population
Final OS	Approximately 155 events

Abbreviations: ITT = intent-to-treat population; OS = overall survival; PFS = progression-free survival.

Analysis of prespecified subgroups

Prespecified subgroup analyses of PFS were conducted for each PFS comparison. Results are displayed in forest plots in the CSR.

The FDA’s Assessment:

FDA generally agrees with the description of the statistical analysis plan for the comparison of the imlunestrant arm and TPC arm in the ITT population and in the *ESR/m*-detected population except the description of the interim analysis of PFS for the comparison of the imlunestrant arm and TPC arm in the *ESR/m*-detected population.

Per SAP Version 5 (the latest version prior to data unblinding), the final analysis of PFS between the imlunestrant arm and TPC arm in the ITT population was planned to be conducted when 480 PFS events were observed. At the time of final PFS analysis between the imlunestrant arm and TPC arm in the ITT population, if approximately 192 PFS events had been observed for the comparison of imlunestrant arm and TPC arm in the *ESR/m*-detected population, the final PFS analysis for the comparison of the imlunestrant arm and TPC arm in the *ESR/m*-detected population was planned to be conducted at the 1-sided alpha level of 0.02. However, if the number of PFS events for the comparison of the imlunestrant arm and TPC arm in the *ESR/m*-detected population had not reached the target number of events (192 PFS events), one interim analysis for efficacy could be conducted if deemed appropriate, and the Lan-DeMets spending function (O’Brien-Fleming type) was planned to be used to determine the boundaries that the interim and final analyses for PFS in the *ESR/m*-detected population.

Of note, Applicant’s description of stratified analyses (stratified log-rank test and stratified Cox proportional hazard model) stratified by the randomization strata (previous treatment with CDK4/6i, presence of visceral metastases, region) are for the primary analysis of PFS for the comparison of the imlunestrant arm and TPC arm in the ITT population. In the primary analysis of PFS for the comparison of the imlunestrant arm and TPC arm in the *ESR/m*-detected population, the stratification factor of region was excluded in the stratified analyses to reduce the number of strata. In a response to FDA’s Information Request dated February 6, 2025, the Applicant clarified that region was removed from all stratified analyses in the *ESR/m*-detected population to reduce the number of strata. This included the analyses of PFS by investigator

Inluriyo (imlunestrant)

assessment, OS, and PFS by BIRC in the *ESR1*m-detected population for the comparison of the imlunestrant arm and TPC arm and the comparison of imlun+abema arm and imlunestrant arm. Similarly, region was also removed from the exploratory stratified PFS and OS analyses in the *ESR1*m-nd population.

Per SAP Version 5, the first interim OS analysis for all comparisons was planned to be conducted at the time of the final PFS analysis for the comparison of the imlunestrant and TPC in the ITT population. For the comparison of the imlunestrant arm and TPC arm in the *ESR1*m-detected population, the timing of the second and third interim OS analyses was anchored to the OS endpoint for the comparison of the imlunestrant arm and TPC arm in the ITT population (i.e., event-driven based on the number of OS events for the comparison of the imlunestrant arm and TPC arm in the ITT population), and the timing of the final OS analysis was event-driven when 155 OS events were observed from the imlunestrant arm and TPC arm in the *ESR1*m-detected population. For each OS comparison, the Lan-DeMets spending function (O'Brien-Fleming type) based on the actual observed number of events was used to determine the boundaries for the interim and final analyses of OS.

Per SAP Version 5, the alpha of 0.025 (1-sided) was initially split between the PFS comparison of the imlunestrant arm and TPC arm in the *ESR1*m-detected population (0.02 alpha) and the PFS comparison of the imlunestrant arm and TPC arm in the ITT population (0.005 alpha). The PFS comparison of imlun+abema arm and imlunestrant arm in the concurrent ITT population was planned to be tested only if any comparison of PFS for imlunestrant arm and TPC arm was statistically significant. The key secondary endpoint OS would be tested only if the corresponding primary PFS endpoint was statistically significant. No multiplicity adjustments were made for any efficacy endpoints in the *ESR1*m-nd population.

The proposed indication for the current submission is the imlunestrant monotherapy in the *ESR1*m-detected population. This review is focused on the benefit/risk assessment in the comparison of imlunestrant monotherapy and TPC in the *ESR1*m-detected population only. The comparison of the imlun+abema arm and imlunestrant arm is not relevant to support the efficacy of imlunestrant monotherapy for the proposed indication under this NDA; therefore, details of efficacy analyses for the comparison of the imlun+abema arm and imlunestrant arm were not included in this review.

Protocol Amendments

The Applicant's Description:

The Sponsor implemented all changes in study conduct via 4 protocol amendments, labeled protocol Amendments (a) to (d).

Table 8.5 outlines the approval dates of each protocol amendment.

Table 8.5. Summary of Protocol Amendments

Protocol Amendment	Date	Key Reasons for Amendment
EMBER-3	15-Mar-2021	NA
EMBER-3 Amendment (a)	08-Oct-2021	- Addition of - a new treatment arm (Arm C). - inclusion Criterion #3, where patients were expected to have received prior treatment with a CDK4/6 inhibitor if approved and reimbursed.
EMBER-3 Amendment (b)	17-Aug-2022	- Primary and secondary endpoints were updated. - The comparison of PFS between Arms A and B in the <i>ESR1</i>-mutation detected population was elevated to a primary objective. - Inclusion Criterion #3 was revised to allow the Sponsor to limit the number of participants who had not received a prior CDK4/6 inhibitor.
EMBER-3 Amendment (c)	11-Nov-2022	- Projected PFS hazard ratios were updated based on Phase 3 results for other oral SERDs. The updated projections necessitated an increase in the estimated total study enrollment. - The sample size for Arms A and B increased from approximately 500 to 640 patients (320 in each arm). - Added that Arm C was expected to enroll approximately 220 patients and would complete at the same time as Arms A and B. - Added exploratory analyses to assess PFS and OS of Arm C compared to Arm B.
EMBER-3 Amendment (d)	31-Jul-2023	The initial alpha allocation for the PFS primary endpoint analysis between Arms A and B for ITT and the <i>ESR1</i> subgroup was changed with greater alpha assigned to the latter. This was based on new external data of oral SERDs in breast cancer.

Abbreviations: CDK4/6 = cyclin-dependent kinase 4/6; *ESR1* = estrogen receptor 1; ITT = intention -to-treat; NA = not applicable; OS = overall survival; PFS = progression-free survival; SERD = selective estrogen receptor degrader.

Source: Table JZLC.3.1

Evaluation of SAP amendments

The SAP v1.0, which supersedes the statistical plan in the protocol, was approved on 26 July 2021 (Table 8.6). The most recent amendment, Version 5, was approved on 24 August 2023 and filed to the IND on 31 August 2023 prior to the primary outcome database lock and sponsor unblinding.

Inluriyo (imlunestrant)

Table 8.6. EMBER-3 SAP Version History

SAP Version	Approval Date	Rationale and Timing of Update
1	26-Jul-2021	Initial version Approved prior to the first patient visit
2	04-Jan-2022	Updated per protocol Amendment (a) - added Arm C - added primary objective for PFS and OS for Arm C vs. Arm A - updated size estimation
3	24-Mar-2022	Clarification on interim analysis timings for Arm A vs. B and Arm C vs. A Approved before the first interim analysis.
4	06-Dec-2022	Updated per protocol Amendments (b) and (c) - added a third primary PFS endpoint and a third OS endpoint in the <i>ESR1</i>-mutation detected population for Arm A vs. Arm B - changed testing scheme to graphical approach - increased the sample size for Arms A, B, and C - increased the event number for PFS between Arms A vs. B - increased the event number for OS analyses and interim analysis Approved before the first interim analysis.
5	24-Aug-2023	Updated per protocol Amendment (d), - changed the initial alpha allocation for PFS between Arm A vs. Arm B in the ITT and PFS between Arm A vs. Arm B in <i>ESR1</i>-mutation detected population - updated the interim analysis plan for OS - added more PFS sensitivity analyses Approved and submitted to IND before the final primary outcome database lock but after futility interim analyses (unblinded interim data were only accessible by the DMC).

Abbreviations: DMC = data monitoring committee; *ESR1* = estrogen receptor 1; IND = investigational new drug application; ITT = intention to treat; OS = overall survival PFS = progression-free survival; SAP = statistical analysis plan.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment of the protocol and SAP amendments with the following addition. SAP Version 5 was the latest version of the SAP finalized before data unblinding. At the pre-NDA meeting held on September 23, 2024, the Applicant asked if FDA would consider an SAP amendment for an updated analysis of OS. The FDA advised the Applicant to submit a proposal for review. The Applicant submitted proposed SAP Addendum v1 in a meeting request dated November 14, 2024 (FDA DARRTs Sequence Number 0165) under IND 145311. Note that SAP Addendum v1 was amended after data unblinding. In SAP Addendum v1, the Applicant proposed to remove the anchoring of the timing for interim OS analyses for the comparison of the imlunestrant arm and TPC arm in the *ESR1m*-detected

Inluriyo (imlunestrant)

population and the comparison of the imlun+abema arm and imlunestrant arm in the ITT population on the OS endpoint for the comparison of imlunestrant arm and TPC arm in the ITT population. Instead, the Applicant proposed time-driven interims for the following OS endpoints: OS for the comparison of the imlunestrant arm and TPC arm in the *ESR1*m-detected population, and OS for the comparison of the imlun+abema arm and imlunestrant arm in the ITT population. After review, in the WRO meeting minutes dated December 20, 2024, the FDA advised the Applicant not to change the remaining formal OS tests between imlunestrant arm and TPC arm in the *ESR1*m population as they were made after data unblinding and could be data driven. Additionally, the FDA stated that changing from event-driven to the proposed calendar-based analyses would be likely to lead to inadequately powered analyses. FDA warned the Applicant that analyses conducted under the SAP Amendment v1 would be considered post-hoc and descriptive only.

Against FDA advice, the Applicant proceeded with SAP Addendum 1 and conducted updated OS analyses with DCO date of January 30, 2025. Topline results of updated OS analyses based on the DCO date of January 30, 2025, were provided and discussed by the Applicant ^{(b) (4)}

meeting held on May 23, 2025. The FDA considered these OS analyses post-hoc and descriptive only. Per meeting minutes, “The FDA agreed with the proposal to return to the plan of the future OS interim and final analyses as pre-specified initially in SAP Version 5 before data unblinding, The FDA reiterated that the Sponsor should only keep and perform the preplanned, event-driven OS analyses and revise the SAP back to Version 5. Sponsor acknowledged.”

Per FDA’s Information Request dated February 6, 2025, the Applicant stated that the interim futility analysis of PFS for the comparison of imlunestrant arm and TPC arm in the ITT population was conducted based on a data cutoff date of February 27, 2023, under the guidance of an independent DMC, who reviewed unblinded data prepared by the independent Statistical Analysis Center.

The first oral selective estrogen receptor degraders (SERD), elacestrant, was approved by the FDA on January 27, 2023 in the ER-positive HER2-negative and *ESR1*-mutated advanced or metastatic breast cancer in postmenopausal women and adult men who have progressed after at least one line of endocrine therapy. In addition, the designs of several registrational intent trials for other oral estrogen receptor antagonists, including camizestrant and vepdegestrant, which prespecified assessment in an *ESR1*m population were public before July 2023. The EMBER-3 protocol was amended (Protocol Amendment [d]) in July 2023. In Protocol Amendment [d], the initial alpha allocations for PFS for the comparisons of the imlunestrant arm and TPC arm in the ITT population and in the *ESR1*m-detected population were changed from 1-sided 0.02 in the ITT population and 1-sided 0.005 in the *ESR1*m-detected population to 1-sided 0.005 in the ITT population and 1-sided 0.02 in the *ESR1*m-detected population. The Applicant stated that the modification of initial alpha allocations for PFS for the comparisons of the imlunestrant arm and

Inluriyo (implunestrant)

TPC arm in the ITT population and in the *ESR/m*-detected population was based on the external data of oral estrogen receptor antagonists where clinically and statistically meaningful improvement in PFS has been primarily driven by the *ESR/m* population.

8.1.2 Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

The EMBER-3 study was conducted in accordance with the protocol and

- consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- applicable ICH GCP Guidelines, and
- applicable laws and regulations.

The FDA's Assessment:

The FDA agrees with the Applicant that the EMBER-3 trial was conducted in compliance with the principals of Good Clinical Practice.

Financial Disclosure

Data:

Eli Lilly and Company (Lilly) submitted a financial disclosure certification document in Module 1.3.4. This documentation provides a listing of all principal investigators and sub-investigators who participated at sites that enrolled patients in EMBER-3, indicating whether the investigators have provided a Certification (Form 3454) or a Disclosure statement (Form 3455).

The Applicant's Position:

Financial Disclosure information was collected from investigators across this multi-site, multi-national study. Patients were randomly assigned across 195 sites in 21 countries (Argentina, Australia, Austria, Belgium, Brazil, China, France, Germany, Greece, India, Italy, Japan, Mexico, the Netherlands, Russia, South Korea, Spain, Taiwan, Turkey, Ukraine, and the United States). See Appendix 19.2 for details.

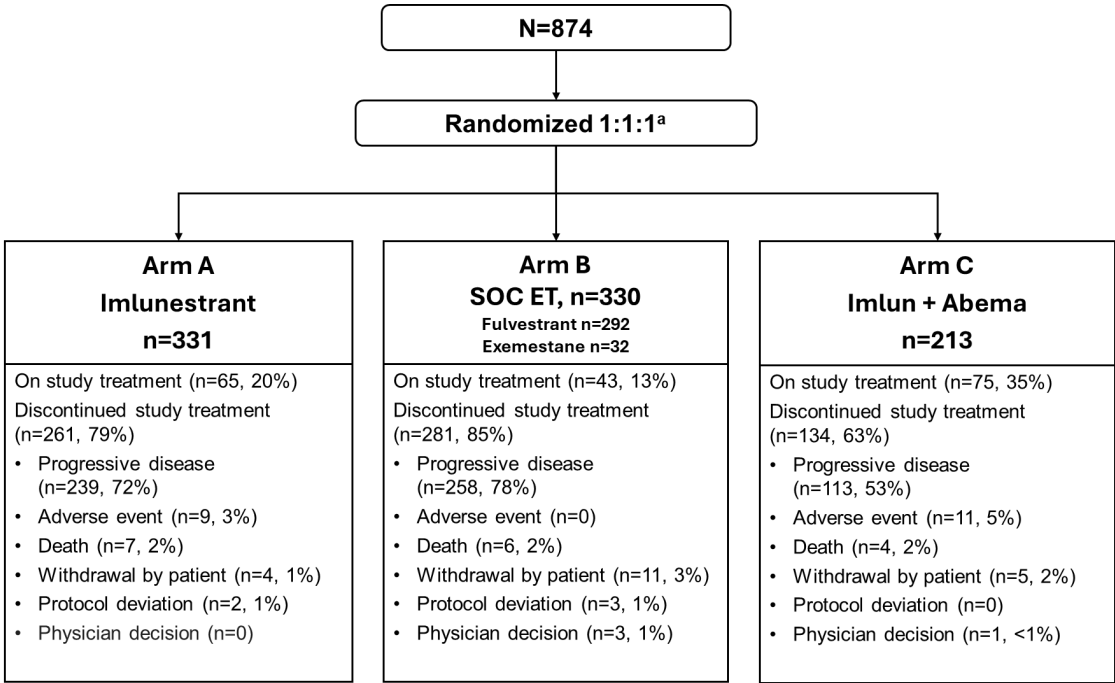
The FDA’s Assessment:

The FDA reviewed Form 3454 and agrees with the Applicant’s assessment that financial interests were unlikely to impact the results of the EMBER-3 trial. For more details regarding the FDA’s assessment of financial disclosures see Section 19.2 of this review.

Patient Disposition

Data:

Figure 8.3 shows the disposition of the 874 patients randomly assigned in EMBER-3. Most patients randomly assigned to the SOC arm were treated with fulvestrant (88%).



Abbreviations: implun+abema = implunestrant in combination with abemaciclib; n = number of patients in the specific category; N = total number of participants; SOC = standard of care investigator’s choice endocrine therapy of fulvestrant or exemestane. ^a 1:1:1 randomization occurred after implementation of the implun+abema treatment arm (Arm C). Enrollment to the implun+abema arm (Arm C) started approximately 6 months after implunestrant arm (Arm A) and SOC (Arm B) enrollment.

Figure 8.3. Patient disposition.

Inluriyo (imlunestrant)

ITT population

The ITT population consisted of all participants randomly assigned to study treatment, regardless of whether any doses of study treatment were taken, or if the correct treatment was administered. Participants were analyzed according to the treatment group to which they were assigned. [Table 8.7](#) provides the disposition in the ITT population, including those who remain on study treatment, who entered posttreatment discontinuation follow-up, and who remained on posttreatment discontinuation follow-up at the time of data cut.

The most common reason for treatment discontinuation was PD, with very few patients discontinuing treatment due to AEs.

Table 8.7. Summary of Patient Disposition in the ITT Population

Category, n (%)	Arm A Imlunestrant (Arm A) N = 331	Arm B SOC N = 330	Arm C imlun+abema N = 213
Enrolled (randomized)			
Treated	326 (98.5)	324 (98.2)	209 (98.1)
Never treated	5 (1.5)	6 (1.8)	4 (1.9)
Discontinuation of all study treatment			
Progressive disease	239 (72.2)	258 (78.2)	113 (53.1)
Adverse event	9 (2.7)	0	11 (5.2)
Withdrawal by subject	4 (1.2)	11 (3.3)	5 (2.3)
Death	7 (2.1)	6 (1.8)	4 (1.9)
Physician decision	0	3 (0.9)	1 (0.5)
Protocol deviation	2 (0.6)	3 (0.9)	0
On post treatment discontinuation follow-up	158 (47.7)	161 (48.8)	77 (36.2)
Off post treatment discontinuation follow-up	95 (28.7)	108 (32.7)	48 (22.5)
Death	55 (16.6)	84 (25.5)	32 (15.0)
Lost to follow-up	11 (3.3)	4 (1.2)	5 (2.3)
Withdrawal by subject	29 (8.8)	20 (6.1)	11 (5.2)

Inluriyo (imlunestrant)

Abbreviations: abema = abemaciclib; imlun = imlunestrant; ITT = intention to treat; n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Source: Table JZLC.4.1

ESR/m-detected population

Determination of baseline *ESR/m* status was important to the primary objective, but not required prior to randomization as *ESR/m* status was not a stratification factor. There were 853 (97.6% of ITT) patients who had a baseline pretreatment ctDNA sample tested and 323 (37%) patients were positive for an *ESR/m*, including 4 patients from China.

A total of 551 (63%) patients were designated *ESR/m*-not-detected, which included those whose blood sample had no *ESR/m* mutation or detectable ctDNA present, or an unknown result (analytical failures or missing samples).

Patients with *ESR/m*-detected population were generally balanced across the treatment arms. [Table 8.8](#) provides the disposition of the *ESR/m* population.

Inluriyo (imlunestrant)

Table 8.8. Summary of Patient Disposition in the *ESR1*-m-detected Population

Category	Arm A Imlunestrant N = 138	Arm B SOC N = 118	Arm C Imlun+Abema N = 67
Enrolled (randomized), n (%)			
Treated	137 (99.3)	117 (99.2)	66 (98.5)
Never treated	1 (0.7)	1 (0.8)	1 (1.5)
Discontinuation of all study treatment, n (%)			
Progressive disease	111 (80.4)	103 (87.3)	(b) (4)
Adverse event	4 (2.9)	0	3 (4.5)
Physician decision	0	0	0
Withdrawal by subject	1 (0.7)	6 (5.1)	1 (1.5)
Death	4 (2.9)	2 (1.7)	2 (3.0)
Protocol deviation	0	2 (1.7)	0
On post treatment discontinuation follow-up, n (%)	72 (52.2)	55 (46.6)	20 (29.9)
Off post treatment discontinuation follow-up, n (%)	43 (31.2)	53 (44.9)	16 (23.9)
Death	28 (20.3)	46 (39.0)	9 (13.4)
Lost to follow-up	5 (3.6)	0	3 (4.5)
Withdrawal by subject	10 (7.2)	7 (5.9)	4 (6.0)

Abbreviations: Abema = abemaciclib; *ESR1*-m = estrogen receptor 1 mutation; Imlun = imlunestrant; ITT = intention to treat; n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Source: Table JZLC.4.2

The Applicant's Position:

Disease progression was the most common cause of study treatment discontinuation, with very few patients discontinuing treatment due to AEs. The frequency of treatment discontinuations due to AEs was low across all arms. Withdrawal after randomization and before treatment started were equal across all 3 arms. In EMBER-3 study, on treatment withdrawals for reasons other than disease progression were minimal and similar across treatment arms.

The FDA's Assessment:

Inluriyo (imlunestrant)

The FDA generally agrees with the Applicant's assessment of patient disposition in the ITT and *ESR1m* populations with the following additions:

Early discontinuations:

The FDA performed an analysis of patients in the intention-to-treat population who withdrew consent or were withdrawn by their treating physician between randomization and 56 days (2 cycles) of therapy. Given the open-label design of the EMBER-3 trial, patients may have considered not starting therapy or discontinuing from the study early if they were assigned to the TPC arm because of the added requirements on the trial to receive open-label approved therapies.

Five patients (1.5%) assigned to the TPC arm and two patients (0.6%) assigned to the imlunestrant arm withdrew from the study before starting therapy. An additional patient (Subject ID: (b) (6)) assigned to the TPC arm withdrew after two doses of fulvestrant based on their physician's decision that "other treatment may be more beneficial." Finally, three patients (0.9%) withdrew consent on the TPC arm versus two patients (0.6%) on the imlunestrant arm within 56 days. One patient (Subject ID: (b) (6)) on the TPC arm was diagnosed with a germline BRCA mutation by Guardant360 testing and withdrew consent; however, no information on subsequent therapy was provided. Overall, discontinuations between randomization and the first two doses of study medication were rare but were numerically higher on the TPC arm. It is unlikely that these small differences led to imbalances between the two arms.

The FDA did not evaluate patient dispositions on Arm C since this was out of scope for the proposed indication under this NDA.

Protocol Violations/Deviations

Data:

Protocol deviations were identified, evaluated, and categorized as important or nonimportant prior to unblinding. A nonimportant deviation was one that did not significantly affect data reliability or patient's rights, safety, or well-being. An important deviation was one that could have significantly affected the completeness, accuracy, and/or reliability of data or potentially affected a patient's rights, safety, or well-being.

Table 8.9 summarizes important protocol deviations for **imlunestrant** treatment arm (Arm A) versus the **SOC** arm (Arm B) in the ITT and the *ESR1m*-detected populations. These were similar across populations.

Inluriyo (imlunestrant)

Table 8.9. Summary of Important Protocol Deviations for ESR/m-detected and ITT Population

Category, n (%)	ESR/m-detected Population		ITT Population	
	Arm A Imlunestrant N=138	Arm B SOC N=118	Arm A Imlunestrant N = 331	Arm B SOC N = 330
Number of patients with at least 1 IPD	47 (34.1)	36 (30.5)	105 (31.7)	107 (32.4)
Visit schedule criteria	18 (13.0)	11 (9.3)	36 (10.9)	35 (10.6)
Eligibility criteria	19 (13.8)	13 (11.0)	41 (12.4)	33 (10.0)
Inclusion Criteria #1-14	14 (10.1)	9 (7.6)	33 (10.0)	19 (5.8)
#2	0	1 (0.8)	0	1 (0.3)
#3	8 (5.8)	5 (4.2)	17 (5.1)	10 (3.0)
#5	2 (1.4)	0	3 (0.9)	1 (0.3)
#6	0	0	1 (0.3)	1 (0.3)
#7	0	0	1 (0.3)	0
#8	4 (2.9)	3 (2.5)	11 (3.3)	5 (1.5)
#10	1 (0.7)	0	1 (0.3)	1 (0.3)
#11	0	0	1 (0.3)	0
Exclusion Criteria #15-30	8 (5.8)	4 (3.4)	13 (3.9)	14 (4.2)
#15	0	0	0	1 (0.3)
#19	0	0	1 (0.3)	0
#20	7 (5.1)	3 (2.5)	9 (2.7)	8 (2.4)
#22	0	0	1 (0.3)	1 (0.3)
#23	1 (0.7)	0	1 (0.3)	0
#27	1 (0.7)	1 (0.8)	1 (0.3)	3 (0.9)
#29	0	0	1 (0.3)	1 (0.3)
Treatment assignment/randomization ^a	15 (10.9)	9 (7.6)	35 (10.6)	29 (8.8)
Safety reporting	5 (3.6)	6 (5.1)	9 (2.7)	14 (4.2)
Study procedure compliance	5 (3.6)	3 (2.5)	10 (3.0)	6 (1.8)
Informed consent	2 (1.4)	1 (0.8)	3 (0.9)	6 (1.8)

Inluriyo (imlunestrant)

Category, n (%)	<i>ESR1</i> m-detected Population		ITT Population	
	Arm A Imlunestrant N=138	Arm B SOC N=118	Arm A Imlunestrant N = 331	Arm B SOC N = 330
Investigational medicinal product and/or investigational device	1 (0.7)	1 (0.8)	1 (0.3)	1 (0.3)
Other	0	0	2 (0.6)	4 (1.2)

Abbreviations: *ESR1*m = estrogen receptor 1 mutation- IPD = important protocol deviations; ITT = intention to treat; n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

^a Refers to stratification errors.

Source: Table JZLC.4.3 and Addendum Table JZLC.3.2

The Applicant's Position:

Lilly reviewed the protocol deviations and considered them unlikely to have substantially affected patient safety or the results and conclusions in this report.

The FDA's Assessment:

The FDA generally agrees with the Applicant's characterization of important protocol deviations in the ITT and *ESR1*m populations. The FDA also performed additional analyses of important protocol deviations by subcategories for the ITT population.

The most common protocol deviations under visit schedule criteria were follow up imaging out of window or not performed (9.4% vs 9.0%) and imaging for suspected progression not performed within 14 days (1.5% vs 0.9%).

The most common protocol deviations under inclusion and exclusion criteria were timing and prior lines of therapy (Inclusion Criteria #3: 5.1% vs 3.0%), measurable disease by RECIST v1.1 or non-measurable bone-only disease (Inclusion Criteria #8: 3.3% vs 1.5%), and presence of symptomatic or untreated brain metastasis (Exclusion Criteria #20: 2.7% vs 2.4%). The FDA requested further detail on the patients that did not meet eligibility criteria 3 (**Table 8.10**).

Table 8.10 Patient Deviations for Eligibility Criteria 3

	<i>ESR1</i> m-detected		ITT	
	Deviation Type and Number		Deviation Type and Number	
Inclusion Criteria	Arm A	Arm B	Arm A	Arm B

Inluriyo (imlunestrant)

	imlunestrant n = 138	TPC n = 118	imlunestrant n = 331	TPC n = 330
3a Progressed while on or within 12 months of completion of (neo)adjuvant AI, alone or in combination with a CDK4/6i, with no treatment for advanced disease. Patients relapsing on or within 12 months of completion of (neo)adjuvant tamoxifen, alone or in combination with a CDK4/6i, were not eligible.	no adjuvant AI (n=1)	0	no adjuvant AI (n=1) disease progression > 12 months from adjuvant AI (n=1) treatment for advanced disease (n=1) no adjuvant AI and received treatment for advanced disease (n=1)	no adjuvant AI and received treatment for advanced disease (n=2)
3b Progressed more than 12 months from completion of (neo)adjuvant endocrine therapy (ET, tamoxifen or an AI), with subsequent progression on, or after only 1 line of therapy with an AI, alone or in combination with a CDK4/6i. Patient may not have received any other therapy in the advanced or metastatic setting.	progression < 12 months with treatment for advanced disease (n=4) no adjuvant ET (n=2)	progression < 12 months with treatment for advanced disease (n=3) no adjuvant ET (n=1)	progression < 12 months with treatment for advanced disease (n=8) no adjuvant ET (n=2)	progression < 12 months with treatment for advanced disease (n=4) no adjuvant ET (n=2)
3c Presented de novo with metastatic disease, with subsequent progression on, or after only 1 line of therapy with an AI, alone or in combination with a CDK4/6i. Patient may not have received any other therapy in the advanced or metastatic setting.	received two lines of therapy in metastatic setting (n=1)	received prior radiation therapy for advanced disease (n=1)	received two lines of therapy in metastatic setting (n=1) no AI in the metastatic setting (n=1) no disease progression on or after AI (n=1)	received prior radiation therapy for advanced disease (n=1) no AI in the metastatic setting (n=1)

Inluriyo (imlunestrant)

The most common protocol deviation for inclusion criteria 3 was for patients who progressed less than 12 months after adjuvant ET and received therapy for advanced disease. Only one patient on the imlunestrant arm had an *ESR1* mutation without prior AI therapy. The most common protocol deviations under treatment assignment were incorrect stratification factor (5.8% vs 5.2%) and incorrect characterization of visceral metastatic disease (4.8% vs 3.6%). Sensitivity analyses, including an unstratified analysis and a stratified analysis using stratification factors based on CRF data, were consistent with the primary analysis (**Table 8.18**).

The FDA agrees that the protocol deviations were unlikely to have substantially impacted the efficacy results and did not alter the overall conclusions for the benefit: risk analysis for the intended indication.

Table of Demographic CharacteristicsData:

Table 8.11 summarizes the patient demographics for the **imlunestrant** treatment arm (Arm A) versus the **SOC** treatment arm (Arm B).

Table 8.11. Summary of Patient Demographics

Category	ESR1m-detected Population		ITT Population	
	Arm A Imlunestrant N = 138	Arm B SOC N = 118	Arm A Imlunestrant N = 331	Arm B SOC N = 330
Age (years)				
Median	61.0	59.5	61.0	62.0
Range	28-85	33-85	28-87	27-89
< 65	91 (65.9)	78 (66.1)	211 (63.7)	197 (59.7)
≥65	47 (34.1)	40 (33.9)	120 (36.3)	133 (40.3)
Sex, n (%)				
Female	138 (100)	118 (100)	327 (98.8)	329 (99.7)
Male	0	0	4 (1.2)	1 (0.3)
Weight, kg				
Median	69.40	69.80	66.95	67.45
Range	42.5-111.0	38.0-127.3	37.0-142.7	38.0-129.1
Race, n (%)				
White	80 (58.0)	76 (64.4)	186 (56.2)	191 (57.9)
Black or African American	7 (5.1)	3 (2.5)	11 (3.3)	7 (2.1)
Asian	35 (25.4)	31 (26.3)	92 (27.8)	96 (29.1)

Inluriyo (imlunestrant)

Category	<i>ESR1</i> m-detected Population		ITT Population	
	Arm A Imlunestrant N = 138	Arm B SOC N = 118	Arm A Imlunestrant N = 331	Arm B SOC N = 330
American Indian or Alaska native	7 (5.1)	3 (2.5)	23 (6.9)	16 (4.8)
Multiple	1 (0.7)	1 (0.8)	2 (0.6)	7 (2.1)
Missing	8 (5.8)	4 (3.4)	17 (5.1)	13 (3.9)
Ethnicity, n (%)				
Hispanic or Latino	25 (18.1)	23 (19.5)	79 (23.9)	80 (24.2)
Not Hispanic or Latino	98 (71.0)	83 (70.3)	218 (65.9)	216 (65.5)
Not Reported	14 (10.1)	12 (10.2)	33 (10.0)	34 (10.3)
Region, n (%)				
East Asia	30 (21.7)	26 (22.0)	83 (25.1)	84 (25.5)
North America/Western Europe	63 (45.7)	54 (45.8.)	127 (38.4)	127 (38.5)
Other	45 (32.6)	38 (32.2)	121 (36.6)	119 (36.1)

Abbreviations: *ESR1*m = estrogen receptor 1 mutation; ITT = intention to treat; n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Source: Table JZLC.4.5

The Applicant's Position:

Demographic and baseline characteristics of patients were adequately reflective of ER+, HER2-ABC, and were generally balanced across treatment arms. Baseline characteristics for age, sex, ECOG, region, menopausal status, presence of visceral metastases, bone-only disease, endocrine resistance, and prior CDK 4/6i use were balanced across treatment arms for ITT and *ESR1*m subgroups (Table 8.11).

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment that patient demographics were well balanced between treatment arms in the *ESR1*m patient population, even though *ESR1* mutation status was not a stratification factor at the randomization. Patients had a better performance status than would be expected for a US population receiving second-line endocrine therapy. No male patients with an *ESR1*m were enrolled. Few Black or African-American patients with *ESR1*m breast cancer were enrolled relative to the prevalence of ER-positive, HER2-negative breast cancer in the US. Collectively, these limit the interpretation of the results for some of the

Inluriyo (imlunestrant)

US population that are likely to receive imlunestrant; however, did not alter the overall conclusions for approval for the intended indication.

Other Baseline Characteristics (for example, disease characteristics, important concomitant drugs)

Data:

Table 8.12 summarizes key patient baseline disease characteristics for the **imlunestrant** treatment arm (Arm A) versus the **SOC** treatment arm (Arm B) for the ITT and *ESR1*-detected populations.

Table 8.12. Summary of Key Baseline Disease Characteristics

Characteristic	ESR1m-detected Population		ITT Population	
	Arm A Imlunestrant N=138	Arm B SOC N=118	Arm A Imlunestrant N=331	Arm B SOC N=330
ECOG performance status, n (%)				
0	85 (61.6)	77 (65.3)	219 (66.2)	208 (63.0)
1	53 (38.4)	41 (34.7)	112 (33.8)	122 (37.0)
Progesterone receptor-positive, n (%)	109 (79.0)	97 (82.2)	257 (77.6)	260 (78.8)
ESR1 mutation, n (%)^a	138 (100)	118 (100)	138 (41.7)	118 (35.8)
PI3K pathway mutations, n (%)^b	72 (52.2)	57 (48.3)	129 (39.0)	128 (38.8)
Measurable disease at baseline, n (%)	112 (81.2)	91 (77.1)	262 (79.2)	251 (76.1)
Site of metastases, n (%)				
Visceral	84 (60.9)	67 (56.8)	189 (57.1)	177 (53.6)
Liver	57 (41.3)	47 (39.8)	107 (32.3)	98 (29.7)
Bone-only	27 (19.6)	30 (25.4)	72 (21.8)	86 (26.1)
Endocrine resistance, n (%)^c				
Primary	0	0	25 (7.6)	36 (10.9)
Secondary	138 (100.0)	118 (100.0)	305 (92.1)	293 (88.8)
Most recent ET, n (%)				
Adjuvant	29 (21.0)	23 (19.5)	106 (32.0)	113 (34.2)
ABC	101 (73.2)	91 (77.1)	208 (62.8)	208 (63.0)
Previous CDK4/6i in any setting, n (%)				
Overall	93 (67.4)	85 (72.0)	195 (58.9)	189 (57.3)
Adjuvant	3 (2.2)	3 (2.5)	14 (4.2)	15 (4.5)
ABC	90 (65.2)	82 (69.5)	181 (54.7)	174 (52.7)
Previous CDK4/6i therapy, n (%)				
Palbociclib	64 (46.4)	61 (51.7)	118 (35.6)	130 (39.4)
Ribociclib	22 (15.9)	22 (18.6)	56 (16.9)	50 (15.2)

Inluriyo (imlunestrant)

Characteristic	ESR/m-detected Population		ITT Population	
	Arm A Imlunestrant N=138	Arm B SOC N=118	Arm A Imlunestrant N=331	Arm B SOC N=330
Abemaciclib	7 (5.1)	2 (1.7)	19 (5.7)	7 (2.1)
Previous CDK4/6i duration, n (%)				
≥12 months	76 (55.1)	66 (55.9)	131 (39.6)	133 (40.3)
<12 months	14 (10.1)	16 (13.6)	50 (15.1)	41 (12.4)

Abbreviations: ABC = advanced breast cancer; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; ECOG = Eastern Cooperative Oncology Group; ESO-ESMO = European School of Oncology-European Society for Medical Oncology; ESR/m = estrogen receptor 1 mutation; ET = endocrine therapy; ITT = intention to treat; n = number of patients in the specific category; N = number of patients; PI3K = phosphoinositide 3-kinase; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

- a Per central assessment from pretreatment plasma samples using prespecified definition with ESR/m circulating tumor DNA (ctDNA) by Guardant 360 (by Guardant Health) and the OncoCompass Target assay (by Burning Rock Biotech used exclusively for patients from China [n = 40]). Includes patients that were ESR1-mutation evaluable and had detectable ESR1-mutation.
- b Includes single nucleotide variants and insertions/deletions of *PIK3CA*, *AKT1*, or *PTEN* analyzed by Guardant 360 ctDNA assay, excluding 40 patients from China.
- c Per ESO-ESMO International Consensus Guidelines for ABC 6 and 7.

The Applicant's Position:

The baseline disease burden observed in the ESR/m-detected population was representative of patients with ER+, HER2-, locally advanced or MBC previously treated with ET, with or without a CDK4/6i and balanced across the treatment arms. This was also consistent for the broader ITT population.

All EMBER-3 stratification factors (previous treatment with any CDK4/6i, presence of visceral metastasis, and region) were evenly distributed within the ESR/m-detected subpopulation.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment that baseline disease characteristics were well balanced between treatment arms in the ESR/m patient population. However, FDA performed an analysis of disease characteristics in ESR/m patients from the United States (US) and Western Europe (WE) that showed more bone-only disease and less visceral disease in patients on the TPC arm (**Table 8.13**). This may explain why the magnitude of PFS benefit was lower for the TPC arm in the US/WE region with a HR of 0.77 (95% CI 0.51, 1.17).

Table 8.13. Disease Characteristics in Select Regions

	All Implunestrant n = 138 (%)	All TPC n = 118 (%)	US/WE Implunestrant n = 63 (%)	US/WE TPC n = 54 (%)
Site of metastasis				
Visceral	84 (61)	67 (57)	37 (59)	25 (46)
Bone-only	27 (20)	30 (25)	15 (24)	21 (39)

PIK3CA mutations and AKT/mTOR pathway alterations were higher in the *ESR1m* population, consistent with co-occurrence in this patient population.

While the trial excluded patients that were HER2-positive by ASCO/CAP Guidelines, the data to perform an analysis of patients that may have had HER2-low or HER2-ultralow breast cancer was substantially missing or not collected, respectively. The therapeutic landscape for HER-low and -ultralow was evolving during the conduct of EMBER-3, impacting available subsequent therapies based on timing and region. Therefore, no further analysis could be conducted for these populations due to this limitation in the data.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment compliance

Treatment compliance for implunestrant and exemestane was assessed through pill counts at each cycle.

Compliance for fulvestrant was assured as the drug was administered at the investigator site.

Concomitant medication

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) received while on study and during the short-term follow-up was recorded. Anticancer therapies (including, chemotherapy, immunotherapy) were not permitted while on study treatment.

The frequency of patients who received GnRH and bone-modifying agents while on treatment was similar across treatment arms within both the overall safety population and the *ESR1m*-detected safety population.

Inluriyo (implunestrant)

APPEARS
THIS WAY
ON
ORIGINAL

provides concomitant therapy information for patients enrolled in the safety population for the **implunestrant** treatment arm (Arm A) and the **SOC** treatment arm (Arm B).

Table 8.14. Categories of Selected Concomitant Therapy in the Safety Population

Category, n (%)	<i>ESR1</i> m-detected Safety Population		Overall Safety Population	
	Arm A Implunestrant N = 137	Arm B SOC N=117	Arm A Implunestrant N = 327	Arm B SOC N = 324
Number of patients that received ≥ 1 form of concomitant therapy	130 (94.9)	113 (96.6)	307 (93.9)	315 (97.2)
Analgesics	85 (62.0)	74 (63.2)	202 (61.8)	177 (54.6)
Bone-modifying agents	72 (52.6)	64 (54.7)	146 (44.6)	153 (47.2)
Antimicrobials	39 (28.5)	30 (25.6)	79 (24.2)	73 (22.5)
GnRH	18 (13.1)	15 (12.8)	60 (18.3)	51 (15.7)
Antidiarrheals	14 (10.2)	10 (8.5)	33 (10.1)	23 (7.1)
Antiemetics and antinauseants	14 (10.2)	15 (12.8)	32 (9.8)	33 (10.2)
G-CSF/GM-CSF	4 (2.9)	1 (0.9)	6 (1.8)	3 (0.9)
Erythropoietic agents	0	2 (1.7)	0	3 (0.9)

Abbreviations; *ESR1*m = estrogen receptor 1 mutation; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; GnRH = gonadotropin hormone-releasing hormone agonist; n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Source: Table JZLC.4.10 and Addendum Table JZLC.3.3

Rescue medication

Not applicable.

The Applicant's Position:

Treatment compliance in this study was high across all treatment arms. The therapeutic classes of concomitant medication used were appropriate and were not considered to have impacted study results.

The FDA's Assessment:

Inluriyo (imlunestrant)

The FDA generally agrees with the Applicant's assessment of concomitant medications.

The FDA also performed an analysis of subsequent therapies (**Table 8.15**). More patients with *ESR1m* disease on the TPC arm received their first CDK4/6 inhibitor after discontinuing EMBER-3: 8 (7%) versus 2 (1.4%) on the imlunestrant arm. Six patients with *ESR1m* on each arm received bevacizumab (anti-VEGF antibody) which is not widely used in the US. Trastuzumab deruxtecan was only given to 3 (2.2%) patients on the imlunestrant arm and none on the TPC arm. Very few patients (<5%) on both arms received a subsequent *PIK3CA* or AKT inhibitor relative to the incidence of these alterations (**Table 8.12**) in the *ESR1m* population.

Table 8.15 Subsequent Anticancer Therapies in the *ESR1m* Population

	<i>ESR1m</i> population imlunestrant n = 138 (%)	<i>ESR1m</i> population TPC n = 118 (%)
Any	88 (64)	88 (75)
1 line	44 (32)	43 (36)
≥ 1 line	44 (32)	45 (38)
Chemotherapy	59 (43)	65 (55)
Targeted therapy		
mTOR	19 (14)	14 (12)
PI3K	6 (4.3)	3 (2.5)
VEGF	6 (4.3)	6 (5)
HER2	6 (4.3)	7 (6)
ER (<i>ESR1m</i>)	2 (1.4)	4 (3.4)
TROP2	1 (0.7)	3 (2.5)
PARP	0	1 (0.8)
CDK4/6	15 (11)	16 (14)
No prior CDK4/6i	2 (1.4)	8 (7)

mTOR = mammalian target of rapamycin; PI3K = phosphatidylinositol kinase 3; VEGF = vascular endothelial growth factor; HER2 = human epidermal growth factor 2; ER = estrogen receptor alpha; TROP2 = trophoblastic cell surface antigen; PARP = poly (ADP-ribose) polymerase; CDK4/6 = cyclin dependent kinase 4 and 6

Inluriyo (imlunestrant)

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)Data:*Progression-free survival by investigator assessment (primary endpoint)*

EMBER-3 met its primary endpoint in the *ESR/m*-detected population.

Imlunestrant demonstrated a statistically significant and clinically meaningful improvement in investigator-assessed PFS compared with **SOC**. Treatment with imlunestrant reduced the hazard of disease progression or death by 38% (stratified HR = 0.617 [95% CI: 0.464, 0.821]). The median PFS was 5.49 months versus 3.84 months (**imlunestrant** versus **SOC**), representing a 1.64-month longer median PFS in the **imlunestrant** arm. A sustained PFS benefit was suggested with separation of PFS curves beyond the median and enhanced benefit at 6- and 12-month landmark analyses favoring **imlunestrant** (Table 8.16).

**Table 8.16. INV-Assessed PFS
ESR/m-detected Population
Imlunestrant versus SOC**

Category	Arm A Imlunestrant N = 138	Arm B SOC N = 118
Number of events, n (%)	109 (79.0)	102 (86.4)
Disease progression	105 (76.1)	98 (83.1)
Death without disease progression	4 (2.9)	4 (3.4)
Number of patients censored, n (%)	29 (21.0)	16 (13.6)
Progression-free survival (months)		
Median PFS, months (95% CI) ^{a,b}	5.49 (3.91, 7.39)	3.84 (3.68, 5.52)
HR (95% CI) stratified ^c	0.617 (0.464, 0.821)	
p-value (2-sided) log-rank stratified ^c	0.0008	
Restricted mean (95%CI) with restriction time = 19.38 ^d		
Months (95% CI)	7.93 (6.81, 9.05)	5.37 (4.58, 6.15)
Difference (95% CI)	2.56 (1.19, 3.93)	
Nominal p-value (2-sided) ^e	0.0002	
Duration of follow-up (months)		
Median, months (95% CI)	16.69 (13.70, -)	13.80 (9.40, -)
Rate (%) of progression-free survival ^f		
6 months (95% CI)	44.1 (35.5, 52.4)	32.1 (23.4, 41.1)
12 months (95% CI)	24.5 (16.9, 32.9)	6.6 (2.7, 13.0)

Inluriyo (imlunestrant)

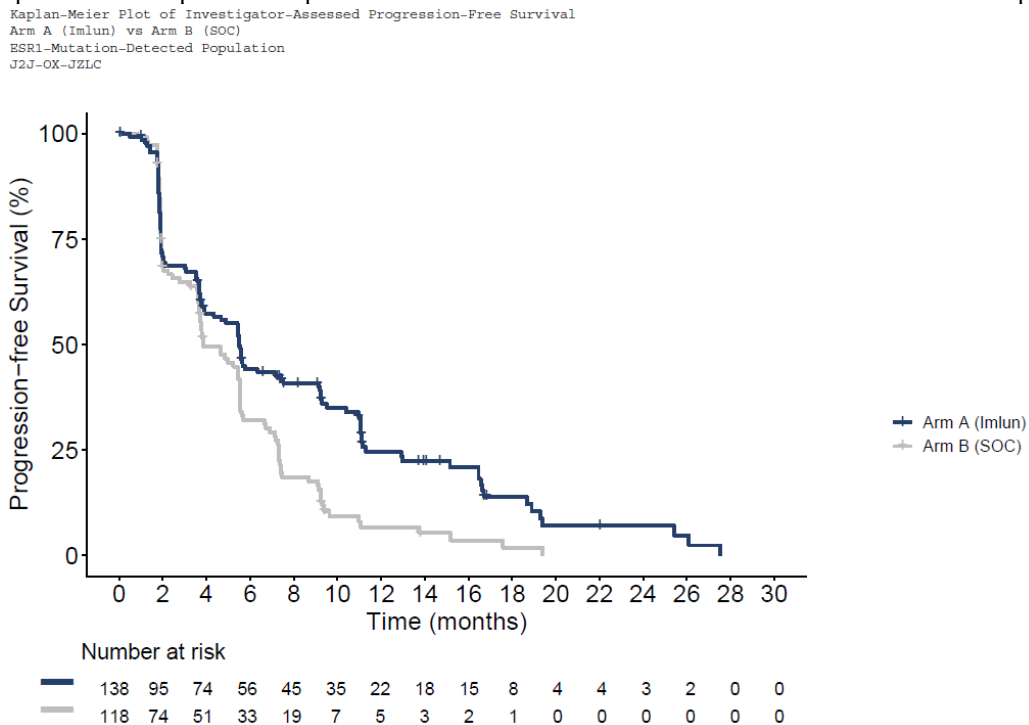
Abbreviations: CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; *ESR/m* = estrogen receptor 1 mutation; HR = hazard ratio; INV = investigator; IWRS = interactive web response system; n = number of patients in the specific category; N = number of patients; PFS = progression-free survival; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

- a Estimate based on the Kaplan-Meier method.
- b 95% CI was calculated using the Brookmeyer and Crowley method.
- c Stratified by visceral metastases status from IWRS, prior CDK4/6i treatment from IWRS.
- d Restriction time is defined by the latest time where the standard error of the survival estimates are ≤ 0.075 .
- e 2-sided p-value based on normal approximation.
- f 95% CI and 2-sided p-value for the difference between rates were calculated based on normal approximation.

Source: Table JZLC.5.10

Inluriyo (implunestrant)

Figure 8.4 presents the Kaplan-Meier plot for PFS in **implunestrant** and for **SOC** in the *ESR1*/m-detected population.



Abbreviations: *ESR1*/m = estrogen receptor 1 mutation; Implun = implunestrant; PFS = progression-free survival; SOC = standard of care investigator’s choice endocrine therapy of fulvestrant or exemestane.
Source: Figure JZLC.5.5

Figure 8.4. **Kaplan-Meier plot of INV-assessed PFS**
***ESR1*/m-detected population**
Implunestrant versus SOC.

Progression-free survival by blinded independent review committee (secondary endpoint)

BIRC-assessed PFS was consistent with the investigator-assessed PFS (Table 8.17)

Table 8.17. **BIRC-Assessed PFS**
Implunestrant versus SOC
***ESR1*/m Population**

Category	Arm A Implunestrant N = 138	Arm B SOC N = 118
Number of events, n (%)	74 (53.6)	71 (60.2)
Disease progression	69 (50.0)	65 (55.1)
Death without disease progression	5 (3.6)	6 (5.1)

Inluriyo (imlunestrant)

Category	Arm A Imlunestrant N = 138	Arm B SOC N = 118
Number of patients censored, n (%)	64 (46.4)	47 (39.8)
Progression-free survival (months)		
Median PFS, months (95% CI) a,b	7.43 (4.83, 11.07)	5.49 (3.84, 6.70)
HR (95% CI) stratified ^c	0.657 (0.469, 0.92)	
Nominal p-value (2 sided) log-rank stratified ^c	0.0129	
Rate (%) of progression-free survival ^d		
6 months (95% CI)	53.4 (44.0, 62.0)	40.0 (29.6, 50.1)
12 months (95% CI)	37.2 (27.2, 47.2)	12.8 (5.0, 24.4)

Abbreviations: BIRC = blinded independent review committee; CDK6/4i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; *ESR1*/m = estrogen receptor 1 mutation; HR = hazard ratio; IWRS = interactive web response system; n = number of patients in the specific category; N = number of patients; PFS = progression-free survival; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

^a Estimate based on the Kaplan-Meier method.

^b 95% CI was calculated using the Brookmeyer and Crowley method.

^c Stratified by visceral metastases status from IWRS, prior CDK6/4i treatment from IWRS.

^d 95% CI and 2-sided p-value for the difference between rates were calculated based on normal approximation.

Source: JZLC.5.12

Progression-free survival sensitivity analyses

The prespecified PFS sensitivity analyses demonstrated HRs consistent with the primary analysis ranging between 0.532 and 0.637, further supporting the robustness of the benefit of treatment with **imlunestrant** compared to **SOC** in the *ESR1*/m-detected population ([Table 8.18](#)).

**Table 8.18. Prespecified Sensitivity Analyses for PFS
ESR1/m-detected Population
Imlunestrant versus SOC**

Analysis Description	Hazard Ratio (95% CI)
Progression-free survival per Investigator (primary)	0.617 (0.464, 0.821)
Progression-free survival per BIRC (secondary)	0.657 (0.469, 0.920)
Sensitivity analyses per different censoring rules^a	
Ignoring new anticancer therapy prior to tumor progression or death ^b	0.611 (0.461, 0.809)
Ignoring absence of adequate postbaseline tumor assessment ^c	0.637 (0.481, 0.844)
Ignoring missing tumor assessments ^d	0.637 (0.481, 0.844)
Ignoring all censoring rules defined in the PFS Censoring	0.623 (0.472, 0.822)

Inluriyo (imlunestrant)

Analysis Description	Hazard Ratio (95% CI)
Scheme tables ^e	
Unstratified analysis	0.605 (0.457, 0.801)
Stratified analysis based on CRF data	0.612 (0.460, 0.815)
Stratified analysis including randomization scheme as another stratification factor ^f	0.602 (0.450, 0.805)
Stratified analysis including the same stratification factors as in ITT analysis	0.623 (0.465, 0.833)
Multivariate Cox regression ^g	0.591 (0.445, 0.784)
Progression-free survival based on the per-protocol population	0.532 (0.395, 0.716)

Abbreviations: BIRC = blinded independent review committee; CDK4/6 = cyclin-dependent kinase 4/6; CI = confidence interval; CRF = case report form; *ESR1*/m = estrogen receptor 1 mutation; ITT = intention to treat; IWRS = interactive web response system; PFS = progression-free survival; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

- a Stratified by Visceral Metastases Status from IWRS, Prior CDK4/6 Inhibitor Treatment from IWRS
b Disease progression or death occurred after the start date of the new therapy were counted as events.
c No postbaseline tumor assessment available, but deaths reported after 2-scan intervals were counted as events.
d Disease progression or death documented after 2 or more missing scan intervals following the last adequate tumor assessment were counted as events.
e All disease progression or death were counted as events, unless there was no baseline tumor assessment.
f Stratified analyses by including randomization scheme (patients were randomly assigned 1:1 under the original protocol versus 1:1:1 under Amendment [a]).
g Multivariate Cox regression model adjusting for prior CDK4/6 inhibitor, age group, and bone-only metastasis.
Source: JZLC.5.14

Progression-free survival subgroup analyses

Investigator-assessed PFS analyses were performed across prespecified subgroups. These subgroups included

- age (<65 and ≥65 years)
- race (Asian, Caucasian, Other)
- geographic region (Asia, Europe, North America, Other)
- investigator choice of SOC (fulvestrant or exemestane)
- presence of visceral metastasis (yes/no),
- bone-only metastasis, and
- prior CDK4/6i (yes/no and specific CDK4/6i).

Consistent treatment effect was observed across all prespecified subgroups in the ITT and *ESR1*/m-detected population.

The Applicant's Position:

Inluriyo (imlunestrant)

EMBER-3 met its primary endpoint in the *ESR/m*-detected population.

Treatment with **imlunestrant** demonstrated a statistically significant and clinically meaningful improvement in investigator-assessed PFS in the *ESR/m*-detected population compared with **SOC**. Imlunestrant led to a 38% reduction in tumor progression compared with **SOC**. The benefit of imlunestrant was sustained throughout with an enhanced PFS advantage seen at 6 and 12 months. These results were also supported by BIRC-assessed PFS, a predefined secondary endpoint, which also showed that there was no evidence of investigator bias favoring imlunestrant in this open-label study.

The observed PFS benefit of imlunestrant was consistent across subgroups with no significant difference observed for age, sex, race/ethnicity, region, visceral metastases, liver metastases, bone-only metastases, prior CDK4/6i treatment, or whether it was administered as first-line or second-line treatment for ABC.

The FDA's Assessment:

This application is based on the results of final PFS analysis and the first interim OS analysis for the comparison of the imlunestrant arm and TPC arm in the *ESR/m*-detected population with DCO date of June 24, 2024 in EMBER-3. All p-values and boundaries presented in Section 8.1.2 are 2-sided. Of note, the significance levels presented in Section 8.1.1 as well as the initial alpha allocated to each hypothesis testing shown in **Figure 8.2** are 1-sided.

The final PFS analysis for the comparison of the imlunestrant arm and TPC arm in the ITT population was planned to be conducted when 480 PFS events were observed from the imlunestrant arm and the TPC arm in the ITT population. At the DCO date of June 24, 2024, 490 PFS events were observed from the imlunestrant arm and the TPC arm in the ITT population. At this DCO date, the number of PFS events observed for the comparison of the imlunestrant arm and TPC arm in the *ESR/m*-detected population was 211, which was greater than the pre-specified 192 PFS events for the final PFS analysis in this population, therefore, no interim PFS analysis for the comparison of imlunestrant arm and TPC arm in the *ESR/m*-detected population was conducted and the PFS analysis conducted with DCO date of June 24, 2024 was the final PFS analysis for the comparison of imlunestrant arm and TPC arm in the *ESR/m*-detected population.

Landmark analyses for time-to-event endpoints are considered exploratory since specific time points are used as opposed to assessing the entire survival distribution. Therefore, any differences between treatment arms at these landmarks must be interpreted with caution.

As *ESR1m* status was not a stratification factor at randomization, this may increase the risk of imbalance in baseline characteristics. To address this concern, the sponsor performed the prespecified sensitivity analysis using a multivariate Cox regression model adjusted for baseline

Inluriyo (imlunestrant)

covariates, and the results appeared to showed treatment benefit consistent with the primary analysis results (**Table 8.18**).

The primary endpoint of investigator-assessed PFS for the comparison of the imlunestrant arm and TPC arm in the *ESR1*m-detected population crossed the initially allocated alpha of 0.04 (2-sided) and was statistically significant. The graphical representation of testing schema was updated with alpha levels recalculated, and the investigator-assessed PFS for the comparison of the imlunestrant arm vs TPC arm in the ITT population was formally tested at 0.038 (2-sided) alpha level. The HR for the investigator-assessed PFS for the comparison of the imlunestrant arm vs TPC arm in the ITT population was 0.87 (95% CI: 0.72, 1.04), the observed median PFS was 5.6 (95% CI: 5.3, 7.3) months in the imlunestrant arm and 5.5 (95% CI: 4.6, 5.6) months in the TPC arm. The 2-sided stratified log-rank test p-value was 0.1158, which didn't cross the significance alpha level of 0.038 (2-sided).

- *Lack of PFS benefit of imlunestrant over TPC in the ESR1m-nd population*

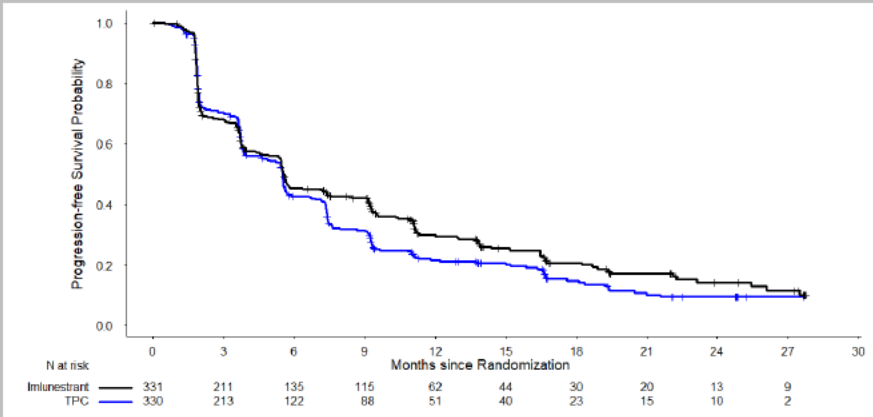
The Applicant conducted an exploratory analysis of investigator-assessed PFS for the comparison of the imlunestrant arm and TPC arm in patients without *ESR1* mutation (n=405, 61.3% of the ITT population). The HR was 1.00 (95% CI: 0.79, 1.27). The observed median PFS was 5.6 (95% CI: 4.4, 9.1) months in the imlunestrant arm and 5.7 (95% CI: 5.5, 7.4) months in the TPC arm. The Applicant's analysis in patients without *ESR1* mutation included 20 patients whose *ESR1* mutation status was failed or missing (13 from the imlunestrant arm and 7 from the TPC arm). The FDA review team conducted an exploratory analysis of investigator-assessed PFS for the comparison of imlunestrant arm and TPC arm in the *ESR1*m-not detected (*ESR1*m-nd) population by excluding these 20 patients whose *ESR1* mutation status was failed or missing (n=385). The HR was 1.04 (95% CI: 0.82, 1.33). The observed median PFS was 5.6 (95% CI: 3.8, 7.3) months in the imlunestrant arm and 5.6 (95% CI: 5.5, 7.4) months in the TPC arm (**Table 8.19**). No treatment benefit for PFS was observed in the *ESR1*m-nd population.

Table 8.19: Investigator-Assessed PFS in the ITT Population the *ESR1*m-nd Population (Imlunestrant versus TPC)

	ITT		<i>ESR1</i> m-nd	
	Imlunestrant (N=331)	TPC (N=330)	Imlunestrant (n=180)	TPC (n=205)
Number of events, n (%)	237 (71.6)	253 (76.7)	121 (67.2)	144 (70.2)
Number of patients censored, n (%)	94 (28.4)	77 (23.3)	59 (32.8)	61 (29.8)
Median PFS, months (95% CI)	5.6 (5.3, 7.3)	5.5 (4.6, 5.6)	5.6 (3.8, 7.3)	5.6 (5.5, 7.4)
Hazard ratio (95% CI)	0.87 (0.72, 1.04)		1.04 (0.82, 1.33)	

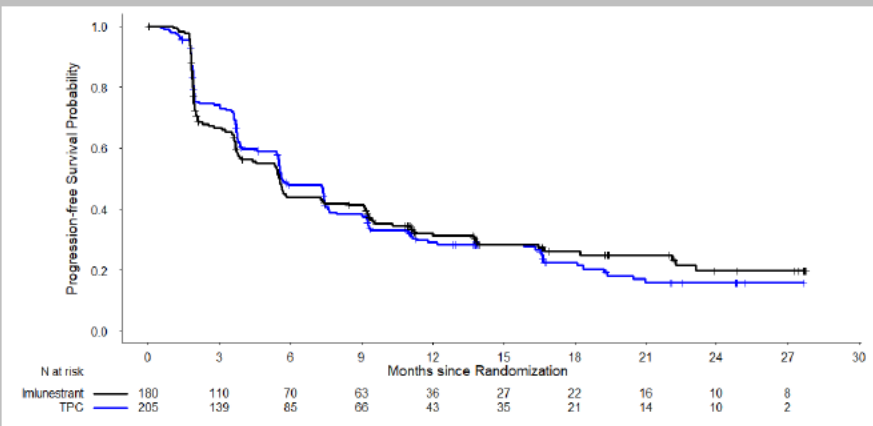
Inluriyo (imlunestrant)

Figure 8.5: Kaplan-Meier Plot for Investigator-Assessed PFS in the ITT Population (Imlunestrant versus TPC)



(Source: FDA analysis)

Figure 8.6: Kaplan-Meier Plot for Investigator-Assessed PFS in the *ESR1*m-nd Population (Imlunestrant versus TPC)



(Source: FDA analysis)

EMBER-3 met its primary endpoint of investigator-assessed PFS in the *ESR1*m-detected population but didn't meet its primary endpoint of investigator-assessed PFS in the ITT population. In the *ESR1*m-nd population, no treatment benefit for PFS was observed with treatment of imlunestrant compared with TPC (Figure 8.5 and Figure 8.6).

- *Non-proportional hazards*

Inluriyo (imlunestrant)

In the *ESR1m*-detected population, the PFS Kaplan-Meier curves overlapped throughout the first 4 months and started to separate thereafter (**Figure 8.4**), which indicated that the assumption of exponential distribution was not met. Late separation in the KM curves persisted and led to an observed benefit in the PFS hazard ratio. The Applicant conducted an exploratory analysis of PFS using the restricted mean survival time (RSMT) to further quantify the treatment benefit for PFS (Table 8.13). The estimated RSMT at 19.4 months was 7.9 months (95% CI: 6.8, 9.1) in the imlunestrant arm vs 5.4 months (95% CI: 4.6, 6.2) in the TPC arm [difference 2.6 months (1.2.-3.9)]. It is noted that RMST results could change if a different cutoff timepoint was chosen; therefore, the RMST analysis is considered to be supportive only.

- *Discordance between PFS per investigator assessment and PFS per BIRC assessment*

The review team assessed the discordance rate of PFS assessments between investigator and BIRC (**Table 8.20**). In the ITT population, more patients in the TPC arm were censored by BIRC but considered as having a PFS event by investigator than patients in the imlunestrant arm (31.5% in the TPC arm vs 26.9% in the imlunestrant arm).

Table 8.20: Discordance Analysis for PFS per Investigator Assessment vs PFS per BIRC Assessment

	Imlunestrant		TPC	
	PFS-BIRC Event	PFS-BIRC Censor	PFS-BIRC Event	PFS-BIRC Censor
ITT	N=331		N=330	
PFS-INV Event	148 (44.7)	89 (26.9)	149 (45.2)	104 (31.5)
PFS-INV Censor	12 (3.6)	82 (24.8)	10 (3.0)	67 (20.3)
<i>ESR1m</i>	N=138		N=118	
PFS-INV Event	68 (49.3)	41 (29.7)	68 (57.6)	34 (28.8)
PFS-INV Censor	6 (4.3)	23 (16.7)	3 (2.5)	13 (11.0)

(Source: FDA’s analysis)

To evaluate whether the observed discordance suggested an investigator bias favoring the imlunestrant arm in the investigator-assessed PFS analysis, the Applicant calculated the early discordance rate (EDR) and the late discordance rate (LDR) for each arm. EDR was the frequency of investigator-assessed progressions before central review as a proportion of all investigator progressions. LDR was the frequency of investigator-assessed progressions after central review as a proportion of all discrepancies. A negative differential discordance for the EDR and/or a positive differential discordance for the LDR between the experimental arm and the control arm beyond a threshold would suggest a possible bias in the investigator assessments

Inluriyo (imlunestrant)

favoring the experimental arm. Threshold values ranging from 0.075 to 0.1 were recommended based on simulation studies in Amit et al. 2011.

Table 8.21: Discordance Analysis for PFS per Investigator Assessment vs PFS per BIRC Assessment

	Imlunestrant	TPC	Difference (Imlunestrant - TPC)
ITT			
Early discrepancy rate	0.426	0.431	-0.005
Late discrepancy rate	0.340	0.310	0.030
ESR1m			
Early discrepancy rate	0.440	0.363	0.078
Late discrepancy rate	0.351	0.339	0.012

(Source: Adapted from CSR Table JZLC.5.5 and Table JZLC.5.13)

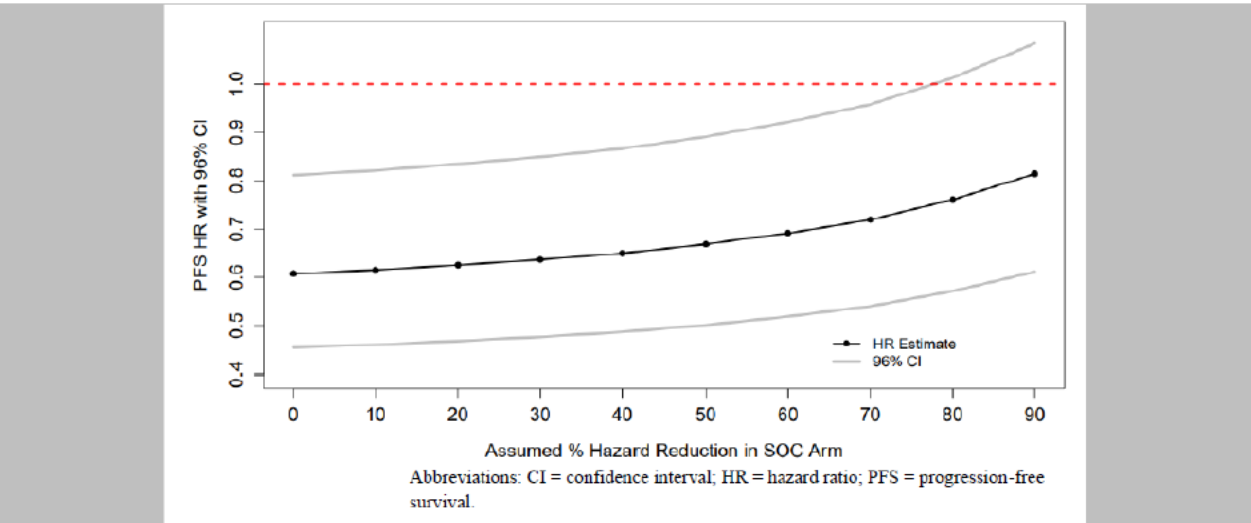
In both the ITT population and the *ESR1m*-detected population, neither EDR rate nor LDR rate crossed the threshold value of 0.075, thus they do not suggest an investigator assessment bias in favor of imlunestrant arm in these populations (**Table 8.21**).

- Impact of early censoring in PFS analysis*

For the comparison of imlunestrant vs TPC in the *ESR1m* population, more patients in the TPC arm were censored early in the PFS analysis compared to those in the imlunestrant arm: 12 patients (10.2%) in the TPC arm were censored within 4 months after randomization compared to 7 patients (5.1%) in the imlunestrant arm. Per FDA's request, the Applicant conducted a tipping point analysis for PFS (**Figure 8.7**). The results suggest that even if the early censored patients in the TPC arm were to have at least 75% lower risk of PFS compared to the other chemotherapy arm patients, the 96% CI of the estimated PFS HR still won't cross 1. Based on the tipping point analysis, early censoring in the TPC arm were unlikely to change the statistical significance conclusion for PFS in the *ESR1m*-detected population.

Figure 8.7: Tipping-point Analysis for Early Censoring on Investigator-assessed PFS in the *ESR1m*-detected Population (Imlunestrant versus TPC)

Inluriyo (imlunestrant)



(Source: Applicant’s response to FDA’s Information Request)

• Impact of palliative radiation therapy

The palliative radiation therapy was permitted in EMBER-3. In a response to an FDA’s information request, the Applicant stated that sixteen patients (9 from the imlunestrant arm and 7 from the TPC arm) received on-therapy palliative radiation in the *ESR1*m-detected population. Per FDA’s information request, the Applicant conducted sensitivity analyses to evaluate the impact of receiving palliative radiation therapy. The sensitivity analyses results are summarized in Table 8.22. The sensitivity analyses showed consistent results with the primary PFS findings.

Table 8.22: Sensitivity Analyses of Investigator-assessed PFS to Assess the Impact of Palliative Radiation Therapy in the *ESR1*m-detected Population (Imlunestrant versus TPC)

Analysis	HR (95% CI)
Patients who received subsequent anticancer therapy (including palliative radiotherapy) without PD are counted as having PFS events at the time of receiving subsequent anticancer therapy.	0.64 (0.49, 0.84)
Patients who received subsequent anticancer therapy (excluding palliative radiotherapy) without PD are censored at the last tumor assessment prior to initiation of subsequent anticancer therapy, and patients who received palliative radiotherapy are counted as having PFS events at the time of receiving palliative radiotherapy.	0.62 (0.47, 0.82)

(Source: Applicant’s responses to FDA’s Information Request)

Inluriyo (imlunestrant)

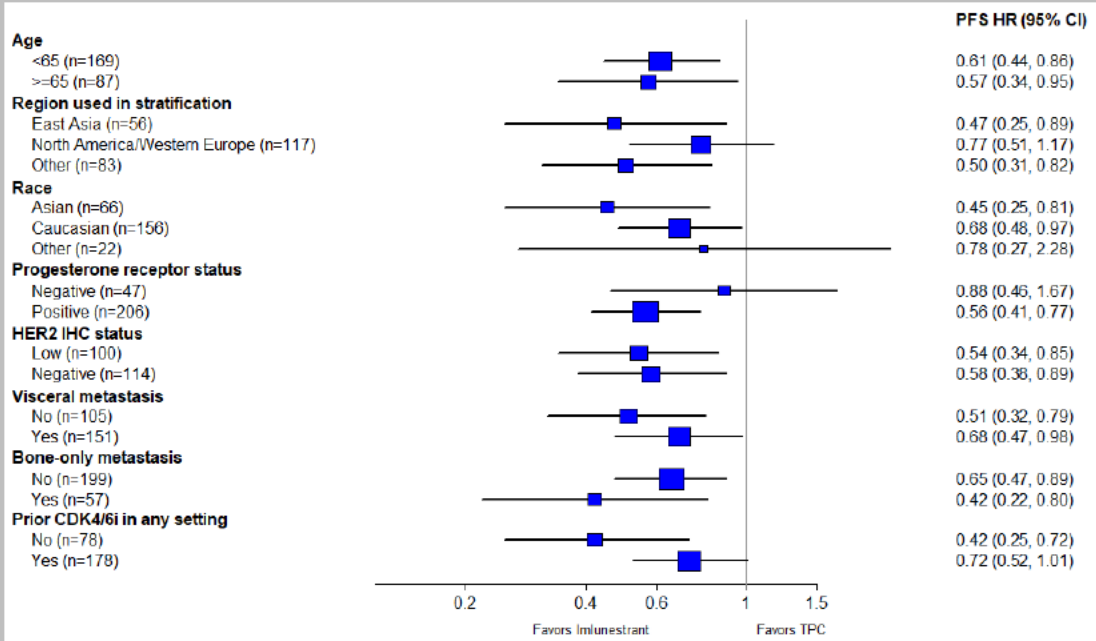
• *ESR1 mutation status based on Guardant 360 ctDNA assay*

Per EMBER3 study schema in Protocol (d), *ESR1* mutation status was planned to be centrally determined in plasma by Guardant 360 ctDNA assay from a blood draw at baseline. Among 256 patients in the *ESR1*m-detected population for the comparison of the imlunestrant arm and TPC arm, all patients were tested with *ESR1* mutation by Guardant 360 ctDNA assay except two patients in the imlunestrant arm who were tested with *ESR1* mutation by another device in China. After excluding these 2 patients from the *ESR1*m-detected population, the hazard ratio for the investigator-assessed PFS was 0.635 (95% CI: 0.478, 0.844). The results are consistent with the primary findings for the investigator-assessed PFS for the comparison of imlunestrant arm and TPC arm in the *ESR1*m-detected population.

• Subgroup analyses of Investigator-assessed PFS

The subgroup analyses of investigator-assessed PFS are considered exploratory, and no formal statistical inference may be drawn. The FDA agrees that generally no apparent outliers are observed in the subgroup analyses of investigator-assessed PFS, as shown in **Figure 8.8**.

Figure 8.8: Investigator-assessed PFS Subgroup Analyses in the *ESR1*m-detected Population (Imlunestrant versus TPC)



(Source: FDA analysis)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Inluriyo (implunestrant)

The FDA review team also conducted subgroup analyses of investigator-assessed PFS by ethnic subgroups. In the Hispanic/Latino subgroup (n=48), the HR was 0.42 (95% CI: 0.22, 0.83), in the Non-Hispanic/Latino subgroup (n=181), the HR was 0.61 (95% CI: 0.43, 0.85), in patients whose ethnicity was not reported or missing (n=27), the HR was 1.20 (95% CI: 0.51, 2.72). Although the subgroup of patients whose ethnicity was not reported or missing had a hazard ratio point estimate greater than 1, this subgroup has a very small sample size, ethnicity is not a stratification factor at randomization and the hazard ratio confidence interval included 1. Therefore, this subgroup result does not raise concerns about the overall efficacy findings and should be interpreted with caution.

Data Quality and Integrity

The Applicant's Position:

Study conduct and reports were in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. The study was subject to an independent audit by the staff of the Global Quality Auditing and Compliance Department or its contractors.

A CRO monitored the study centers.

Monitors

- visited at regular intervals
- maintained a Visit Log
- reviewed adherence to the protocol
- reviewed compliance with GCP, and
- reviewed the completeness, accuracy, and consistency of the data.

Study site personnel recorded data in a sponsor/CRO-owned database. The sponsor/CRO applied data quality checks using manual and electronic verification methods and maintained an audit trail to support data query resolution and any modifications to the data.

This study underwent an audit conducted by the Sponsor as part of an independent quality assessment.

The FDA's Assessment:

No OSI audit of the CRO was performed during this review because they were audited in 2023 and concurrently to this review for another regulatory submission. Inspection for the Applicant was conducted, and no significant issues were found.

Inluriyo (implunestrant)

Efficacy Results – Secondary and Other Relevant EndpointsData:Interim overall survival

As of data cutoff, the interim OS results are immature with

- 32 deaths and a censoring rate of 76.8% in the **implunestrant** arm, and
- 48 deaths and a censoring rate of 59.3% in the **SOC** arm.

A trend towards OS improvement has been observed with **implunestrant** in the *ESR/m*-detected population as shown by the stratified HR (95% CI) of 0.546 (0.348, 0.856), though statistical significance was not met at this interim (Table 8.23 and Figure 8.9).

**Table 8.23. Overall Survival
ESR/m-detected Population
Implunestrant versus SOC**

	<i>ESR/m</i> -detected Population	
Status	Arm A Implunestrant N = 138	Arm B SOC N = 118
Survival status, n (%)		
Died	32 (23.2)	48 (40.7)
Censored	106 (76.8)	70 (59.3)
Overall survival (months)		
Median, months (95% CI)	NR (23.20, -)	21.22 (16.23, 26.84)
HR (95% CI) stratified ^a	0.546 (0.348, 0.856)	
p-value (2-sided) log-rank stratified ^a	0.0076	
Median follow-up time, months (95% CI)	16.36 (14.42, 18.20)	17.41 (16.03, 19.38)
Rate (%) of overall survival^b		
12 months (95% CI)	86.6 (79.2, 91.4)	80.4 (71.1, 87.0)
24 months (95% CI)	57.4 (41.4, 70.5)	42.5 (29.5, 54.9)

Abbreviations: CDK6/4 = cyclin-dependent kinase 4/6; CI = confidence interval; *ESR/m* = estrogen receptor 1 mutation; HR = hazard ratio; IWRS = interactive web response system; N = number of patients; n = number of patients in the specific category; N = number of patients; NR = not reached; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

^a Stratified by Visceral Metastases Status from IWRS, JZLC Prior CDK 4/6 Inhibitor Treatment from IWRS.

^b 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation.

Source: Table JZLC.5.15

Inluriyo (imlunestrant)

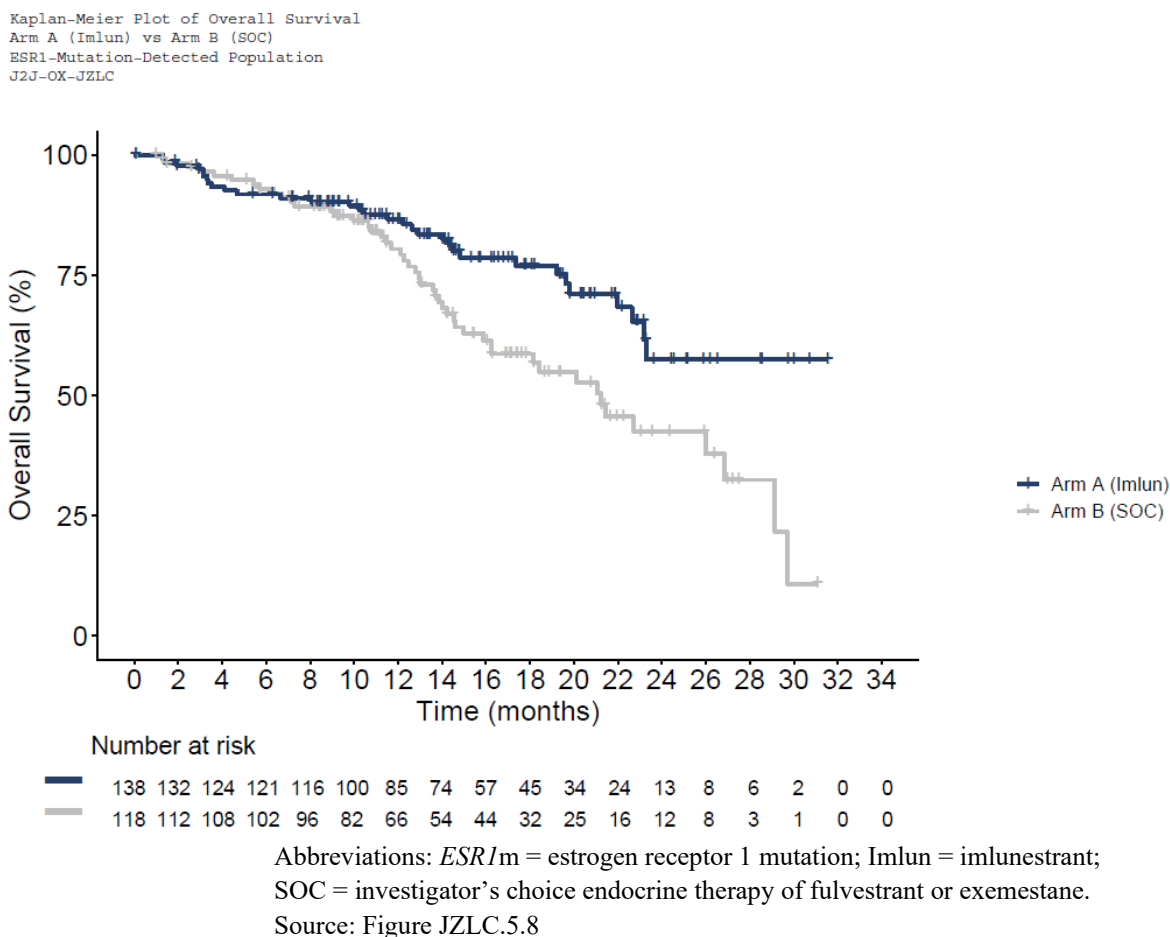


Figure 8.9. Kaplan-Meier plot of overall survival, *ESR1*m-detected population imlunestrant versus SOC.

Objective response rate, duration of response, and clinical benefit rate

The majority of patients had measurable disease, among these patients, the ORR of 14.3% in the **imlunestrant** arm was higher than that in the **SOC** arm, where it was 7.7% (Table 8.24). Among patients who responded, the median DoR was longer in the **imlunestrant** arm than in the **SOC** arm (10.02 months versus 5.59 months), indicating a sustained treatment effect.

Inluriyo (imlunestrant)

**Table 8.24. Summary of Secondary Endpoints
ESR1m-detected Population
Imlunestrant versus SOC**

	Arm A Imlunestrant N = 138	Arm B SOC N = 118
Number of ORR-evaluable^a patients	112	91
ORR, n (%)	16 (14.3)	7 (7.7)
95% CI for ORR	7.8-20.8	2.2-13.2
Stratified risk difference, % (95% CI) ^b	6.3 (-2.3, -14.9)	
Nominal p-value ^c	0.1811	
Median DoR, months (95% CI)	10.02 (3.98, 14.59)	5.59 (2.92, 7.79)
CBR (CR + PR + SD $\geq$24 weeks or Non-CR/Non-PD $\geq$24 weeks), n (%)	64 (46.4)	43 (36.4)

Abbreviations: CBR = clinical benefit rate; CDK6/4i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; CR = complete response; DoR = duration of response; ESR1m = estrogen receptor 1 mutation; Imlun = imlunestrant; IWRS = interactive web response system; n = number of patients per category; N = number of patients in the population; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SD = stable disease; SOC = standard of care.

^a Per RECIST v1.1.

^b Risk difference is defined as the incidence rate in Arm A (Imlun) minus that in Arm B (SOC), stratified by visceral metastases status from IWRS and prior CDK4/6i treatment from IWRS.

^c p-value is calculated by the Exact Cochran-Mantel-Haenszel test stratified by the randomization strata visceral metastases status from IWRS, prior CDK 4/6i treatment from IWRS.

Time-to-chemotherapy, progression-free survival-2, and chemotherapy-free survival

Time to chemotherapy, PFS2, and CFS showed a treatment effect that favored imlunestrant with HRs of 0.672 (95% CI: 0.472, 0.957), 0.600 (95% CI: 0.418, 0.861), and 0.651 (95% CI: 0.474, 0.894) respectively.

The Applicant's Position:

The totality of efficacy data from these secondary or exploratory endpoints demonstrates consistency with the benefit observed for the primary endpoint in the ESR1m-detected population.

Based on the Sponsor's assessment, no deaths were attributed to imlunestrant toxicity. The numerical data primarily reflect deaths secondary to disease progression.

Although OS data are immature, results demonstrate no trend toward detriment for patients treated with imlunestrant. ORR data favored imlunestrant and the low rate of response across

Inluriyo (imlunestrant)

both arms was reflective of responses observed with ET monotherapy in patients with ER+, HER2- locally advanced or MBC previously treated with endocrine therapy.

The FDA’s Assessment:

The FDA generally agrees with the Applicant’s description of OS Interim Analysis 1 (IA1) results for the comparison of the imlunestrant arm vs TPC arm in the *ESR1*m-detected population. There were 80 deaths observed in the *ESR1*m-detected population (52% information fraction of the OS final analysis in the *ESR1*m-detected population). The updated alpha allocated for interim and final analyses of OS in the *ESR1*m-detected population is 5.5×10^{-6} (2-sided). The p-value for the OS IA1 for the comparison of the imlunestrant arm vs the TPC arm in the *ESR1*m-detected population did not cross the efficacy boundary of 2.2×10^{-10} (2-sided). There was no potential detriment in overall survival in the *ESR1*m-detected population at IA1.

Landmark analyses for time-to-event endpoints are considered exploratory since specific time points are used as opposed to assessing the entire survival distribution. Therefore, any differences between treatment arms at these landmarks must be interpreted with caution.

The OS curves for the comparison of the imlunestrant arm and the TPC arm in the *ESR1*m-detected population overlapped for the first 3 months, favored to the TPC arm from about 3 to 7 months, and began to separate in favor of the imlunestrant arm from Month 7 onward. The Applicant provided a table showing the number of OS events by time interval, and it was noted that the number of events that occurred before Month 7 was small.

Table 8.25 Overall Survival Events by Time Interval in the *ESR1*m-detected Population (Imlunestrant versus TPC)

Time Interval	Number of OS events within time interval	
	Imlunestrant (N=138)	TPC (N=118)
0-3 months	4 (2.9)	3 (2.5)
3-7 months	8 (5.8)	7 (5.9)
>7 months	20 (14.5)	38 (32.2)

(Source: CSR Table JZLC.5.16)

Although the OS curves began to separate from Month 7 in favor of the imlunestrant arm, the censoring for OS is heavy starting from Month 7-8 since many patients were administratively censored, therefore, there is still uncertainty in the OS result and further review of the preplanned remaining interim and final OS analyses for the comparison of the imlunestrant arm and the TPC arm in the *ESR1*m-detected population with more mature data is important for both efficacy and safety. The Applicant committed to submit SAP version 5 pre-specified interim and final OS results as a PMC (**Section 13**).

Inluriyo (imlunestrant)

- OS results in the ITT population and the *ESR1m-nd* population

Since EMBER-3 did not meet its primary endpoint of investigator-assessed PFS for the comparison of the imlunestrant arm and the TPC arm in the ITT population, the OS for the comparison of the imlunestrant arm and the TPC arm in the ITT population cannot be formally tested. For the comparison of the imlunestrant arm and the TPC arm in the ITT population, the HR for OS was 0.69 (95% CI: 0.50, 0.96). The median OS was not reached in the imlunestrant arm and was 26.8 (95% CI: 25.8, NE) months in the TPC arm. The FDA review team conducted an exploratory analysis of OS for the comparison of the imlunestrant arm and the TPC arm in the *ESR1m-nd* population. The HR was 0.91 (95% CI: 0.56, 1.47). The median OS was not reached in either arm.

Table 8.26: Overall Survival in the ITT Population and the *ESR1m-nd* Population (Imlunestrant versus TPC)

	ITT		<i>ESR1m-nd</i> ^a	
	Imlunestrant (N=331)	TPC (N=330)	Imlunestrant (n=180)	TPC (n=205)
Number of events, n (%)	62 (18.7)	90 (27.3)	29 (16.1)	41 (20.0)
Number of patients censored, n (%)	269 (81.3)	240 (72.7)	151 (83.9)	164 (80.0)
Median OS months (95% CI)	NR (NE, NE)	26.8 (25.8, NE)	NR (NE, NE)	NR (26.3, NE)
Hazard ratio (95% CI)	0.69 (0.50, 0.96)		0.91 (0.56, 1.47)	

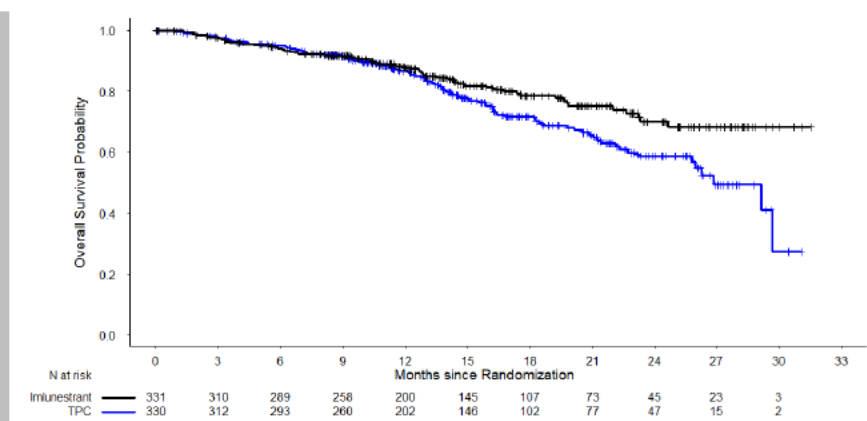
NR = not reached, NE = not estimable

^a Excluded patients with failed or missing *ESR1* mutation test

(Source: Adapted from CSR Table JZLC.5.7 and FDA analysis)

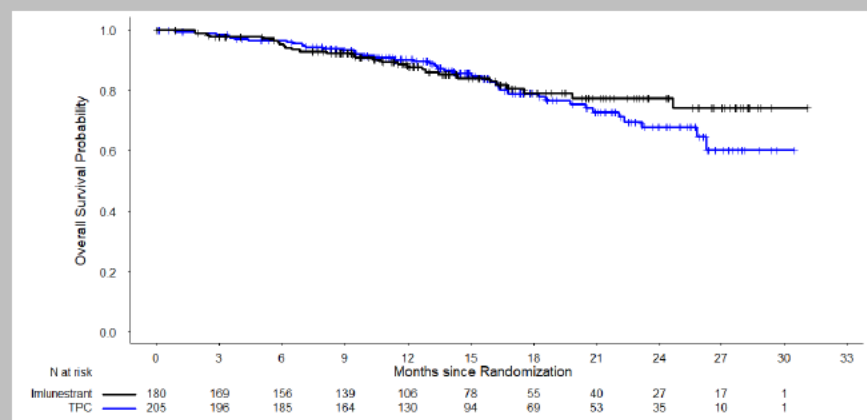
Figure 8.10: Kaplan-Meier Plot for Overall Survival in the ITT Population (Imlunestrant versus TPC)

Inluriyo (imlunestrant)



(Source: FDA analysis)

Figure 8.11: Kaplan-Meier Plot for Overall Survival in the *ESR1*m-nd* Population (Imlunestrant versus TPC)



* Excluded patients with failed or missing *ESR1* mutation test

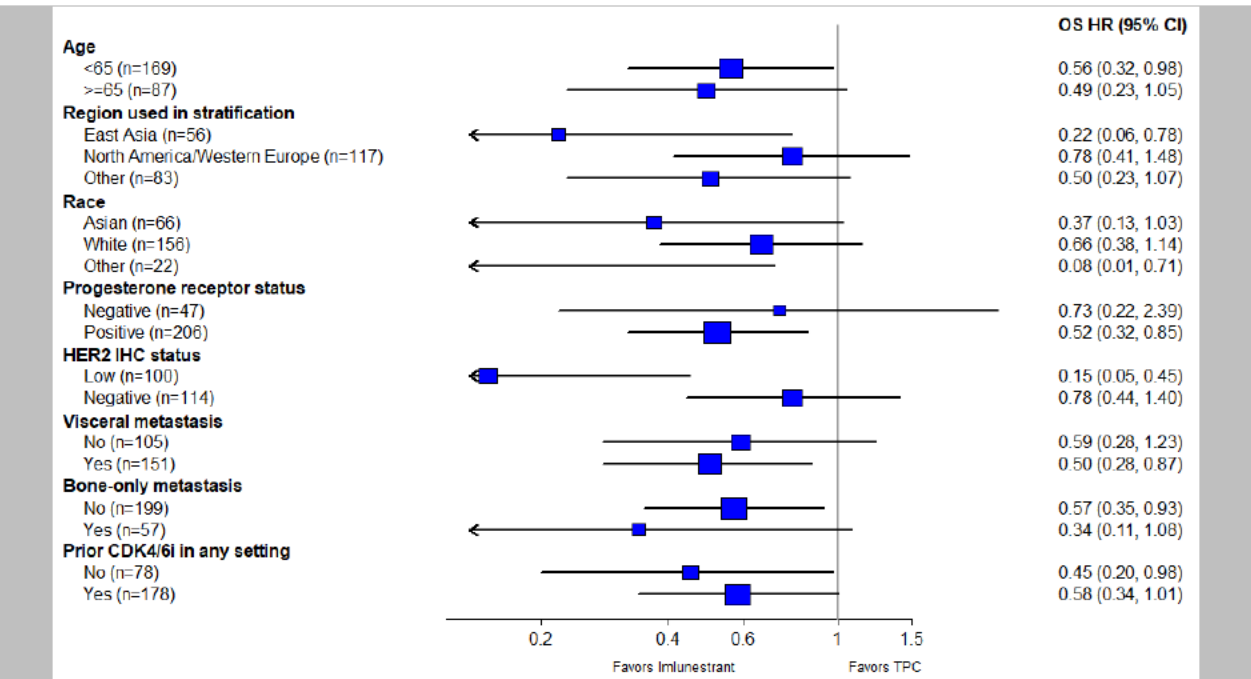
(Source: FDA analysis)

- Subgroup analyses of OS in the *ESR1*m-detected population

FDA conducted subgroup analyses of OS for the comparison of the imlunestrant arm vs the TPC arm in the *ESR1*m-detected population. As shown in **Figure 8.12**, OS results across these subgroups are generally consistent with the primary findings of OS.

Figure 8.12: OS Subgroup Analyses in the *ESR1*m-detected Population (Imlunestrant versus TPC)

Inluriyo (imlunestrant)



(Source: FDA analysis)

• Impact of withdrawal of consent in the OS analysis

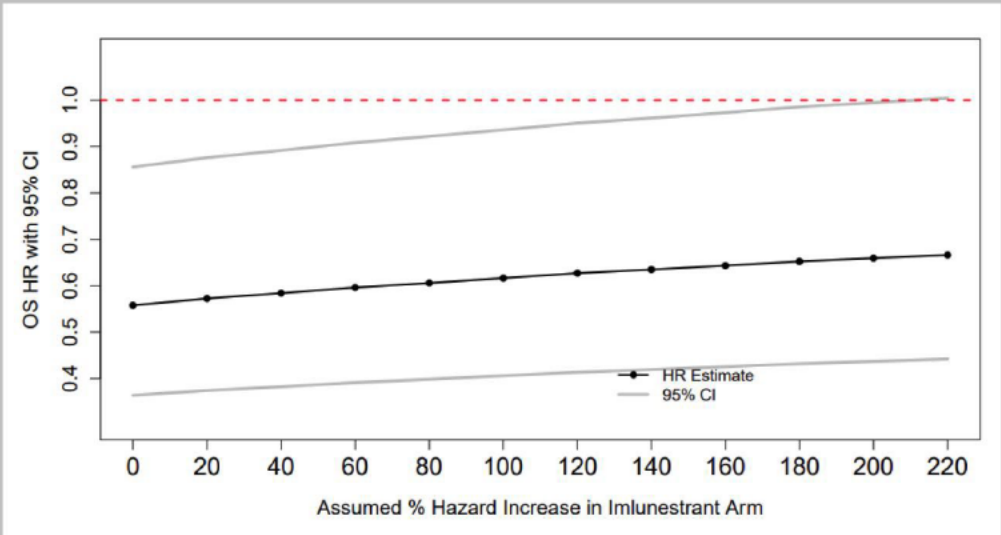
In the OS analysis for the comparison of the imlunestrant arm and the TPC arm in the *ESR1*-mutated population, more patients in the imlunestrant arm were censored due to withdrawal of consent or being lost to follow-up compared to those in the TPC arm (10.8% vs 5.9%). The FDA requested that the Applicant use public registries to retrieve survival data for patients who were censored for OS due to withdrawal of consent or being lost to follow-up and update the OS results. The Applicant stated that they were “working with a vendor to identify and retrieve the survival status of patients who were censored for OS while following local laws and regulations which vary by country.” The Applicant also stated that future OS analyses would include retrieved OS information. In a response to FDA’s follow-up Information Request regarding conducting an updated IA1 OS analysis by including retrieved OS information, the Applicant stated that as of March 2025, survival data for only 2 patients have been retrieved, thus an updated IA1 OS analysis would be premature.

Per the FDA’s request, the Applicant conducted a tipping point analysis to evaluate the impact of withdrawal of consent or being lost to follow-up in the OS analysis. In the tipping-point analysis, 15 patients who were censored for OS due to withdrawal of consent or lost to follow-up in the imlunestrant arm were assumed to have an increased hazard rate compared with the remaining patients in this arm. The results show that the point estimates of the HR were below 1 across all scenarios and the 95% CI of the HR (assumed nominal significance level) only included 1 when

Inluriyo (implunestrant)

patients who withdrew consent or were lost to follow-up in the implunestrant arm were assumed to have an increase of hazard by 200% to 220% (Figure 8.13).

Figure 8.13: Tipping-point Analysis for Withdrawal of Consent on OS in the *ESR1*m Population (Implunestrant versus TPC)



(Source: Applicant’s response to FDA’s Information Request)

The Applicant also conducted additional sensitivity analyses to evaluate the impact of the withdrawal of consent or being lost to follow-up in the OS analysis. The sensitivity analyses results are generally consistent with the primary interim OS analysis results (Table 8.27).

Table 8.27: Sensitivity Analyses of OS in the *ESR1*m-detected Population (Implunestrant versus TPC)

Analysis	HR (95% CI)
Impute OS for the patients with early censoring in the TPC arm (from best 20% in TPC)	0.59 (0.37, 0.92)
Impute OS for the patients with early censoring in the TPC arm (from best 20% in both arms)	0.59 (0.38, 0.92)
Exclude these 22 patients with early censoring in both arms from the analysis	0.57 (0.37, 0.90)
Assume these 22 patients as events at time of censoring	0.70 (0.47, 1.03)

(Source: Applicant’s response to FDA’s Information Request)

Inluriyo (imlunestrant)

- *Descriptive analysis of OS in the ESR1m-detected population with additional follow-up*

The Applicant submitted SAP Addendum v1 in a meeting request dated November 14, 2024 (Sequence Number 0165). SAP Addendum v1 was amended after data unblinding. In SAP Addendum v1, the Applicant proposed to remove the anchoring of the OS testing on the OS endpoint for the comparison of the imlunestrant arm versus the TPC arm in the ITT population, and to update the event-driven OS interims to time-driven interims for the following OS endpoints: OS for the comparison of the imlunestrant arm and the TPC arm in the ESR1m-detected population, and OS for the comparison of the imlun+abema arm and the imlunestrant arm in the ITT population. The FDA advised the Applicant not to change the remaining formal OS tests between the imlunestrant arm and the TPC arm in the ESR1m-detected population as they were made after data unblinding and could be data driven. Additionally, the FDA stated that changing from event-driven to calendar-based analyses would likely lead to inadequately powered analyses. The FDA warned the Applicant that analyses conducted under SAP Amendment v1 would be considered post-hoc and descriptive only.

Despite FDA's warning, the Applicant proceeded with SAP Addendum v1 and conducted updated OS analyses with a DCO date of January 30, 2025. Topline results of updated OS analyses based on the DCO date of January 30, 2025 were provided and discussed

(b) (4)

. The FDA considered these OS analyses post-hoc and descriptive only. The descriptive analyses of OS with a DCO date of January 30, 2025 showed that the hazard ratio was 0.60 (95% CI: 0.41, 0.88) for the comparison of the imlunestrant arm and the TPC arm in the ESR1m-detected population. The observed median OS was 34.4 (95% CI: 25.0, NE) months in the imlunestrant arm and 22.7 (95% CI: 18.4, 28.9) months in the TPC arm. The descriptive OS analysis results are consistent with the OS results conducted at IA1 with a DCO date of June 24, 2024.

- *Secondary endpoints*

For the comparison of the imlunestrant arm and the TPC arm, the multiplicity plan accounted for PFS in the ESR1m-detected population, PFS in the ITT population, OS in the ESR1m-detected population, and OS in the ITT population. There was no multiplicity plan for other secondary endpoints for this comparison. The p-value for the ORR analysis in the ESR1m-detected population shown in Table 8.21 is considered nominal p-value only. The FDA noted that the ORRs in both the imlunestrant arm and the TPC arm were generally low in the ITT population, the ESR1m-detected population, and the ESR1m-nd population. In the ESR1m-detected population, patients with measurable disease at baseline had an ORR of 14.3% (95% CI: 7.8, 20.8) in the imlunestrant arm and 7.7% (95% CI: 2.2, 13.2) in the TPC arm. In the ITT population, patients with measurable disease at baseline had an ORR of 12.2% (95% CI: 8.2, 16.2) in the imlunestrant arm and 8.4% (95% CI: 4.9, 11.8) in the TPC arm. In the ESR1m-nd population, patients with measurable disease at baseline had an ORR of 10.6% (95% CI: 5.5,

Inluriyo (imlunestrant)

15.6) in the imlunestrant arm and 8.3% (95% CI: 4.0, 12.7) in the TPC arm. CBR is not an endpoint used by the FDA for regulatory decision making, because it includes stable disease, which may not represent meaningful clinical benefit from the drug, making it less stringent than ORR which only counts actual tumor shrinkage.

Secondary endpoints of time-to chemotherapy, PFS2, and chemotherapy-free survival were not endpoints that the FDA considers in regulatory decision making. These endpoints lack standardized definitions across trials and are confounded by physician and patient treatment choices unrelated to drug efficacy and serve as indirect measures rather than direct assessments of how the drug affects cancer progression or patient survival.

Dose/Dose Response

The Applicant's Position:

Refer to Section [6.2.2.1](#)

The FDA's Assessment:

See Clinical Pharmacology review in Section 6.2.2.1 for more information regarding dose and dose response evaluation.

Durability of Response

The Applicant's Position:

Duration of response was investigated as a secondary objective and discussion can be found in [Efficacy Results – Secondary and Other Relevant Endpoints](#).

The FDA's Assessment:

See FDA assessment in Section 8.1.2.

Persistence of Effect

The Applicant's Position:

Not applicable for advanced cancer indications.

The FDA's Assessment:

See FDA assessment of OS in [Efficacy Results – Secondary and Other Relevant Endpoints](#).

Inluriyo (implunestrant)

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

Data:

Compliance for PRO measures at baseline ranged from 87.2% to 88.5% for the **implunestrant** arm and 87.7% for the **SOC** arm.

The Applicant's Position:

The majority of patients receiving fulvestrant IM experience reactions, including pain. Implunestrant eliminates this by virtue of oral administration. Patient-reported injection site pain, swelling, or redness was assessed among the *ESR/m*-detected patients on the **SOC** arm that received fulvestrant IM using a single PRO-CTCAE item (yes/no). Of the patients on the **SOC** arm who received fulvestrant IM, 72.3% reported injection site pain, swelling, or redness at any time while on treatment, with roughly 30% reporting these symptoms during the first week of each cycle.

Implunestrant did not demonstrate an advantage with regard to the worsening of pain. Among the *ESR/m*-detected populations, the secondary PRO endpoint was time to sustained worsening of “worst pain” measured by the Worst Pain numeric rating scale from randomization until the date of the first increase (≥ 2 points) in the weekly average of the worst pain score with confirmation in the next consecutive week. At data cutoff, a total of 41 patients reported a sustained worsening of worst pain score, including 23 patients (17.4%) in the **implunestrant** arm and 18 patients (16.1%) in the **SOC** arm. Overall, there were few events, high rates of censoring, and no difference between arms (stratified HR = 0.980 [95% CI: 0.527, 1.822], stratified log-rank test $p = 0.9531$).

Patients who received implunestrant maintained or improved both their physical function and overall QOL, while those on SOC experienced a worsening in physical function and overall QOL. The Physical Functioning and GHS/QOL domain scores of the EORTC-QLQ-C30 were evaluated by a longitudinal MMRM using the change from baseline. The change from baseline for all visits while on treatment was included in the model. The analysis included all cycles through which at least 25% of patients in each arm had an assessment. Within the *ESR/m*-detected population, the mean physical function scores from baseline through cycle 7 were maintained or improved for patients in the **implunestrant** arm, while the mean physical function scores worsened from baseline for the **SOC** arm. The least-square mean change difference between arms was positive in value at all time points ranging from 2.54 to 6.17, favoring the **implunestrant** arm.

Similarly, within the *ESR/m*-detected population, the mean GHS/QOL scores from baseline through cycle 7 were maintained or improved for patients in the **implunestrant** arm, while the mean GHS/QOL scores worsened from baseline for the **SOC** arm. The least-square mean change difference between arms was >9.5 points at cycles 5 and 7, favoring the **implunestrant** arm.

Inluriyo (implunestrant)

The FDA's Assessment:

The FDA disagrees with the Applicant's interpretation of patient-reported outcome results. After cycle 3 day 1 many patients were no longer on therapy because of disease progression, treatment discontinuation, and death and were therefore not expected to complete PROs, making an on-treatment assessment of the patient experience challenging. However, of those patients who were expected to complete an assessment, completion rates remained high (>80%) for those still on trial therapy through cycle 11 day 1.

While route of administration does inform the specific associated adverse events, focusing on one item such as injection site pain, swelling, or redness is not indicative of the totality of patient experience with a specific therapy. FDA does note that the Applicant collected weekly PRO-CTCAE diarrhea (frequency) using PRO-CTCAE, and frequency of diarrhea was similar between Arm A and B at most timepoints.

Time to event patient-reported outcome results are also challenging to interpret, especially when intercurrent events which may preclude capture of PROs and high censoring. Therefore, FDA cannot draw conclusions from the PRO results. FDA does not agree that there is no observed difference between arms, nor can FDA conclude that there was relative improvement or maintenance of QOL given the limitations noted regarding high rate of attrition and censoring.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

8.1.3 Integrated Review of Effectiveness

The FDA's Assessment:

The FDA's conclusions regarding the efficacy of implunestrant for the treatment of patients with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer were based on the results from EMBER-3, a randomized, active-controlled, open-label, multicenter trial comparing implunestrant versus treatment of physician's choice (TPC: fulvestrant or exemestane). The primary endpoints were investigator assessed PFS in the *ESR1*m population and the ITT

Inluriyo (imlunestrant)

population (*ESR1*m and *ESR1*m-not detected). The secondary endpoints were OS in the *ESR1*m and ITT populations.

The PFS endpoint was met in the *ESR1*m population (median PFS 7.4 months versus 5.5 months, HR 0.62, 95% CI: 0.46-0.82; p-value 0.0008). (b) (4) was removed (b) (4)

before the trial started enrolling. While exploratory analyses by individual *ESR1* mutations may suggest differential efficacy for imlunestrant, the evidence does not support a detriment for patients with specific *ESR1* mutations and therefore the review team recommends granting approval consistent with the proposed CDx. The PFS endpoint in the ITT population did not cross the prespecified significance alpha level.

EMBER-3 was an active-controlled trial with a replacement design. For such trials even a modest improvement in an efficacy endpoint may support a favorable regulatory action provided the control arm is active, and the investigational treatment is not more toxic than the control. At the time that the study was designed single agent endocrine therapy was an acceptable option for second line therapy. Subsequently, it has been observed that fulvestrant monotherapy underperforms after progression on a CDK4/6i therapy.

The secondary OS endpoint in the *ESR1*m population did not reach its prespecified significance alpha level. However, there was a trend favoring the imlunestrant arm in the *ESR1*m population (HR 0.91, 95% CI: 0.56-1.47). OS could not be tested in the ITT population since PFS failed to meet its prespecified threshold. The exploratory endpoint of objective response rate also favored imlunestrant (14% versus 8%). A postmarketing commitment (PMC) has been issued by the FDA and agreed to by the Applicant to obtain the next prespecified interim and final OS results for the *ESR1*m population

Finally, the approval of elacestrant for patients with an *ESR1*m and emerging data from other oral SERDs, summarized in Section 2.2, suggest that the benefit of these therapies is greater for patients with an *ESR1*m.

The FDA concluded that clinical benefit was demonstrated for imlunestrant in the *ESR1*m population. Although the median PFS improvement was modest it should be interpreted in the context of a replacement design. The PFS results were robust across multiple sensitivity analyses and supported by no potential trend toward OS detriment. The FDA revised the indicated population to patients with evidence of disease progression after endocrine therapy based on the population included in the trial.

While male patients were eligible to enroll on EMBER-3, there were no male patients in the *ESR1*m population. The FDA included male patients in the indication based on extrapolation from the data in female patients and the biologic rationale that there were no expected efficacy or

Inluriyo (implunestrant)

safety differences between male and female patients with an *ESR/m* (FDA Guidance: Male Breast Cancer, 2020).

8.1.4 Assessment of Efficacy Across Trials

The Applicant's Position:

Efficacy data are provided from a single study.

Primary Endpoints

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

Secondary and Other Endpoints

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

Subpopulations

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

Additional Efficacy Considerations

The FDA's Assessment:

Inluriyo (implunestrant)

Not applicable. Any additional efficacy analysis performed by FDA was summarized in other Sections of this review.

8.1.5 Integrated Assessment of Effectiveness

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Refer to FDA assessment under Integrated Review of Effectiveness above.

8.2 Review of Safety

The Applicant's Position:

The safety population of EMBER-3 included all participants randomly assigned to study treatment who took at least 1 dose of study treatment (N = 859) with 327 patients assigned to Arm A and 324 patients assigned to Arm B. The Safety Population for Arms A and B is henceforth called the Overall Safety Population. The *ESR/m*-detected safety population in Arm A and Arm B (N=254) was a subset of the overall safety population.

The safety profile of **implunestrant** monotherapy was generally favorable and similar to **SOC**. The implunestrant safety profile was manageable through routine monitoring as evidenced by low rates of dose reduction or treatment discontinuation due to AEs.

The safety profile of the *ESR/m*-detected safety population was similar to that of the overall safety population.

The safety profile of **implunestrant** monotherapy was consistent with the mechanism of action of SERDs, and events commonly experienced by patients with ABC.

- The incidence of most TEAEs was similar between treatment arms and the majority were low grade (Grade 1 or 2).
- The most frequently reported TEAEs in the **implunestrant** arm were fatigue, diarrhea, and nausea, which were easily detectable based on clinical signs and symptoms. The majority of these events were observed early in treatment. A higher incidence of low grade diarrhea and fatigue in the **implunestrant** arm was not considered clinically relevant.

Inluriyo (implunestrant)

- The incidence of SAEs and deaths due to AEs were similar across treatment arms. The incidence of Grade ≥ 3 TEAEs showed a slightly lower incidence in **implunestrant** arm (17.1%) compared with **SOC** (20.7%).
- Overall, TEAEs were manageable with supportive therapies and/or dose adjustments (withheld or reductions).
- The frequency of discontinuations or dose adjustments due to AEs was low across both arms.

The FDA's Assessment:

The FDA safety analyses were based on the FDA's independent review of data from the EMBER-3 (J2J-OX-JZLC) pivotal trial. The FDA independent analyses were based on 651 patients who received at least one dose of study treatment in Arm A (implunestrant) or Arm B (treatment of physician's choice, TPC) of the trial, including 327 patients who received implunestrant and 324 patients who received TPC (fulvestrant-292 patients, or exemestane-32 patients). The FDA assessed safety in all patients in Arm A and Arm B, as well as in patients with *ESR/m*-detected status in these two arms. *ESR/m*-detected status for the FDA review of safety was defined as in the review of efficacy (section 8.1.1). The FDA agrees that the safety profile of the *ESR/m*-detected safety population was similar to the safety profile of the overall safety population.

Most patients in EMBER-3 experienced at least one treatment emergent adverse event (TEAE), and all grade TEAEs occurred at a similar frequency in the implunestrant arm (83%) and the TPC arm (84%). The most common ($\geq 10\%$) TEAEs, including lab abnormalities, in patients who received implunestrant included hemoglobin decreased, musculoskeletal pain, calcium decreased, neutrophils decreased, fatigue, diarrhea, nausea, increased ALT, increased AST, triglycerides increased, platelets decreased, cholesterol increased, abdominal pain, and constipation. Grade ≥ 3 TEAEs were slightly higher in the TPC arm (19%) compared to the implunestrant arm (15%). The most common ($\geq 1\%$) clinically relevant grade 3 TEAEs in patients who received implunestrant were musculoskeletal pain, anemia, and neutropenia. The FDA agrees with the Applicant that most TEAEs in both the implunestrant arm and the TPC arm were Grade 1-2. Serious adverse events (SAEs) were similar between patients who received implunestrant (10%) and patients who received TPC (11%). The most common SAE ($\geq 1\%$) was pleural effusion and occurred only in patients who received implunestrant (1.2%). The most common SAE ($\geq 1\%$) in the TPC group (1.5%) was fracture.

The incidence of TEAEs leading to dosage interruption was higher in patients who received implunestrant (10%) compared to patients who received TPC (7%), and the most common ($\geq 1\%$) TEAE leading to dosage interruption in patients receiving implunestrant was vomiting (1.5%).

Inluriyo (imlunestrant)

The incidence of TEAEs leading to drug discontinuation was higher in patients receiving imlunestrant (4.3%) compared to those receiving TPC (1.4%). Dose reductions were low (2.4%) in patients receiving imlunestrant and did not occur in patients receiving TPC.

Important safety signals for imlunestrant included GI TEAEs (diarrhea, constipation, nausea, and vomiting). Diarrhea, constipation, nausea, and vomiting all occurred in a higher proportion of patients who received imlunestrant compared to TPC: 22% vs. 12%, 10% vs. 6%, 17% vs. 13%, and 9% vs. 4.9%, respectively. The frequency of fatigue was also higher in patients who received imlunestrant (23%) vs. TPC (13%). Dyslipidemia, including hypertriglyceridemia and hypercholesterolemia, was seen in patients in EMBER-3. The incidence of hypertriglyceridemia and hypercholesterolemia were similar across patients who received imlunestrant (21% and 10%, respectively) and patients who received TPC (22% and 12%, respectively). Musculoskeletal pain occurred at similar frequency in patients who received imlunestrant (30%) vs. TPC (30%). The only TEAE with notable higher frequency in patients receiving TPC was injection site reactions, which occurred in 6% of patients who received fulvestrant. For further details, refer to the FDA's assessment in Section 8.2.4.

The FDA disagrees with the Applicant's statement that imlunestrant monotherapy was generally favorable and similar to TPC. As noted, GI TEAEs occurred in a greater proportion of patients who received imlunestrant compared to TPC. Although most TEAEs were Grade 1-2, the FDA notes that even certain Grade 1-2 TEAEs, e.g., nausea or diarrhea, can adversely impact a patient's quality of life. Fatigue was also experienced by a higher proportion of patients who received imlunestrant compared to those who received TPC.

The safety profile of imlunestrant is manageable with labeling for the indicated patient population with *ESR1m*-detected status.

8.2.1 Safety Review Approach

Data:

The safety assessment of imlunestrant for the treatment of patients with ER+, HER2- locally advanced or MBC previously treated with ET was primarily derived from the Phase 3 registrational study, EMBER-3. Two Phase 1 studies, EMBER and EMBER-2, were also evaluated for safety and provided supporting data including the 400 mg QD dosage.

Across studies, 408 patients with ER+ HER2- ABC received at least 1 dose of 400 mg imlunestrant QD dose. Patients treated with 400 mg imlunestrant monotherapy included

Inluriyo (imlunestrant)

- 327 with ABC in EMBER-3
- 51 with ABC in EMBER, and
- 30 with EBC in EMBER-2.

The overall safety population for the comparison of **imlunestrant** treatment arm (Arm A) versus the **SOC** treatment arm (Arm B) in EMBER-3 includes 651 patients who initiated treatment:

- 327 patients with **imlunestrant**, and
- 324 patients with investigator's choice of **SOC** ET fulvestrant (n = 292) or exemestane (n = 32).

The *ESR/m*-detected safety population for the comparison of imlunestrant treatment arm (Arm A) versus the SOC treatment arm (Arm B) in EMBER-3 includes 254 patients who initiated treatment:

- 137 patients with imlunestrant, and
- 117 patients with investigator's choice of SOC ET fulvestrant (n=111) or exemestane (n=6)

The safety population included all participants randomly assigned to study treatment and who took at least 1 dose of study treatment.

Supportive analysis sets provide a side-by-side presentation of data from the respective cohorts from EMBER-3 and EMBER who received imlunestrant 400 mg QD. This presentation format facilitates an evaluation of the safety profile across studies.

The pooled analysis sets of EMBER-3 and EMBER increase the size of the datasets for patients receiving imlunestrant 400 mg QD and increases the robustness of the safety assessment. EMBER-2 data supplement the understanding of the safety profile in ET-naïve patients.

Results of the supportive and the pooled analyses are not presented or discussed within the text unless the results differ notably from the results of the primary analysis sets, or if they offer additional insights in characterizing specific safety parameters. The results of the supportive and pooled analyses for EMBER-3 and EMBER are available in Module 2.7.4.7 Summary of Clinical Safety Appendix. These analyses are based on the safety population, as a review of *ESR/m* status data did not indicate a clinically meaningful difference between the safety profile between *ESR/m* status subgroups.

Safety endpoints included AEs, SAEs, deaths, and clinical laboratory abnormalities per NCI CTCAE v5.0, vital signs, ECGs, and ECOG PS.

The Applicant's Position:

The clinical development of imlunestrant evaluated a series of important scientific and clinical questions with the goal of understanding the benefits and risks of imlunestrant therapy in the intended patient population, as assessed relative to fulvestrant and exemestane.

Inluriyo (imlunestrant)

The FDA's Assessment:

The FDA generally agrees with the Applicant's description of the safety assessment in EMBER-3. The FDA's primary analysis of safety focused on the 651 patients who received at least one dose of treatment in the EMBER-3 trial, including 327 who received imlunestrant and 324 who received treatment of physician's choice (TPC) – fulvestrant or exemestane. There were 254 patients with *ESR/m*-detected status in the EMBER-3 safety population, 137 who received imlunestrant and 117 who received TPC. There were 397 patients with *ESR/m*-not detected (no mutation detected, no ctDNA detected, or test result missing) in the EMBER-3 safety population, 190 who received imlunestrant and 207 who received TPC.

The FDA's safety review of the EMBER-3 trial is based on data submitted with an initial cutoff date of June 24, 2024. The 120-day safety update did not reveal any new safety signals.

The FDA did not independently review the safety data from the pooled EMBER-3 and EMBER studies and did not pool data from EMBER or EMBER-2 with data from EMBER-3 as the EMBER and EMBER-2 trials included a different patient population from the intended indication. EMBER included patients with more heterogeneous prior therapies and EMBER-2 was a perioperative study that included patients who were endocrine therapy naïve. However, the FDA agrees in general that the safety data from patients in the EMBER trial with ER+/HER2-advanced breast cancer were considered supportive.

The FDA's safety analysis for EMBER-3 focused on deaths and TEAEs including SAEs, TEAEs leading to trial drug discontinuation, dose reduction, or dose interruption, grade 3-4 TEAEs, and all-grade TEAEs. The FDA also reviewed laboratory data. The Applicant identified transaminase increases as an AE of special interest. FDA conducted additional assessments of dyslipidemia, which the FDA identified as an AE of special interest. Dyslipidemia, including both hypercholesterolemia and hypertriglyceridemia, did not occur at greater frequency in patients who received imlunestrant vs those who received TPC. There was no grade 3-4 TEAEs for hyperlipidemia or hypercholesterolemia, no deaths or SAEs due to dyslipidemia, and the use of concomitant medications for the management of dyslipidemia did not differ significantly across the imlunestrant arm and the TPC arm. For these reasons dyslipidemia was not included in Section 5 of the USPI (Warnings and Precautions). However, FDA added information regarding monitoring for dyslipidemia in the Patient Counseling Section of the USPI as it was noted in a clinically significant percentage of patients and has also been noted for other approved SERDs. Additionally, EMBER-3 had an active control TPC arm (fulvestrant or exemestane), and although the incidences of dyslipidemia were similar in both arms, FDA identified dyslipidemia as an important AE that should be conveyed to providers and patients. Additional details

Inluriyo (imlunestrant)

regarding AEs of special interest are included in the Analysis of Submission-Specific Safety Issues.

For assessment of TEAEs, the FDA grouped related preferred terms as follows:

- Abdominal pain: Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness
- Diarrhea: Colitis, Diarrhea, and Enterocolitis
- Musculoskeletal pain: Arthralgia, Arthritis, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Neck pain, Pain in extremity, Spinal pain, and Cancer pain
- Stomatitis: Mouth ulceration, Mucosal inflammation, and Stomatitis
- Vomiting: Hematemesis, and Vomiting
- Fatigue: Fatigue, and Asthenia

8.2.2 Review of the Safety Database

Overall Exposure

Data:

Exposure for the *ESR1*m-detected and overall safety populations is presented in [Table 8.28](#).

Inluriyo (imlunestrant)

Table 8.28. Summary of Exposure for the *ESR1*m- Detected and Overall Safety Populations

Category	<i>ESR1</i> m-detected Safety Population			Overall Safety Population		
	Arm A Imlunestrant N = 137	Arm B SOC N=117		Arm A Imlunestrant N=327	Arm B SOC N = 324	
		Fulvestrant N = 111	Exemestane N =6		Fulvestrant N = 292	Exemestane N = 32
Cycles received per patient, median (min-max)	6 (3-12)	5 (3-8)	6 (1-12)	6 (1-32)	5 (1-32)	7 (1-25)
Relative dose intensity, %, median (Q1-Q3) ^a	99.65(97.62 – 100.00)	100 (100.00-100.00)	101.72 (98.68 – 108.57)	99.67 (97.34-100)	100 (100-100)	100 (98.86-101.14)

Abbreviations: *ESR1*m = estrogen receptor 1 mutation; max = maximum; min = minimum; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

^a Relative dose intensity (%) = (dose intensity / planned dose intensity) × 100

Source: JZLC.4.11, Addendum Table JZLC.3.5, Addendum Table JZLC.3.6, Addendum Table JZLC.3.7, Addendum Table JZLC.3.11, Addendum Table JZLC.3.12, Addendum Table JZLC.3.13

The Applicant's Position:

The exposure to study drugs in both the overall and the *ESR1*m detected safety population was adequate to support the characterization of the safety profile of imlunestrant.

The FDA's Assessment:

Inluriyo (imlunestrant)

The FDA agrees with the Applicant's description of exposure to study drugs in both the overall safety population and the *ESR/m*-detected safety population, and that this is adequate to support characterization of a safety profile for imlunestrant.

FDA also assessed duration of exposure in the *ESR/m*-detected population relative to the overall safety population. Exposure to study drugs was similar in both populations across the two study arms. FDA agrees with the Applicant's summary of exposure in **Table 8.28**.

Relevant characteristics of the safety population:

Data:

Please see [Table 8.11](#) for the relevant patient demographics and [Table 8.12](#) for baseline disease characteristics. Demographic and baseline characteristics of patients were adequately reflective of ER+, HER2- ABC, and were generally balanced across treatment arms. Baseline characteristics for age, sex, ECOG, region, menopausal status, presence of visceral metastases, bone-only disease, endocrine resistance, and prior CDK4/6i use were balanced across treatment arms for ITT and *ESR/m*-detected populations.

A minimal difference in the demographics and disease characteristics of patients in the ITT population compared to the overall safety population was observed.

The Applicant's Position:

EMBER-3 enrolled a population that was reflective of these patients, allowing for appropriate characterization of the safety profile.

The FDA's Assessment:

Table 8.10 and Table 8.11 referenced by the Applicant present demographics, baseline characteristics, and disease characteristics of the intention-to-treat (ITT) population not the safety population. The ITT population (N=661) included 331 patients in the imlunestrant arm and 330 patients in the treatment of physician's choice (TPC) arm. The safety population (N=651) included 327 patients in the imlunestrant arm and 324 patients in the TPC arm. The ITT population included 138 patients with *ESR/m*-detected status in the imlunestrant arm and 118 in the TPC arm. The safety population included 137 patients with *ESR/m*-detected status in the imlunestrant arm and 117 in the TPC arm. The FDA assessed the demographics of the overall safety population and patients with *ESR/m*-detected status within that population. In general, FDA agrees that baseline characteristics and disease characteristics were balanced in the safety population.

Inluriyo (imlunestrant)

FDA generally agrees with the Applicant that the enrolled population allowed for characterization of the safety profile of imlunestrant, was generally reflective of ER+/HER2-metastatic breast cancer and was generally balanced across the two arms. However, FDA notes that there were no male patients with *ESR*/m-detected status in the safety population and few Black or African-American patients were enrolled in the safety population relative to the prevalence of ER+/HER2- advance breast cancer in the US. No patients with ECOG ≥ 2 were enrolled in EMBER-3.

Adequacy of the safety database

Data:

Please review the data in Section 8.2.1 for details.

The Applicant's Position:

The size of the safety database for imlunestrant was sufficient to adequately characterize the safety profile. EMBER-3 was well designed with appropriate endpoints and a robust safety review process. The safety profile of imlunestrant was studied in a representative population for which the sponsor is seeking an indication. Safety findings are noted in Section 8.2.4. The Sponsor considers these safety risks to be manageable through labeling and standard clinical practice.

The FDA's Assessment:

FDA agrees with the Applicant's position that the size of the safety database was adequate for assessment of the safety of imlunestrant. The FDA's independent analysis of safety relied on data from the EMBER-3 pivotal trial, as previously stated. FDA generally agrees that the safety population in the trial is representative of the population for which the Applicant is seeking an indication, with any caveats noted throughout this safety review, where applicable. In the FDA's review of safety, important safety signals for imlunestrant included diarrhea, nausea, vomiting, musculoskeletal pain, and fatigue. The FDA considers these safety risks to be manageable through labeling.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

Not applicable.

The Applicant's Position:

This NDA submission contains all required components of the electronic common technical document. Analysis-ready safety datasets are provided for EMBER-3.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of data integrity for the safety analysis.

Categorization of Adverse Event

Data:

Consolidated terms

Preferred terms identified by medical evaluation as clinically identical or synonymous were grouped together under a single consolidated term to minimize the excess granularity of MedDRA preferred terms and allow meaningful interpretation of data. Consolidated terms are italicized. CTCAE v5.0 was used to assess safety and tolerability.

Evaluation of AESI

The safety evaluation plan also included an analysis of AESIs (Section 8.2.5.1). All analyses evaluated for AESIs were for treatment-emergent events.

AESIs were determined to be events that were

- of clinical significance
- potentially associated with other SERD agents, or
- observed in preclinical evaluation or earlier clinical studies of implunestrant, although in some instances a causal association with implunestrant could not be clearly established.

The only AESI for implunestrant is transaminase increased.

The Sponsor reviewed deaths due to AEs, SAEs, and TEAEs to identify any significant safety concerns.

Inluriyo (imlunestrant)

TEAEs were also presented by subgroups based on the values collected at baseline (that is, the last nonmissing measurement collected on or before the study drug's first dose date/time).

The Applicant's Position:

Routine clinical tests were conducted as directed by the Schedule of Activities in the EMBER-3 protocol. A central laboratory analyzed clinical chemistry, fasting lipid panel, PK, and biomarker samples. Local laboratories were used to analyze hematology, coagulation, and hormone levels. The study monitors evaluated the local laboratories' use of internal and external quality control, quality assurance, and accreditation schemes.

The Applicant's Position:

EMBER-3 was designed with routine scheduled visits. Tests were appropriate for monitoring safety at the designated intervals. The testing standards were suitable for the indicated population, and the assessments performed were appropriate.

The FDA's Assessment:

In general FDA agrees with the Applicant's assessment for categorization of adverse events.

FDA categorization of adverse events used preferred terms (PTs) to group terms and further consolidate synonymous adverse events, as outlined in section 8.2.1. The FDA PTs for abdominal pain, vomiting, diarrhea, and musculoskeletal pain were slightly different than the ones used by the Applicant as previously noted in this review. The FDA PT for abdominal pain included hepatic pain, the PT for vomiting included hematemesis, the PT for diarrhea included enterocolitis and colitis, and the PT for musculoskeletal pain included cancer pain and back pain. These differences^{(b) (4)} of the adverse events reflecting these PT which the Applicant agreed to. The following safety sections in this Assessment Aid detail FDA safety findings for deaths, TEAEs, SAEs, Grade 3-4 AEs, and adverse events of special interest.

8.2.4 Safety Results

Deaths

Data:

Overall, the majority of patient deaths on study and during long-term follow-up were due to disease progression in both the overall and the *ESRm*-detected safety population. The frequencies of deaths due to any cause on treatment or up to 30 days after discontinuation from study treatment were low across all arms (Table 8.29).

Inluriyo (implunestrant)

At the time of data cutoff, there were 62 deaths in the **implunestrant** arm and 90 deaths in the **SOC** arm. The frequency of death due to AEs on treatment or up to 30 days after discontinuation from study treatment was low in both the overall safety population [**implunestrant** arm (3.7%), **SOC** arm (4.9%)] and *ESR/m*-detected safety population [**implunestrant** arm (4.4%), **SOC** arm (6.0%)]. All patients who died either while receiving implunestrant or during short-term follow-up have CSR narrative summaries submitted for review.

In EMBER, no deaths due to TEAEs were reported in patients with ABC treated with implunestrant 400 mg.

No clear patterns were identified that would indicate a common pathophysiology associated with implunestrant.

**Table 8.29. Summary of Deaths
ESR/m-detected and Overall Safety Population
Implunestrant versus SOC**

Category	ESR/m-detected Safety Population		Overall Safety Population	
	Arm A Implunestrant N= 137 n (%)	Arm B SOC N = 117 n (%)	Arm A Implunestrant N=327 n (%)	Arm B SOC N = 324 n (%)
All deaths	32 (23.4)	48 (41.0)	62 (19)	90 (27.8)
Total deaths on therapy or within 30 days of treatment discontinuation	6 (4.4)	7 (6.0)	12 (3.7)	16 (4.9)
Adverse events	2 (1.5)	2 (1.7)	5 (1.5)	6 (1.9)
Cardiac arrest	0	0	1 (0.3)	2 (0.6)
Acute myocardial infarction	0	0	1 (0.3)	0
Right ventricular failure	1 (0.7) ^a	0	1 (0.3) ^a	0
Hypovolaemic shock	0	0	1 (0.3)	0
Upper gastrointestinal hemorrhage	1 (0.7)	0	1 (0.3)	0
Abdominal infection	0	1 (0.9)	0	1 (0.3)
Blood calcium increased	0	0	0	1 (0.3)
Chronic kidney disease	0	0	0	1 (0.3)
Death	0	0	0	1 (0.3)
Study disease	4 (2.9) ^b	5 (4.3)	7 (2.1) ^b	10 (3.1)
Total deaths after 30 days of treatment discontinuation	26 (19.0)	41 (35.0)	50 (15.3)	74 (22.8)
Adverse event	2 (1.5)	2 (1.7)	3 (0.9) ^c	4 (1.2) ^d

Inluriyo (imlunestrant)

Category	ESR/m-detected Safety Population		Overall Safety Population	
	Arm A Imlunestrant N= 137 n (%)	Arm B SOC N = 117 n (%)	Arm A Imlunestrant N=327 n (%)	Arm B SOC N = 324 n (%)
Study disease	24 (17.5)	39 (33.3)	47 (14.4)	70 (21.6)

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; ESR/m = estrogen receptor 1 mutation; LTFU = long-term follow-up; n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

- a AE was considered related to imlunestrant by the investigator.
- b One patient was reported to have died due to study disease but also suffered a septic shock due to a dengue infection considered fatal by the investigator.
- c Adverse events in LTFU were gastrointestinal hemorrhage, pleural effusion, and pneumonitis.
- d Adverse events in LTFU were cardiac arrest, death, COVID-19, and sepsis.

Source: Table JZLC.5.35, Table JZLC.8.1, and Addendum Table JZLC.3.19

The Applicant's Position:

The majority of deaths were due to study disease and were higher in the SOC arm. The frequency of deaths due to TEAEs was similar across treatment arms in both the overall and ESR/m-detected safety populations with the majority of patients in the **imlunestrant** arm having significant relevant medical history or risk factors leading to the fatal events.

The FDA's Assessment:

The FDA's independent analysis of deaths in the EMBER-3 trial is generally aligned with the Applicant's position. However, the FDA's review of deaths for patients on treatment or within 30 days of treatment discontinuation only identified 8 (2.5%), not 16 (4.9%), deaths in the treatment of physician's choice (TPC) arm in the ITT population, and 4 (3.4%), not 7 (6.0%), deaths in the TPC arm in the ESR/m-detected population. The difference in the number of deaths resulted from a difference in the Applicant's definition of "on therapy or within 30 days of treatment discontinuation" compared to the standard FDA definition. The Applicant's definition was based on a **study discontinuation date** which varied from the time of the last day treatment was received compared to the FDA definition which is based solely on the last day treatment was received. The Applicant reported using the same definition for deaths "on therapy or within 30 days of treatment discontinuation" for both the imlunestrant arm and the TPC arm.

FDA agrees that most deaths in both treatment arms were due to disease progression. The difference in definition of deaths "on therapy or within 30 days of treatment discontinuation"

Inluriyo (imlunestrant)

also led to a difference between the Applicant's and the FDA's assessment of the number of deaths due to TEAEs in the TPC arm as noted below. For the TPC arm, per the Applicant's definition, there were 6 deaths due to AEs within 30 days vs. using the FDA definition, there were 3 deaths within 30 days of the last treatment dose on the TPC arm. For the imlunestrant arm, there were 5 deaths by both the Applicant and FDA definition.

Below is a summary of the narratives for the 5 deaths associated with TEAEs reported in patients who received imlunestrant in EMBER-3, that occurred on therapy or within 30 days of treatment discontinuation. Of note, a sixth death occurred in a patient who received imlunestrant within 30 days of treatment discontinuation. However, this death was due to septic shock due to confirmed dengue fever, and based on the review of the narrative, it is less likely that imlunestrant contributed to this death.

1. Patient (b) (6):

Tumor mutation status: *ESR1*m-detected

This 39-year-old Asian female in India with baseline anemia and thrombocytopenia, and metastases in the liver and bones, died on day 107 from right ventricular failure, two weeks after the last dose of imlunestrant. The patient's baseline anemia and thrombocytopenia worsened while on treatment with imlunestrant and on day 29 imlunestrant was held for 5 days. The patient was also treated with romiplostim. Imlunestrant was re-started at a lower dose on day 35. However, on day 92 the patient again experienced worsened anemia and thrombocytopenia and imlunestrant was held and not re-started. Five days later the patient went to the hospital with fatigue, breathlessness, cough, and symptoms of ongoing cardiac failure. She was admitted for severe thrombocytopenia and received a platelet transfusion. The severe thrombocytopenia was not considered related to imlunestrant by the investigator. An echocardiogram suggested moderate pulmonary hypertension considered to be secondary to right cardiac failure. FDA requested results of the echocardiogram and cardiac evaluation; however, the Applicant stated that echocardiogram results were not provided and a cardiology evaluation was not done. A bone marrow biopsy was done and confirmed progression of disease in the bone marrow. The patient was discharged 9 days after this admission, and on that same day she experienced breathlessness and fatigue. She ultimately died the following day. The cytopenias noted were likely secondary to bone marrow involvement of the tumor and this may have contributed to the ultimate cardiac failure. Chronic anemia may have led to the development of pulmonary HTN. The right ventricular failure was assessed as related to disease progression and there is insufficient evidence to suggest a causal association between the patient's right ventricular failure and imlunestrant. FDA agrees with the Applicant's assessment.

2. Patient (b) (6):

Tumor mutation status: *ESR1*m-detected

Inluriyo (imlunestrant)

This 64-year-old white female patient in Mexico with baseline anemia and elevated uric acid, and metastatic disease to the bones and thyroid gland, died of upper gastrointestinal hemorrhage on day 142, one day after the last dose of imlunestrant. She had no dose omissions or dose reductions reported. The patient had sudden, massive hematemesis on day 142 and died on the way to the hospital. She continued to have anemia and increased blood uric acid throughout the study and was started on allopurinol on day 65. Thirteen days prior to starting imlunestrant the patient's PTT was abnormal (51.8 seconds), though her INR was 1.12. Three days prior to starting the study drug her PTT was 38 seconds and her INR was 1.12. There were no other known risk factors for upper gastrointestinal bleeding, however, she was taking tramadol and paracetamol before and throughout the study for treatment of ongoing hip and back pain. She did not have known helicobacter pylori infection, gastroduodenal ulcer disease or severe esophagitis/gastritis/duodenitis or esophagogastric varices. Imaging done approximately 1 month before her death did not reveal disease progression. No autopsy was performed, and no endoscopy had been performed. The upper gastrointestinal hemorrhage is thought by the Applicant not to be related to imlunestrant. It is difficult to assess the cause of upper gastrointestinal hemorrhage due to confounding factors and complicated medical course and FDA cannot rule whether imlunestrant contributed to the upper gastrointestinal hemorrhage event.

3. Patient (b) (6):

Tumor mutation status: ESR/m-not detected

This 69-year-old American Indian/Alaska Native female in Mexico with metastases to bone and a history of hypertension, gout, and renal atrophy, died of an acute myocardial infarction on day 288. The last dose of study drug was on day 281. She had no dose omissions or dose reductions reported. The patient had experienced intense chest pain on day 267 and was diagnosed with a myocardial infarction. She underwent catheterization and percutaneous coronary intervention at that time for single vessel 70% injury. The patient was discharged from the hospital 3 days after these interventions. She had also received prior treatment with epirubicin and docetaxel for metastatic breast cancer. The acute myocardial infarction is thought not to be related to imlunestrant. The patient had known risk factors for a cardiac event. FDA agrees with the Applicant's assessment.

4. Patient (b) (6):

Tumor mutation status: ESR/m-not detected

This 64-year-old American Indian/Alaskan Native female in Mexico with metastases in the liver and history of diabetes mellitus type 2, hypertension, and anemia, died on day 77 from hypovolemic shock. The last dose of imlunestrant was received on day 57. On day 14 she reported gastroesophageal reflux and was treated with omeprazole, sucralfate, and cisapride. On day 54 her imaging studies showed progression of disease in the liver and on day 57 her baseline anemia worsened. She was also noted to have increased blood urea nitrogen, uric acid, and aspartate aminotransferase as well as decrease in albumin on that day. She had no dose omissions

Inluriyo (imlunestrant)

or dose reductions reported. On day 75 she experienced gastrointestinal bleeding of unknown cause and died on day 77 of hypovolemic shock reportedly secondary to digestive tract bleeding. The gastrointestinal bleeding is thought not to be related to imlunestrant. FDA agrees with the Applicant's assessment. The FDA agrees with the Applicant's assessment and cannot exclude that imlunestrant therapy did not contribute to death due to confounding factors.

5. Patient (b) (6):

Tumor mutation status: ESR1m- not detected

This 72-year-old white female in the United States with metastases in the lung and a history of hypertension, diabetes mellitus 2, hypercholesterolemia, and pulmonary embolism on apixaban died on day 54 of cardiac arrest. The last dose of imlunestrant was on day 54 and she had no dose omissions or reductions. On day 54 she reported heart racing, vomiting and profuse sweating. She died in the ambulance on the way to the hospital within 30 minutes of the onset of her symptoms. Imaging done two days prior revealed progression of disease in multiple bone lesions. The cardiac arrest was thought not to be related to imlunestrant by the investigator and the Applicant. The FDA considers that there is insufficient information to determine if the study treatment contributed to death but cannot exclude the possibility.

Below is a summary of the death narratives for the 6 deaths identified by the Applicant as related to TEAEs that occurred in patients in the TPC arm of the EMBER-3 trial while on therapy or within 30 days of discontinuation. As stated above, the Applicant had a different definition for deaths "while on therapy or within 30 days of treatment discontinuation." Based on the FDA's definition and review, there were only 3 deaths in the TPC arm. Patient (b) (6) died 33 days after last treatment, patient (b) (6) died 52 days after last treatment, and patient (b) (6) died 46 days after last treatment.

1. Patient (b) (6):

Tumor mutation status: Not evaluable

This 68-year-old white female from Mexico with metastases to lung, liver, and bone, and a history of hypertension and diabetes mellitus type 2 complicated by diabetic retinopathy, died of elevated calcium levels on day 62. The patient had previously been treated with cyclophosphamide, epirubicin, docetaxel, and anastrozole. On day 28 she was advised by the investigator to present to a health system because she had been noted to have clinical deterioration and poor performance status. She had also stopped attending scheduled activities and was non-compliant with denosumab treatment. When she presented to a health system for care she was told her calcium was significantly elevated, however, no laboratory results or additional details are available. She received her last dose of fulvestrant on day 29 and on day 62 the patient was admitted to the hospital due to elevated calcium levels; she died the same day. The investigator stated that paraneoplastic syndrome could not be ruled out and that this death was not considered related to study drug. FDA agrees with this assessment. Of note, this death

Inluriyo (imlunestrant)

occurred after the FDA 30-day definition (33 days after last dose of therapy).

2. Patient (b) (6):

Tumor mutation status: *ESR1m*-detected

This 78-year-old White female from Greece with metastases to liver and bone and history of diabetes mellitus, hyperlipidemia, hyperthyroidism, and chronic kidney disease died on day 165 after a 10-day hospitalization due to chronic kidney disease. No other information or details regarding the fatal event were provided. She received her last dose of fulvestrant on day 113 and had been noted to have chronic kidney disease after signing consent but prior to receiving the first dose of study drug. The investigator did not consider the event related to study drug. FDA agrees with this assessment. Of note, this death occurred after the FDA 30day definition (52 days after last dose of therapy).

3. Patient (b) (6):

Tumor mutation status: *ESR1m*-not detected

This 59-year-old Asian female from India with metastases to liver and no known hypertension, diabetes mellitus, or cardiac disorder died on day 15 after collection of blood samples from cardiac arrest. This was a witnessed cardiac arrest after which cardiopulmonary resuscitation was started and the patient was admitted to the intensive care unit. Cardiac activity resumed; however, the patient experienced a second cardiac arrest in the intensive care unit. Cardiopulmonary resuscitation was started and the patient was placed on a ventilator. She deteriorated and two days later was comatose. On day 18 the family opted for no further escalation of treatment and comfort care. On day 26 after one fulvestrant dose the patient had another cardiac arrest and resuscitation was not successful. The investigator's opinion is that the cardiac arrest was not related to the study drug. FDA generally agrees with this assessment.

4. Patient (b) (6):

Tumor mutation status: *ESR1m*-not detected

This 47-year-old American Indian/Alaskan Native female from Mexico with metastases to liver and bone died on day 103 of unknown cause. Her last dose of fulvestrant was on day 57 and she was discontinued from the study on day 85 due to progression of disease in her bone metastases. The patient died at home and it was not possible to acquire more information. In the opinion of the investigator the death was not related to study drug. FDA agrees with this assessment. Of note, this death occurred after the FDA 30-day definition (46 days after last dose of therapy).

5. Patient (b) (6):

Tumor mutation status: *ESR1m*-detected

This 73-year-old White female from Argentina with history of hypertension, chronic obstructive pulmonary disease, and obesity died on day 204 due to an abdominal infection. She received her last dose of fulvestrant on day 176. On day 38 she was hospitalized for pneumonia and on day 42 she experienced atrial fibrillation, both of which were treated with antibiotics analgesics,

Inluriyo (implunestrant)

hydrocortisone, and enoxaparin. She was discharged from the hospital on day 46 and had recovered from the pneumonia. On day 195 she presented to the hospital with abdominal pain and dyspnea. She was diagnosed with an abdominal infection secondary to an intestinal perforation identified on tomography. She was admitted to the hospital and had surgery to correct a perforation of diverticulum in the sigmoid colon. She was also treated with antibiotics as she developed an abscess. The investigator assessed this death not to be related to study drug. FDA agrees with this assessment.

6. Patient (b) (6):

Tumor mutation status: *ESR1*m-not detected

This 76-year-old White female from France with metastatic breast cancer and history of cardiomegaly, hypertension, chronic obstructive pulmonary disease, and ongoing alcohol use died on study day 497 due to cardiac arrest. On day 411 the patient had cardiac decompensation that lasted approximately 2 weeks. She received the last dose of fulvestrant on day 479 and on day 491 was hospitalized due to ileal occlusion. She underwent surgery one day after hospitalization, but showed signs of respiratory distress two days after the surgery. On day 497 the patient was found in cardiac arrest and the patient died that same day despite cardiopulmonary resuscitation. The investigator did not consider the cardiac arrest related to the study drug. FDA agrees with this assessment.

Serious Adverse Events

Data:

The incidence of TE-SAEs was similar across treatment arms (**implunestrant** arm [10.4%] compared to the **SOC** arm [11.4%]) (**Table 8.30**). TE-SAE incidence was also similar in the *ESR1*m-detected safety population across the treatment arms (implunestrant arm [11.7%] compared to the SOC arm [14.5%]). The most common TE-SAEs occurring in more than 2 patients in each arm in the overall safety population were *pleural effusion* (1.2%) in the **implunestrant** arm, and *fracture* (1.5%) and *pneumonia* (0.9%) in the **SOC** arm. The pleural effusions occurred in patients with either a history of pleural effusion, disease progression, or concurrent sepsis. Six patients (1.8%) in each arm had fatal TE-SAEs, including a fatal septic shock captured as due to study disease as per **Table 8.30**. Narratives for fatal TE-SAEs are provided in the CSR.

Inluriyo (imlunestrant)

Table 8.30. Summary of TE-SAEs Occurring in ≥ 2 Patients in Either Treatment Arm by Decreasing Frequency in the Imlunestrant Arm
ESR1m-detected and Overall Safety Population
Imlunestrant versus SOC

PT, n (%)	ESR1m-detected Safety Population		Overall Safety Population	
	Arm A Imlunestrant N=137	Arm B SOC N=117	Arm A Imlunestrant N=327	Arm B SOC N=324
Patients with ≥ 1 TE-SAE^a	16 (11.7)	17 (14.5)	34 (10.4)	37 (11.4)
Pleural effusion	3 (2.2)	0	4 (1.2)	0
Atrial fibrillation	1 (0.7)	0	2 (0.6)	0
<i>Pneumonia</i>	0	1 (0.9)	2 (0.6)	3 (0.9)
Pulmonary embolism	1 (0.7) ^b	0	2 (0.6) ^b	0
Pyrexia	1 (0.7)	0	2 (0.6)	0
Septic shock	2 (1.5)	0	2 (0.6)	0
<i>Fracture</i>	0	1 (0.9)	1 (0.3)	5 (1.5)
<i>Abdominal pain</i>	1 (0.9)	1 (0.9)	1 (0.3)	2 (0.6)
Cardiac arrest	0	0	1 (0.3)	2 (0.6)
Small intestinal obstruction	0	0	0	2 (0.6)

Abbreviations: ESR1m = estrogen receptor 1 mutation; n = number of patients in the specific category; N = number of patients; PT = preferred term; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane; TE-SAE = treatment-emergent serious adverse event.

Note: Consolidated terms are *italicized*.

^a Includes TE-SAEs that occurred while on treatment or in short-term follow-up.

^b Considered related to imlunestrant by the investigator.

Source: JZLC.5.34 and Addendum Table JZLC.3.17.

The frequency of TE-SAEs in patients with ABC given imlunestrant 400 mg in EMBER was low and similar to that in EMBER-3. Each SAE was reported only once in EMBER. No additional safety findings were identified.

The Applicant's Position:

The frequencies of TE-SAEs were similar across treatment arms, occurring in 34 (10.4%) of patients who received **imlunestrant** and 37 (11.4%) of patients who received SOC in the overall safety population. The frequencies are similar for the ESR1m-detected safety populations as compared to the overall safety population in each arm. The only TE-SAE with an incidence of

Inluriyo (imlunestrant)

>1% in patients who received **imlunestrant** was pleural effusion (1.2%). There were no SAEs of pleural effusion in patients who received **SOC**.

The FDA's Assessment:

The FDA conducted an independent review of SAEs and agrees with the Applicant that frequencies of TE-SAEs were similar across both treatment arms, in both the ITT and the *ESR/m*-detected population, and that the only SAE occurring at $\geq 1\%$ in the imlunestrant arm was pleural effusion (1.2%) in EMBER-3. FDA reviewed the narratives for the 4 patients in the imlunestrant arm who experienced pleural effusion and agrees that these occurred in patients with prior pleural effusion, disease progression, or concurrent sepsis. FDA did not independently assess the frequency of TE-SAEs in patients with advanced breast cancer given imlunestrant 400 mg in the EMBER trial but generally agrees with the Applicant's findings that no new SAE signals were seen.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

The incidence of treatment discontinuations due to TEAEs (including deaths on therapy due to TEAEs) was low and similar between the **imlunestrant** arm (4.3%) and the **SOC** arm (1.2%) in the overall safety population. The majority of discontinuations were due to SAEs (9, 2.8% in **imlunestrant** arm and 4, 1.2% in the **SOC** arm) including fatal events (5, 1.5% and 4, 1.2%, respectively). The most frequent event, and the only event occurring in more than 1 patient leading to discontinuation in the **imlunestrant** arm, was alanine aminotransferase (ALT) increased (3, 0.9%).

The Applicant's Position:

The frequency of treatment discontinuations due to AEs was low in both treatment arms with no individual TEAE leading to discontinuation in $\geq 1\%$ of the participants.

The FDA's Assessment:

The FDA conducted an independent review of TEAEs leading to treatment discontinuation in EMBER-3 agrees with the frequencies reported by the Applicant. However, FDA disagrees that incidence of discontinuations due to TEAEs was similar between the imlunestrant arm and the standard of care arm. More patients in the imlunestrant arm discontinued treatment due to a TEAE compared to the treatment of physician's choice arm (4.3% vs. 1.2%, respectively). FDA otherwise agrees with the Applicant's assessment of discontinuations.

Inluriyo (imlunestrant)

Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects

Data:

The incidence of dose withheld/delay was similar between the **imlunestrant** arm (34, 10.4%) and the **SOC** arm (23, 7.1%) in the overall safety population. The most common TEAEs leading to dose withheld for imlunestrant were vomiting (5, 1.5%), aspartate aminotransferase (AST) increased (3, 0.9%), and COVID-19 (3, 0.9%).

The dose reductions due to TEAE were low and occurred in 8 of 327 (2.4%) patients in the **imlunestrant** arm in the overall safety population. The only TEAE leading to dose reduction occurring in more than 1 patient was AST increased (2, 0.6%). No dose reductions in the **SOC** arm were reported.

The Applicant's Position:

Overall, the incidence of dose adjustments due to TEAEs was low and similar in the **imlunestrant** arm compared to the **SOC** arm (10.4% versus 7.1%).

The FDA's Assessment:

The FDA conducted an independent assessment of TEAEs leading to dose withheld/delayed. FDA disagrees that the incidence of dose adjustments due to TEAEs was similar in the imlunestrant arm compared to the treatment of physician's choice (TPC) arm. More patients in the imlunestrant arm experienced dose withheld/delay than patients in the TPC arm (10.4% vs 7.1%, respectively). Diarrhea, neutrophil count decreased, anemia, and alanine aminotransferase increased were additional TEAEs that led to dose withheld/delayed in ≥ 1 patient in the imlunestrant arm (2, 0.6%, each).

FDA agrees with the Applicant's position on dose reductions.

Significant Adverse Events

The Applicant's Position:

Significant AEs are reported and described in SAEs preceding this section, in the following "Treatment-Emergent Adverse Events and Adverse Reactions" paragraph, and in Section 8.2.5.1.

Refer to [Dropouts and/or Discontinuations Due to Adverse Effects](#) and [Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects](#) for discussion of TEAEs leading to

Inluriyo (implunestrant)

discontinuation of study treatment and TEAEs leading to any dose adjustments of study treatment, respectively.

The FDA's Assessment:

FDA agrees with the Applicant's position. Refer to the next section "Treatment-Emergent Adverse Events and Adverse Reactions" and section 8.2.5.1 for further details.

Treatment-Emergent Adverse Events and Adverse Reactions

Data:

In the overall safety population, the incidence of TEAEs were similar across both treatment arms. Within the *ESR/m*-detected safety population a higher incidence of any-grade TEAEs was noted in the **implunestrant** arm than the SOC (**implunestrant** arm: 89.8% vs SOC: 79.5%).

As the incidence of Grade ≥ 3 TEAEs, TE-SAEs, deaths due to AEs, were all similar within the *ESR/m*-detected safety population (implunestrant vs SOC) and between *ESR/m*-detected and overall safety populations for both arms, the TEAEs incidence difference was not considered clinically meaningful. The most common any-grade TEAEs in the **implunestrant** arm were *Fatigue*, *Diarrhea*, and *Nausea*.

[Table 8.31](#) presents a summary of AEs.

Inluriyo (imlunestrant)

**Table 8.31. Overview of Adverse Events
ESR1m-detected and Overall Safety Population
Imlunestrant versus SOC**

Category, n (%)	ESR1m-detected Safety Population		Overall Safety Population	
	Arm A Imlunestrant N=137	Arm B SOC N=117	Arm A Imlunestrant N=327	Arm B SOC N=324
Patients with ≥ 1 TEAE	123 (89.8)	93 (79.5)	270 (82.6)	273 (84.3)
Patients with Grade 1 TEAE ^a	41 (29.9)	29 (24.8)	89 (27.2)	92 (28.4)
Patients with Grade 2 TEAE ^a	56 (40.9)	38 (32.5)	125 (38.2)	114 (35.2)
Patients with Grade ≥ 3 TEAE	26 (19.0)	26 (22.2)	56 (17.1)	67 (20.7)
Patients with Grade 3 TEAE ^a	20 (14.6)	22 (18.8)	46 (14.1)	54 (16.7)
Patients with Grade 4 TEAE ^a	3 (2.2)	2 (1.7)	4 (1.2)	7 (2.2)
Patients with ≥ 1 SAE ^b	16 (11.7)	18 (15.4)	34 (10.4)	38 (11.7)
Patients with TEAE leading to dose adjustment	16 (11.7)	7 (6.0)	34 (10.4)	23 (7.1)
Patients who discontinued study treatment due to AE	6 (4.4)	1 (0.9)	14 (4.3)	4 (1.2)
Patients who discontinued study treatment due to SAE	3 (2.2)	1 (0.9)	9 (2.8)	4 (1.2)
Patients who died due to AE on study treatment or within 30 days of discontinuation of study treatment ^c	0 (0.0)	1 (0.9)	5 (1.5) ^d	6 (1.9)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ESR1m = estrogen receptor 1 mutation; n = number of patients in the specific category; N = number of patients; SAE = serious adverse event; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane; TEAE = treatment-emergent adverse event.

^a Includes patients with maximum CTCAE grade.

^b Includes serious events that occurred during the study treatment and short-term follow-up.

^c Deaths are also included as SAEs and discontinuations due to AEs.

^d One additional patient was reported to have died due to study disease but also experienced an SAE considered fatal by the investigator.

Source: JZC.5.31 and Table JZLC.8.229

Table 8.32 presents the TEAEs by maximum CTCAE grade occurring in 5% patients in either treatment arm, preferred term by decreasing frequency in the **imlunestrant** arm.

Inluriyo (implunestrant)

Table 8.32. Summary of TEAEs by Maximum CTCAE Grade Occurring in 5% of Patients in Either Treatment Arm, Preferred Term by Decreasing Frequency in the Imlunestrant Arm ESR1m-Detected and Overall Safety Population Imlunestrant versus SOC

Preferred or Consolidated Terms	ESR1m-detected Safety Population				Overall Safety Population			
	Arm A Imlunestrant N=137		Arm B SOC N=117		Arm A Imlunestrant N=327		Arm B SOC N=324	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥1 TEAE, n (%)	123 (89.8)	26 (19.0)	93 (79.5)	26 (22.0)	270 (82.6)	56 (17.1)	273 (84.3)	67 (20.7)
<i>Fatigue</i>	35 (25.6)	1 (0.7)	17 (14.5)	1 (0.9)	74 (22.6)	1 (0.3)	43 (13.3)	2 (0.6)
Diarrhea	33 (24.1)	0	15 (12.8)	0	70 (21.4)	1 (0.3)	38 (11.7)	0
Nausea	33 (24.1)	1 (0.7)	20 (17.1)	0	56 (17.1)	1 (0.3)	42 (13.0)	0
Arthralgia	22 (16.1)	0	18 (15.4)	0	46 (14.1)	2 (0.6)	46 (14.2)	1 (0.3)
Aspartate aminotransferase increased	16 (11.7)	0	13 (11.1)	1 (0.9)	41 (12.5)	3 (0.9)	41 (12.7)	3 (0.9)
Back pain	18 (13.1)	1 (0.7)	4 (3.4)	0	35 (10.7)	2 (0.6)	23 (7.1)	1 (0.3)
Alanine aminotransferase increased	12 (8.8)	0	10 (8.5)	1 (0.9)	34 (10.4)	1 (0.3)	33 (10.2)	2 (0.6)
<i>Anemia</i>	12 (8.8)	3 (2.2)	16 (12.7)	5 (4.3)	33 (10.1)	7 (2.1)	41 (12.7)	9 (2.8)
Constipation	14 (10.2)	0	8 (6.8)	0	32 (9.8)	0	18 (5.6)	1 (0.3)
<i>Abdominal pain</i>	12 (8.7)	1 (0.7)	5 (4.3)	1 (0.9)	29 (8.9)	1 (0.3)	18 (5.6)	2 (0.6)
Vomiting	17 (12.4)	1 (0.7)	7 (6.0)	0	29 (8.9)	2 (0.6)	16 (4.9)	1 (0.3)
<i>Cough</i>	13 (9.5)	0	3 (2.6)	0	28 (8.6)	0	15 (4.6)	0
Headache	14 (10.2)	0	9 (7.7)	0	28 (8.6)	0	29 (9.0)	0
Decreased appetite	16 (11.7)	1 (0.7)	6 (5.1)	1 (0.9)	26 (8.0)	1 (0.3)	12 (3.7)	1 (0.3)

Inluriyo (imlunestrant)

Preferred or Consolidated Terms	ESR1m-detected Safety Population				Overall Safety Population			
	Arm A Imlunestrant N=137		Arm B SOC N=117		Arm A Imlunestrant N=327		Arm B SOC N=324	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
<i>Dyspnea</i>	12 (8.8)	1 (0.7)	9 (7.7)	2 (1.8)	25 (7.6)	2 (0.6)	18 (5.6)	3 (0.9)
<i>Hot flush</i>	9 (6.6)	0	5 (4.3)	0	22 (6.7)	0	22 (6.8)	0
<i>COVID-19</i>	11 (8.0)	0	9 (7.7)	0	21 (6.4)	0	25 (7.7)	1 (0.3)
Blood alkaline phosphatase increased	8 (5.8)	2 (1.5)	5 (4.3)	0	18 (5.5)	3 (0.9)	23 (7.1)	2 (0.6)
<i>Thrombocytopenia</i>	9 (6.5)	3 (2.2)	6 (5.1)	2 (1.7)	18 (5.5)	3 (0.9)	16 (4.9)	4 (1.2)
<i>Leukopenia</i>	8 (5.8)	1 (0.7)	2 (1.8)	0	17 (5.2)	2 (0.6)	15 (4.6)	0
<i>Neutropenia</i>	7 (5.1)	4 (2.9)	4 (3.4)	2 (1.7)	17 (5.2)	7 (2.1)	15 (4.6)	6 (1.9)
Pyrexia	10 (7.3)	0	5 (4.3)	0	17 (5.2)	1 (0.3)	11 (3.4)	0
Pain in extremity	6 (4.4)	1 (0.7)	6 (5.1)	0	15 (4.6)	2 (0.6)	24 (7.4)	0
Gamma-glutamyltransferase increased	4 (2.9)	1 (0.7)	2 (1.7)	1 (0.9)	14 (4.3)	5 (1.5)	17 (5.2)	6 (1.9)
<i>Hyperglycaemia</i>	4 (3.4)	0	3 (2.6)	0	13 (4.0)	0	19 (5.9)	1 (0.3)
<i>Injection site reaction</i>	0	0	9 (7.8)	0	0	0	26 (8.0)	0

Abbreviations: COVID-19 = coronavirus disease 2019; CTCAE = Common Terminology Criteria for Adverse Events; ESR1m = estrogen receptor 1 mutation; n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane; TEAE = treatment-emergent adverse event.

Note: Consolidated terms are *italicized*.

Source: Table JZLC.5.32 and Table JZLC.8.228

Inluriyo (implunestrant)

Any Grade Treatment-Emergent Adverse Events

The safety profile of implunestrant monotherapy was consistent with the mechanism of action of SERDs and events commonly experienced by patients with ABC.

Incidence of any grade TEAEs was similar across treatment arms. The majority of TEAEs were Grade 1 or 2.

The most common any grade TEAEs in the **implunestrant** arm were *fatigue*, diarrhea, and nausea, with *fatigue* and diarrhea occurring over 5% more frequently in the **implunestrant** arm compared to the **SOC** arm.

Diarrhea was a frequently reported TEAE for the **implunestrant** arm (21.4%). The majority of events were Grade 1 (60, 18.3%), occurred early in treatment (median time to first onset was 30 days), and did not lead to any discontinuations or dose reductions in either arm. The majority of patients experienced only 1 episode of diarrhea.

Nausea was a frequently reported TEAE for the **implunestrant** arm (17.1%). The majority of events were Grade 1 (44, 13.5%), occurred during the first month of treatment (36, 11%), median time to onset (19.5 days) and did not lead to any discontinuations, with 1 dose reduction. The majority of patients experienced only 1 episode of nausea.

The most common any grade TEAEs in the **SOC** arm were arthralgia, *fatigue*, and nausea.

Injection site reaction was the only any grade TEAE to occur 5% more frequently in the **SOC** arm compared to the **implunestrant** arm (8.0% versus 0%).

Grade ≥ 3 Treatment-Emergent Adverse Events

The incidence of Grade ≥ 3 TEAEs was similar in the **implunestrant** arm (17.1%) and the **SOC** arm (20.7%). These events were predominantly Grade 3 (14.1% versus 16.7%), with lower but similar incidences for Grade 4 (1.2% versus 2.2%) and Grade 5 (1.8% versus 1.9%) TEAEs for **implunestrant** and **SOC** arm, respectively. Grade 5 TEAEs are discussed further in the CSR.

The most common Grade ≥ 3 TEAEs in both the **implunestrant** and **SOC** arms were associated with laboratory investigations, which were reported with similar incidences in both arms. The most common Grade ≥ 3 TEAEs for implunestrant occurring $>1\%$ were *anemia* (2.1%), *neutropenia* (2.1%), and gamma-glutamyltransferase increased (1.5%). The most common Grade ≥ 3 TEAEs for the **SOC** arm occurring $>1\%$ were *anemia* (2.8%), *neutropenia* (1.9%), gamma-glutamyltransferase increased (1.9%), and *thrombocytopenia* (1.2%). There were no clinically meaningful differences in Grade ≥ 3 TEAE incidences noted between treatment arms.

The Applicant's Position:

- In the overall safety population, the incidence of TEAEs were similar across both treatment arms. Within the *ESR1m*-detected safety population, a higher incidence of any-grade TEAEs was noted in the **implunestrant** arm as compared to **SOC** arm.

Inluriyo (imlunestrant)

- The incidence of any grade and Grade ≥ 3 TEAEs was similar between both arms, with fatigue, diarrhea, and nausea reported as the most frequently experienced TEAEs in the **imlunestrant** arm.
- The incidence of TE-SAEs and deaths due to AEs were similar across treatment arms.
- The imlunestrant safety profile was manageable through routine monitoring and standard clinical practice as evidenced by low rates of dose adjustments or treatment discontinuation due to AEs.

The safety profile in the *ESR1*-m-detected safety population was consistent with the overall safety population.

The FDA's Assessment:

The FDA conducted an independent assessment of TEAEs in the EMBER-3 trial. The FDA agrees with the Applicant that the safety profile for patients with *ESR1*-m detected status was similar to the safety profile for all patients in the EMBER-3 trial. FDA also agrees with the frequencies of all-grade TEAEs, grade ≥ 3 TEAEs, SAEs, TEAEs leading to dosage interruption, dose reduction, and drug discontinuation presented in the Applicants Overview of TEAEs table (Table 8.26). Based on FDA's assessment of TEAEs leading to death while on treatment or within 30 days of last treatment, FDA disagrees there were 6 deaths in the treatment of physician's choice (TPC) arm as 3 of the 6 deaths occurred at time points greater than 30 days since last treatment was received. See Section 8.2.4 for more details.

The FDA's analysis of all-grade and grade ≥ 3 TEAEs that occurred at a frequency $\geq 10\%$ is shown in **Table 8.33** below and this information is also included in Section 6 of the imlunestrant USPI. Though all-grade anemia occurred at a frequency of $\geq 10\%$, it was not included in **Table 8.33** as hemoglobin decreased collected as a laboratory abnormality occurred at a higher frequency and was included in Table 4 of the USPI for imlunestrant. In FDA's review, musculoskeletal pain (which included the preferred terms arthralgia and back pain), was also a common all-grade (30%) and grade ≥ 3 (3.7%) TEAE in the imlunestrant arm. The all-grade incidence of musculoskeletal pain was similar in the TPC arm (29%), but the incidence of grade ≥ 3 musculoskeletal pain was lower in the TPC arm (1.9%).

While diarrhea did not lead to any discontinuations or dose reductions, there were 2 cases of diarrhea that led to dose withheld/delayed. Further information about dosage interruption, dose reduction, and drug discontinuation can be found in the corresponding sections above.

The FDA agrees that fatigue and diarrhea occurred over 5% more frequently in the imlunestrant arm compared to the TPC arm.

Inluriyo (imlunestrant)

The FDA agrees with the Applicant's description of injection site reaction in patients who received fulvestrant and also notes that no patients who received imlunestrant experienced injection site reaction.

The FDA agrees with the Applicant that the incidence of any grade TEAEs and Grade ≥ 3 TEAEs was similar across treatment arms. The majority of TEAEs were Grade 1 or 2. FDA disagrees with the Applicant that the safety profile of imlunestrant monotherapy was consistent with the mechanism of action of SERDs and events commonly experienced by patients with HR+/HER2-advanced breast cancer. Since imlunestrant is a new molecular entity (NME) this is the first assessment of this drug's safety database and all safety findings are new. The FDA agree with the Applicant that the safety profile of imlunestrant was manageable through routine monitoring.

Table 8.33: Adverse Reactions ($\geq 10\%$) in Patients Who Received INLURIYO in EMBER-3

Adverse Reaction ^a	INLURIYO N=327		Fulvestrant or Exemestane N=324	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Musculoskeletal Disorders				
Musculoskeletal Pain	30	3.7	29	1.9
General Disorders and Administration Site Conditions				
Fatigue ^b	23	0.3	14	0.6
Gastrointestinal Disorders				
Diarrhea	22	0.6	12	0.0
Nausea	17	0.3	13	0.0
Constipation	10	0	6	0.3
Abdominal pain ^b	10	0.3	6	0.6

^a Adverse reactions were graded using NCI CTCAE version 5.0.

^b Includes other related terms

Laboratory Findings

Data:

Findings from analysis of laboratory data for serum hematology and chemistry were generally similar between the **imlunestrant** arm and the **SOC** arm in the overall and the *ESR/m*-detected

Inluriyo (imlunestrant)

safety population. The percentage of patients with reported treatment-emergent laboratory abnormalities was consistent with, but generally higher than, the percentage of patients with laboratory abnormalities reported as TEAEs, as only those deemed clinically relevant were to be reported as AEs.

Treatment-emergent laboratory abnormalities by the maximum postbaseline CTCAE grade for AST/ALT increased are summarized in [Table 8.34](#).

Table 8.34. Summary of Treatment-Emergent Maximum Postbaseline CTCAE Laboratory Toxicities for ALT and AST ESR1m-detected and Overall Safety Population Imlunestrant versus SOC

Laboratory Parameter	ESR1m-detected Safety Population		Overall Safety Population	
	Arm A Imlunestrant N=137	Arm B SOC N=117	Arm A Imlunestrant N=327	Arm B SOC N=324
Serum alanine aminotransferase (U/L)				
Total, n ^a	130	109	314	303
Any Grade, n (%)	58 (44.6)	34 (31.2)	103 (32.8)	94 (31.0)
Grade 3 or 4, n (%)	1 (0.8)	1 (0.9)	4 (1.3)	3 (1.0)
Serum aspartate aminotransferase (U/L)				
Total, n ^a	133	108	321	309
Any Grade, n (%)	50 (37.6)	35 (32.4)	102 (31.8)	98 (31.7)
Grade 3 or 4, n (%)	2 (1.5)	3 (2.8)	6 (1.9)	7 (2.3)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common

Terminology Criteria for Adverse Events; ESR1m = estrogen receptor 1 mutation; n = number of patients in the specific category; N = number of patients in analysis population; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Note: Postbaseline grades were derived based on baseline status per CTCAE Version 5.

^a Refers to all treated patients with at least 1 assessment at baseline and during treatment or the short-term follow-up period for the specified laboratory parameter.

Source: Table JZLC.5.43 and Table JZLC.8.234

Following analysis of laboratory values at baseline and worst CTCAE grade, postbaseline hematology and chemistry laboratory data indicated no additional safety findings as compared to TEAE data. Details regarding TEAEs of elevated transaminases are provided in the AESI section (Section [8.2.5.1](#)).

In the ESR1m-detected safety population there was a higher frequency of elevated ALT and AST in the imlunestrant arm compared to SOC (ALT: 44.6% vs 31.2%; AST: 37.6% vs 32.4%). The frequency of Grade 3 or 4 ALT / AST elevations was low in both arms.

Inluriyo (implunestrant)

In addition, the incidence of any grade ALT/AST elevation in the implunestrant arm was higher in the *ESR/m*-detected safety population compared to the overall safety population (ALT: 44.6% vs 32.8%; AST: 37.6% vs 31.8%). However, the Grade-3 or 4 ALT/AST elevations were similar.

Serum lipids were evaluated during the EMBER-3 study due to the known mechanism of action and effects of ET on lipid levels. A similarly increased incidence of treatment-emergent maximum postbaseline serum lipids was noted across treatment arms in both the overall and the *ESR/m*-detected safety population.

In the overall safety population, the incidence of any grade high cholesterol in the **implunestrant** arm compared to **SOC** arm was 10.2% versus 12.3%, respectively. In the *ESR/m*-detected safety population, the incidence of any grade high cholesterol in the **implunestrant** arm compared to **SOC** arm was similar at 10.5% versus 9.9%, respectively and consistent with the overall safety population.

In the overall safety population, the incidence of any grade high triglycerides in the **implunestrant** arm compared to **SOC** arm was 21.0% versus 22.0%, respectively. . In the *ESR/m*-detected safety population the incidence of any grade high triglycerides in the **implunestrant** arm compared to **SOC** arm was 18.6% versus 20.0%, respectively and was similar to the overall safety population. Of note, the increases in cholesterol that were observed were driven by increases in high-density lipoprotein rather than low-density lipoprotein in both the treatment arms.

The Applicant's Position:

Serum hematology and chemistry findings were generally similar across treatment arms and were consistent with the TEAEs reported. No additional safety findings were noted.

The FDA's Assessment:

The FDA conducted an independent safety analysis of laboratory abnormalities in the EMBER-3 trial based on laboratory values that worsened from baseline and disagrees with the Applicant's description of AST/ALT increase as summarized in the Table 8.28 above as the Applicant was not using baseline values in all cases to calculate the change in lab value (Grade worsened compared to baseline). FDA sent additional requests for information to the Applicant to recalculate the change in grade from baseline and independently verified these values.

The FDA laboratory analysis is shown in **Table 8.35** below, which is also included in section 6 of the implunestrant USPI. FDA disagrees with the Applicant that the laboratory data indicated no additional safety findings compared to the TEAE data as these reflect more accurately the incidence of abnormalities potentially related to therapy regardless of attribution. FDA found hemoglobin decreased, neutrophil decreased, platelet decreased, triglycerides increased, cholesterol increased, calcium decreased, aspartate aminotransferase (AST) increased, and alanine aminotransferase (ALT) increased to be relevant safety findings identified in review of

Inluriyo (imlunestrant)

the laboratory data for the EMBER-3 trial. Though these laboratory abnormalities were experienced at similar frequencies in both arms, they occurred at high frequencies and are clinically meaningful. Further information about AST increased and ALT increased is found in **Section 8.2.5** of this review.

Table 8.35: Select Laboratory Abnormalities (≥10%) That Worsened from Baseline in Patients Who Received INLURIYO in EMBER-3

Lab Abnormality ^a	INLURIYO ^b		Fulvestrant or Exemestane ^b	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Hematology				
Hemoglobin decreased	30	1.2	35	3.4
Neutrophils decreased	26	4	29	4.7
Platelets decreased	16	1.8	14	1.3
Chemistry				
Calcium decreased	26	0	19	0.6
Aspartate aminotransferase increased	25	1.9	27	2.3
Alanine aminotransferase increased	21	1.3	23	1.0
Triglycerides increased	21	0	22	1.2
Cholesterol increased	10	0	12	0

^a Graded according to NCI CTCAE version 5

^b The denominator used to calculate the rate varied from 252 to 325 based on the number of patients with a baseline value and at least one post-treatment value.

Vital Signs

The Applicant's Position:

Vital signs, including blood pressure and pulse rate, were collected at regular intervals during the study.

Inluriyo (imlunestrant)

No clinically meaningful changes were noted in vital signs by visit during the study in overall safety population or *ESR*/m-detected safety population.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Electrocardiograms (ECGs)

The Applicant's Position:

Single local ECGs were obtained after baseline for patients in the **imlunestrant** arm and were taken on Day 1 of Cycles 1, 2, and 4, and at short-term follow-up. In addition to TEAEs, all patients were randomly assigned to the **imlunestrant** arm had QTc interval documented after 10 August 2022.

Analyses of ECGs did not reveal any safety concerns relative to the analysis of TEAE data.

Vital signs and ECG analyses observed in EMBER-3 were consistent with the respective patient population in EMBER.

The FDA's Assessment:

The FDA agrees with the Applicant that ECG analysis did not reveal any additional safety issues in the EMBER-3 trial. No clinically meaningful change (≥ 20 msec mean increase in QTc interval) was noted. FDA did not review the ECG data for patients in the EMBER trial. Refer to FDA QT Study Review dated 5/20/2025 for additional information.

QT

Data:

Imlunestrant monotherapy

- Of the 327 patients treated with imlunestrant monotherapy, 3 patients experienced a TEAE of ECG QT prolonged and 1 patient experienced a TEAE of syncope. These events were of low grade (Grade 1 [n = 3] and Grade 2 [n = 1]) and were not serious.
- Of the 3 patients who experienced a TEAE of ECG QTc prolongation, 2 patients had prolonged QTc interval at baseline. In the additional patient, the event occurred 1 month after the discontinuation of imlunestrant.

Inluriyo (imlunestrant)

- Grade 1 TEAE of syncope was reported in a patient who had discontinued the study drug 29 days prior to the event. Of note, a Grade 2 event of general health deterioration was reported 23 days prior to the TEAE of syncope.
- No dose reduction, dose hold, or dose discontinuations were reported due to these events.

The Applicant's Position:

No increased incidence of AEs that signal a potential for proarrhythmic effects (ICH E14 Section 4) were noted.

The FDA's Assessment:

The Interdisciplinary Review Team for Cardiac Safety (QT-IRT) at the FDA conducted a review of QT and concluded that imlunestrant does not demonstrate mean QTc interval prolongation ≥ 20 msec, though it cannot be concluded that imlunestrant has no impact on QTc because there was no positive control in studies performed. They also concluded that available data for imlunestrant do not support concluding a low likelihood of proarrhythmic risk due to delayed repolarization. See the QT Study Review dated 5/20/2025 for additional information.

Immunogenicity

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

Inluriyo (implunestrant)

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Adverse Events of Special Interest

Data:

Based on considerations of preclinical toxicology and safety data observed during healthy volunteer early phase studies and ongoing clinical trials, transaminase increases are deemed an AESI for implunestrant. After evaluation of the EMBER-3 data, there were no cases that met Hy’s Law criteria.

The incidence of elevated transaminase events in any grade and Grade ≥3 was similar between the **implunestrant** arm and the **SOC** arm (15.6% versus 14.8% any grade, respectively; and Grade ≥3 was 1.2% for both (Table 8.36).

In the *ESR/m*-detected safety population the incidence of TE-elevated transaminase events was similar between treatment arms, any grade (implunestrant: 14.6% versus SOC: 12%) and Grade ≥3 (implunestrant: 0.7 % versus SOC: 1.7%). The majority of transaminase elevations were low grade, did not require dose adjustments, and led to few discontinuations in both the overall (1.2%) and *ESR/m*-detected safety population (1.5%) (Table 8.37).

This allowed the majority of patients who experienced these events to continue on therapy (92.2% **implunestrant** arm versus all patients in **SOC** arm). Only 1 case of hepatotoxicity, in a patient with liver metastases at baseline, was serious.

The most frequently reported preferred terms of transaminase elevations were ALT and AST increased, which had similar incidences in both treatment arms. The events in both arms occurred early in treatment (median time to first onset any grade TEAE was 58 days for **implunestrant** and 42.5 days for **SOC**)

Table 8.36. Treatment-Emergent Elevated Transaminases by Decreasing Frequency Safety Population; Implunestrant versus SOC

Laboratory Parameter	ESR/m-detected Safety Population				Overall Safety Population			
	Arm A Implunestrant N=137		Arm B SOC N=117		Arm A Implunestrant N=327		Arm B SOC N=324	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥1 Elevated Transaminases, n (%)	20 (14.6)	1 (0.7)	14 (12.0)	2 (1.7)	51 (15.6)	4 (1.2)	48 (14.8)	4 (1.2)
Alanine aminotransferase increased	12 (8.8)	0	10 (8.5)	1 (0.9)	34 (10.4)	1 (0.3)	33 (10.2)	2 (0.6)

Inluriyo (imlunestrant)

Laboratory Parameter	ESR1m-detected Safety Population				Overall Safety Population			
	Arm A Imlunestrant N=137		Arm B SOC N=117		Arm A Imlunestrant N=327		Arm B SOC N=324	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Aspartate aminotransferase increased	16 (11.7)	0	13 (11.1)	1 (0.9)	41 (12.5)	3 (0.9)	41 (12.7)	3 (0.9)
Hepatic enzyme increased	0	0	0	0	0	0	2 (0.6)	0
Hepatotoxicity	2 (1.5)	1 (0.7)	0	0	2 (0.6)	1 (0.3)	0	0
Hypertransaminasemia	0	0	0	0	1 (0.3)	0	0	0
Transaminases increased	0	0	0	0	0	0	1 (0.3)	0

Abbreviations: *ESR1m* = estrogen receptor 1 mutation; n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Source: Table JZLC.5.41, Addendum Table JZLC.3.29, and Table JZLC.8.228

Inluriyo (imlunestrant)

Table 8.37. Summary of Characteristics of Treatment-Emergent Elevated Transaminase Adverse Events
Safety Population
Imlunestrant versus SOC

	<i>ESR1</i> m-detected Safety Population		Overall Safety Population	
	Arm A Imlunestrant N = 137	Arm B SOC N = 117	Arm A Imlunestrant N = 327	Arm B SOC N = 324
Patients with ≥ 1 Elevated Transaminases, n (%)	20 (14.6)	14 (12.0)	51 (15.6)	48 (14.8)
Incidences per patient, n (%)				
1	11 (8.0)	5 (4.3)	24 (7.3)	19 (5.9)
2	7 (5.1)	5 (4.3)	20 (6.1)	16 (4.9)
≥ 3	2 (1.5)	4 (3.4)	7 (2.1)	13 (4.0)
Incidences of Grade ≥ 3 AEs per patient, n (%)				
1	1 (0.7)	2 (1.7)	3 (0.9)	3 (0.9)
2	0	2 (1.7)	1 (0.3)	1 (0.3)
≥ 3	0	0	0	0
TE-SAEs, n (%)	1 (0.7)	0	1 (0.3)	0
Dose adjustments, n (%)				
None	19 (13.9)	14 (12.0)	46 (14.1)	46 (14.2)
Dose reduction of study drug	0	0	2 (0.6)	0
Dose withheld/delay of study drug	1 (0.7)	0	5 (1.5)	0
Treatment discontinuation, n (%)	2 (1.5)	0	4 (1.2)	0
Time to onset of first AE (any grade)				
Median (range), days	56 (1-521)	26.5 (1-253)	58.0 (1-521)	42.5 (1-476)
Time to onset of first Grade ≥ 3 AE				
Median (range), days	11 (11-11)	250.5 (248-253)	186.5 (11-283)	239.0 (55-253)

Abbreviations: AE = adverse event; *ESR1*m = estrogen receptor 1 mutation; n = number of patients in the specific category; N = number of patients; TE-SAE = treatment-emergent serious adverse event; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Source: Table JZLC.5.42 and Addendum Table JZLC.3.29.

Consistent with the reported incidence of Grade ≥ 3 TEAEs of ALT and AST increased, the

Inluriyo (imlunestrant)

incidence of Grade ≥ 3 laboratory evaluations of ALT and AST increased was also low. The CSR provides a summary of abnormal hepatic laboratory results in the **imlunestrant** arm and the **SOC** arm.

The Applicant's Position:

The AESI of transaminase increase are monitorable and manageable with few patients discontinuing or dose reducing, allowing most patients who experience these events to continue therapy.

The FDA's Assessment:

The Applicant designated elevated transaminases as an AE of special interest and the FDA designated dyslipidemia as an AE of special interest. The FDA conducted independent safety analyses focused on elevated transaminases and dyslipidemia.

Elevated Transaminases

FDA generally agrees with the Applicant's position, the information presented by the Applicant in **Table 8.37** above, and that the most frequently reported preferred terms of transaminase elevations were ALT and AST increased, which occurred in similar frequency in both arms and were predominantly low grade. An independent review by FDA of cases that met Hy's Law criteria revealed no cases. There were three cases of patients with AST or ALT $> 3 \times$ ULN or total bilirubin elevation $> 2 \times$ ULN that were reviewed by FDA, and all patients had liver metastases and/or abnormal liver enzymes at baseline. Due to confounding, it is difficult to conclude whether changes were directly related to treatment with imlunestrant.

Of note, AST or ALT increased were among the most common causes of dose withheld/delay, AST increased was a common cause for dose reduction, and ALT increased was the only cause for discontinuation in more than 1 patient in the imlunestrant arm. See relevant sections above on Dropouts/Discontinuations/Dose Interruptions for further details. AST and ALT increased are included in section 6 of the USPI for imlunestrant. The FDA agrees with the Applicant that elevated transaminases can be monitored and managed in patients taking imlunestrant with appropriate labeling.

Dyslipidemia – Hypertriglyceridemia and hypercholesterolemia

Since dyslipidemia has been associated with other endocrine therapies used to treat ER+/HER2-breast cancer, such as aromatase inhibitors, selective estrogen receptor modulators, and selective estrogen receptor degraders, the FDA conducted additional analyses to assess TEAEs of hypertriglyceridemia and hypercholesterolemia more comprehensively in patients who received imlunestrant in the EMBER-3 trial.

Inluriyo (imlunestrant)

Hypertriglyceridemia and hypercholesterolemia occurred in 21% and 10% of patients who received imlunestrant in the EMBER-3 trial, and in 22% and 12% of patients who received TPC. Grade ≥ 3 triglycerides increased occurred in 0 patients in the imlunestrant arm and in 1.2% of patients in the TPC arm. Grade ≥ 3 cholesterol increased occurred in 0 patients in both the imlunestrant and TPC arm. There were no dose adjustments, dose holds, or treatment discontinuations due to hypertriglyceridemia or hypercholesterolemia.

FDA reviewed the monitoring and management of lipid panel labs as described in the protocol for the EMBER-3 trial, the use of concomitant medications for the management of dyslipidemia, and protocol deviations associated with missing lipid panel labs. No significant aberrancies or differences between the imlunestrant arm and the TPC arm were identified. FDA also requested an analysis of frequency of triglycerides increased and cholesterol increased by geographic region from the Applicant. This analysis revealed no significant differences in the frequency of all grade or Grade ≥ 3 triglycerides increased or cholesterol increased across North America/Western Europe, East Asia, or Other; although, these analyses are limited due to small sample size and exploratory nature of the analysis.

Based on the totality of information reviewed, FDA did not include triglycerides increased and cholesterol increased in the Warnings and Precautions section of the USPI for imlunestrant, but these were included in the safety sections of the USPI. Prescribers are recommended to monitor the lipid panel at baseline and periodically throughout treatment with imlunestrant.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Patient-reported outcomes have been previously discussed in Section 8.1.2.

The FDA's Assessment:

See FDA Assessment of patient-reported outcomes in Section 8.1.2.

8.2.7 Safety Analyses by Demographic Subgroups

Data:

Not applicable.

Inluriyo (imlunestrant)

The Applicant's Position:

Supportive analyses were performed to assess the safety and tolerability of imlunestrant across selected subgroups (for example, age group, race, region, and selected baseline disease characteristics). Overall, the safety profile within each subgroup per treatment arm was consistent with the overall safety population. Although numerical differences were noted in the subpopulations by age/region, these differences are expected in the patient population and are not considered to be clinically significant.

The FDA's Assessment:

The FDA performed an independent analysis of safety based on age ≤ 65 years and >65 years. The FDA agrees there were no clinically significant differences in the safety profile of imlunestrant based on age using an age cutoff of 65 years. There were too few patients >75 years to assess for differences in safety using an age cutoff of 75 years. There were numerical differences in all grade TEAEs and Grade ≥ 3 by region, but FDA agrees with the Applicant these differences do not appear clinically significant.

While there were no clinically significant differences in the safety profile across race groups in the analysis conducted by FDA, no definitive conclusions can be drawn given there were few Black or African American patients in the safety population of the EMBER-3 trial relative to the prevalence of ER+/HER2- advanced breast cancer in this population in the US. There were only 5 male participants in the EMBER-3 trial, which limited assessment of differences in safety based on sex, but did not alter FDA's overall conclusions about the safety profile of imlunestrant.

FDA did not conduct an analysis of safety based on baseline characteristics. The FDA examined safety in the *ESR1*m-detected subgroup and the entire EMBER-3 trial safety population and did not note major differences in safety.

8.2.8 Specific Safety Studies/Clinical Trials

The Applicant's Position:

No specific studies were conducted to evaluate safety concerns.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Inluriyo (implunestrant)

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Human carcinogenicity studies have not been conducted with implunestrant.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Human Reproduction and Pregnancy

The Applicant's Position:

Patients who were pregnant, breastfeeding, or expecting to conceive or father children were excluded from implunestrant clinical trials. Thus, there is no clinical data regarding exposure of implunestrant in pregnant or lactating patients. The potential risks regarding the use of implunestrant in patients of reproductive potential, use during pregnancy and use during lactation will be addressed in product labeling.

The FDA's Assessment:

The FDA agrees with the Applicant's position. Potential risks for the use of implunestrant in patients of reproductive potential, use during pregnancy and use during lactation were included in Section 17 of the USPI for implunestrant as indicated above.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

As per the agreed initial pediatric study plan issued by the FDA on 26 July 2021, Lilly requested a full pediatric study waiver.

The FDA's Assessment:

The FDA agrees the Applicant requested a full pediatric waiver.

Inluriyo (implunestrant)

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

Overdose

As of 24 June 2024, no new AE of implunestrant overdose was reported.

Drug abuse potential

Not applicable.

Withdraw and rebound

Not applicable.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable, as implunestrant is not currently marketed in any region.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Potential safety concerns beyond the risks conveyed in the proposed labeling are not expected. Routine pharmacovigilance practices will be used to monitor for unexpected events.

The FDA's Assessment:

Inluriyo (imlunestrant)

The safety assessment for imlunestrant for this NDA review is primarily based on the 327 patients treated in the imlunestrant arm of the EMBER-3 trial. The FDA will continue to monitor post-marketing reports and safety reports submitted after approval.

8.2.11 Integrated Assessment of Safety

Data

A pooled safety analysis for patients with ER+, HER2- ABC in EMBER-3 and EMBER receiving the 400-mg dose as monotherapy was reviewed. The pooled analysis sets increase the size of the datasets for patients receiving imlunestrant 400 mg daily and increase the robustness of the safety assessment. Review of the pooled data did not reveal any additional safety findings.

The Applicant's Position:

Results of analyses performed for individual safety parameters using the analysis sets described were reviewed, and they revealed an overall consistency in results between the primary analysis sets and the supportive and the pooled analysis sets.

The FDA's Assessment:

The FDA safety assessment for imlunestrant considered the data from the EMBER trial as supportive and determined the safety data from EMBER-3 was adequate for the NDA review as it represented the indicated population. The safety profile of imlunestrant monotherapy is based on review of data from the overall safety population in the EMBER-3 trial, including both patients with *ESR1*m-detected and *ESR1*m-not detected status. The overall safety population in the EMBER-3 trial consisted of 651 patients (327 in the imlunestrant arm, and 254 of these with *ESR1*m-detected status). As no differences were identified between the safety profile of imlunestrant in patients with *ESR1*m-detected and *ESR1*m-not detected status, the safety review was reported for the overall safety population.

The safety profile for imlunestrant monotherapy was consistent with the anticipated safety concerns for selective estrogen receptor degraders (SERDs). The most common TEAEs included fatigue, diarrhea, nausea, and musculoskeletal pain. The majority of TEAEs were low grade, but clinically significant as they can impact quality of life. The frequency of fatigue and diarrhea was numerically higher in the imlunestrant arm compared to the TPC arm. For further details refer to Section 8.2.4. Elevated transaminases and dyslipidemia were AEs of special interest, with elevated transaminases including the preferred terms ALT increased and AST increased. ALT

Inluriyo (imlunestrant)

increased and AST increased were among the most common causes for dose delays, interruptions, and discontinuations in the imlunestrant arm. For additional FDA conclusions regarding safety, refer to Section 8.2.

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

The FDA's Assessment:

The randomization for EMBER-3 was stratified on the following factors: prior CDK4/6i therapy, visceral metastases, and region. The *ESR1* mutation status was not a stratification factor at the time of randomization. Although the key measured demographics and baseline disease characteristics are generally balanced between treatment arms, there is still a risk of potential imbalance between treatment arms for unmeasured baseline characteristics.

EMBER-3 did pre-specify formal testing of treatment benefit of PFS and OS in the *ESR1*-m-detected population. EMBER-3 demonstrated a statistically significant improvement in investigator-assessed PFS in the *ESR1*-m-detected population. These results were robust to several sensitivity analyses, including a restricted mean survival time analysis. EMBER3 did not meet its primary endpoint of investigator-assessed PFS in the ITT population and no benefit was demonstrated in the *ESR1*-m-detected population.

At the time of the primary PFS analyses, the IA1 for the key secondary endpoint of OS for the comparison of the imlunestrant arm and the TPC arm in the *ESR1*-m-detected population did not reach statistical significance. However, no trend toward a survival detriment was observed in the *ESR1*-m-detected population. Therefore, the FDA agrees with the Applicant's proposed indication for patients with a detected *ESR1*-m.

OS curves for the comparison of the imlunestrant arm and the TPC arm in the *ESR1*-m-detected population overlapped for the first 3 months, favored to the TPC arm from about 3 to 7 months, and began to separate in favor of the imlunestrant arm from Month 7 onward. It was noted that the number of OS events that occurred before Month 7 was small. Although OS curves began to separate from Month 7 in favor of the imlunestrant arm, the censoring for OS was heavy starting from Month 8 since many patients were administratively censored, therefore, there is still uncertainty in the OS result and further review of the preplanned remaining interim and final OS analyses for the comparison of the imlunestrant arm and the TPC arm in the *ESR1*-m-detected population with more mature data is important for both efficacy and safety. The Applicant committed to submit SAP version 5 pre-specified interim and final OS results as a PMC.

8.4 Conclusions and Recommendations

The FDA's Assessment:

EMBER-3 was a randomized, active-controlled, open-label, multicenter trial that enrolled 661 patients with ER-positive, HER2-negative advanced or metastatic breast cancer to receive either imlunestrant monotherapy or TPC. The trial demonstrated a statistically significant and clinically meaningful improvement in investigator-assessed PFS in the *ESR/m* population. This finding was further supported by a favorable trend in OS HR in the *ESR/m* population. The trial did not meet the prespecified efficacy threshold for the ITT population and exploratory analyses suggested that there was not benefit in the *ESR/m-nd* population.

Imlunestrant was associated with increased fatigue, gastrointestinal adverse events, and elevated transaminases compared to treatment of physician's choice.

The FDA disagrees with the Applicant's assessment that an oral route of administration is inherently superior to other routes of administration. In this instance patients are required to take imlunestrant in a fasted state. Additionally, orally administered drugs may be associated with increased gastrointestinal toxicity.

The review team recommends regular approval for imlunestrant for the following indication:

Imlunestrant (INLURIYO) is indicated for the treatment of adults with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

8.4.1 Approach to Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (*enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response*):

Approved Indication: *Imlunestrant (INLURIYO) is indicated for the treatment of adults with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.*

Inluriyo (imlunestrant)

2. SEE was established with *(check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)*

a. Adequate and well-controlled clinical investigation(s):

i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**

ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

b. ☒ One adequate and well-controlled clinical investigation and confirmatory evidence^{1,2,3}

OR

c. ☐ Evidence that supported SEE from a prior approval (*e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch*)²

3. Complete response, if applicable

a. ☒ SEE was established

b. ☐ SEE was not established (*if checked, omit item 2*)

¹ FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)

² FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)

³ *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (2023)]

X

X

Primary Statistical Reviewer
Hui Zhang, PhD

Statistical Team Leader
Xin (Cindy) Gao, PhD

Inluriyo (imlunestrant)

X

X

Primary Clinical Reviewer

Joshua Donaldson, MD, PhD (Efficacy)

Maria Garcia-Jimenez, MD, MHS (Safety)

Clinical Team Leader

Preeti Narayan, MD

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

No advisory committee meeting was held for this NDA application.

Inluriyo (implunestrant)

10 Pediatrics

The Applicant's Position:

As per the agreed initial pediatric study plan issued by the FDA on 26 July 2021, Lilly requested a full pediatric study waiver.

The FDA's Assessment:

The FDA agreed with Applicant's Initial Pediatric Study Plan (iPSP) submitted under the associated IND in July 2021. In the iPSP, the Applicant requested a full waiver which the FDA granted at time of approval.

Inluriyo (imlunestrant)

11 Labeling Recommendations

The Applicant’s Position:

This is the first proposed label submitted for imlunestrant. Therefore, a summary of the significant labeling changes is not provided.

The FDA’s Assessment:

The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidance and current labeling practices of the Office of Oncologic Diseases. The table below summarizes key changes by the FDA.

Section	Applicant’s Proposed Labeling	FDA’s Proposed Labeling
Highlights of Prescribing Information	The Applicant proposed the following indication: <i>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.</i>	FDA revised indication as noted in Section 1, to be consistent with the patient population enrolled in EMBER-3. Dosage and Administration edited for clarity to include “on an empty stomach” from “without food”. Dose reduction information added for moderate or severe hepatic impairment and (b) (4) Adverse Reactions (ARs) updated to align with Section 6 ARs and laboratory abnormalities.

Inluriyo (imlunestrant)

		“If concomitant use cannot be avoided, decrease the INLURIYO dosage” added as drug interaction for use with strong CYP3A inducers.
Indications and Usage (Section 1)	The Applicant proposed the following indication: <i>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.</i>	For consistency with 21 CFR 201.57(c)(2)(i)(B), the indication was revised to reflect the patients who demonstrated clinical benefit when treated with imlunestrant: <i>Imlunestrant (INLURIYO) is indicated for the treatment of adults with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.</i>
Dosage and Administration (Section 2)		Section 2.1 edited to add “in a plasma specimen” for presence of <i>ESR1</i> mutation(s). Section 2.2 edited for clarity and brevity. Edited details for when empty stomach (at least 2 hours before food, or 1 hour after food) Section 2.3 edited to add actual dosage “to 200mg once daily” for the recommended dose

Inluriyo (imlunestrant)

		reduction for clarity. Table 2 edited for clarity to instruct when to discontinue for hepatotoxicity. Section 2.4 edited per FDA labeling guidance and to monitor for increased adverse reactions.
Dosage Forms and Strengths (Section 3)		FDA revised Section 3 for clarity, brevity and consistency with current labeling practices.
Contraindications (Section 4)	None	None
Warnings and Precautions (Section 5)	Applicant proposed Embryo-Fetal Toxicity as a W/P.	FDA revised Section 5 for clarity, brevity and consistency with current labeling practices. FDA edited W&P 5.1 Embryo-Fetal Toxicity for clarity and to specify findings in an animal reproduction study.
Clinical Trials Experience (Section 6)		FDA revised Section 6.1 for order and content and for clarity, brevity, and consistency with current labeling practices. A range (min to max) was added to median duration of exposure to treatment. The frequency of fatal adverse reactions was changed to 1.8% from ^(b)₍₄₎%, to include all fatal adverse reactions that occurred in the imlunestrant treatment

Inluriyo (imlunestrant)

		arm during treatment or during short term follow-up. The frequency of treatment discontinuation due to adverse reactions was changed to include treatment discontinuation due to fatal adverse reactions ((b) (4) % to 4.6%). The terms for adverse reactions leading to treatment discontinuation were updated to reflect FDA preferred terms. Additional clinically relevant adverse reactions that occurred at <10% were added (pruritus (3.7%), dyspepsia (2.8%), and stomatitis (2.4%)). FDA edited Table 3 to include additional grouped PT terms for select ARs. FDA edited Table 4 to include hemoglobin decreased, neutrophils decreased, platelets decreased, calcium decreased, and cholesterol increased as these were all clinically meaningful laboratory abnormalities that occurred in ≥10% of patients who received imlunestrant.
--	--	--

Inluriyo (imlunestrant)

Use in Specific Populations (Section 8)		Section 8.1 edited to reflect FDA labeling practices and update animal data based on a embryo-fetal development study. Section 8.2 edited for clarity. Section 8.3 edited to remove “(b) (4)”, Pregnancy testing edited to state “Verify the pregnancy status.” and deleted “(b) (4)”. Section 8.6 (b) (4)
Description (Section 11)		FDA revised pharmacological class to be consistent with the established pharmacologic class also included in the Highlights indication statement and to remove arbitrary or undefined terminology (e.g., “(b) (4)”). FDA edited to align with Section 3.
Clinical Pharmacology (Section 12)		Section 12.1 edited for clarity and to be concise. FDA removed imlunestrant activity (b) (4)

Inluriyo (implunestrant)

		based on the clinical trial patient population and <u>insufficient nonclinical data</u> (b) (4) Section 12.2 revised to add “Implunestrant exposure-response relationships and the time course of pharmacodynamics have not been fully characterized.” per 21 CFR § 201.57(c)(13)(i)(B) Added language to Section 12.2 consistent with the “QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry” draft guidance. Section 12.3 was revised and reorganized per FDA Guidance for the Clinical Pharmacology Section of labeling. Section 12.3 revised to add carbohydrate and protein content. (b) (4) subsection deleted (b) (4) since
--	--	---

Inluriyo (imlunestrant)

		(b) (4) Extensive edits made by FDA to DDI studies to align with clinical pharmacology labeling practices.
Nonclinical Toxicology (Section 13)		Section 13.1 extensively edited by FDA to include details mutagenesis study results and information from nonclinical studies impacting fertility. FDA added Section 13.2 to include relevant toxicities seen in non-clinical studies (i.e., hyperplasia in the ovary and mammary gland; epithelial hyperplasia of the urinary bladder).
Clinical Studies (Section 14)	The Applicant proposed:	(b) (4) FDA added clarification regarding prior endocrine therapy, including the requirement for prior aromatase inhibitor therapy. FDA replaced (b) (4) with an additional investigational combination regimen to avoid implied off-label use or promotional issues. FDA added that patients must have had specific <i>ESR1</i>

Inluriyo (imlunestrant)

	(b) (4) The Applicant proposed: ESR1m status was (b) (4) using the Guardant360 CDx assay.	mutations in the ligand binding domain. FDA removed (b) (4) FDA removed (b) (4) including for the ITT population. FDA added demographic data from EMBER-3 on pre- and peri-menopausal women (11%), missing race data (4.7%), and multiracial (0.8%) categories. FDA clarified that the primary endpoint was achieved in the <i>ESR1m</i> population. FDA added that OS was immature with 31% of deaths observed in the <i>ESR1m</i> population. FDA added 95% CI to ORR for imlunestrant 14.3% (95% CI 7.8, 20.8) and fulvestrant or exemestane 7.7% (95% CI 2.2, 13.2)
--	--	---

Inluriyo (imlunestrant)

		FDA added complete response rate and partial response rate for imlunestrant 0.9% and 13.4% and fulvestrant or exemestane 0% and 7.7%, respectively. FDA replaced (b) (4) with INLURIYO and fulvestrant or exemestane to clarify the specific treatment provided, respectively.
How Supplied/Storage and Handling (Section 16)		FDA edited Disposal subsection to add information on FDA recommended drug disposal guidance.
Patient Counseling Information (Section 17)		FDA added dyslipidemia as this is an important AR for healthcare providers and patients to monitor and manage. Section also edited for clarity.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

Based on the risk-benefit profile of implunestrant, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance. No REMS is recommended for implunestrant.

13 Postmarketing Requirements and Commitment

The FDA’s Assessment:

The following postmarketing commitment (PMC) was issued by FDA and agreed to by the Applicant:

PMC 4902-1

Complete the pre-specified, event-driven overall survival (OS) analyses comparing the imlunestrant monotherapy and standard-of-care endocrine therapy arms from the ongoing clinical trial, EMBER-3 (Study J2J-OX-JZLC), titled “A Phase 3, Randomized, Open-Label Study of Imlunestrant, Investigator’s Choice of Endocrine Therapy, and Imlunestrant plus Abemaciclib in Patients with Estrogen-Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer Previously Treated with Endocrine Therapy”, to further characterize the clinical benefit of imlunestrant in patients with estrogen-receptor positive, HER2 negative *ESR1-mutated* breast cancer.

Interim Report Submission: 02/2026

Trial Completion (monotherapy in the *ESR1-mutated* population): 11/2026

Final Report Submission: 05/2027

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA’s review:		Is a PMC/PMR needed?
☐	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	☒ Yes ☐ No
☐	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	☐ Yes ☒ No
☐	Other considerations (e.g.: PK/PD), if applicable:	☐ Yes ☒ No

Inluriyo (imlunestrant)

14 Division Director (DHOT) (NME ONLY)

X

Tiffany Ricks, PhD

Inluriyo (imlunestrant)

15 Division Director (OCP)

X

Nam Atiqur Rahman, PhD

Inluriyo (imlunestrant)

16 Division Director (OB)

X

Shenghui Tang, PhD

Inluriyo (imlunestrant)

17 Division Director (Clinical)

X

Laleh Amiri-Kordestani, MD

Inluriyo (imlunestrant)

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

R. Angelo de Claro, MD

19 Appendices

19.1 References

The Applicant's References:

- Amit O, Mannino F, Stone AM, et al. Blinded independent central review of progression in cancer clinical trials: results from a meta-analysis. *Eur J Cancer*. 2011;47(12):1772-1778. <https://doi.org/10.1016/j.ejca.2011.02.013>
- Dello Russo C, Navarra P. Local investigators significantly overestimate overall response rates compared to blinded independent central reviews in uncontrolled oncology trials: a comprehensive review of the literature. *Front Pharmacol*. 2022;13:858354. <https://doi.org/10.3389%2Ffphar.2022.858354>
- Bhave MA, Quintanilha JCF, Tukachinsky H, et al. Comprehensive genomic profiling of *ESR1*, *PIK3CA*, *AKT1*, and *PTEN* in HR(+)HER2(-) metastatic breast cancer: prevalence along treatment course and predictive value for endocrine therapy resistance in real-world practice. *Breast Cancer Res Treat*. 2024;207(3):599-609. <https://doi.org/10.1007/s10549-024-07376-w>
- Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-263. <https://doi.org/10.3322/caac.21834>
- Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. *Stat Med*. 2009;(4):586-604. <https://doi.org/10.1002/sim.3495>
- Cardoso F, Paluch-Shimon S, Schumacher-Wulf E, et al. 6th and 7th international consensus guidelines for the management of advanced breast cancer (ABC guidelines 6 and 7). *Breast*. 2024;76:103756. <https://doi.org/10.1016/j.breast.2024.103756>
- [FDA] Food and Drug Administration. FDA approves alpelisib for metastatic breast cancer | FDA (archive-it.org). May 2019. Accessed February 08, 2024. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-alpelisib-metastatic-breast-cancer>
- Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Engl J Med*. 2022;386(10):942-950. <https://doi.org/10.1056/NEJMoa2114663>
- Jhaveri KL, Lim E, Jeselsohn R, et al. Imlunestrant, an oral selective estrogen receptor degrader, as monotherapy and in combination with targeted therapy in estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Phase Ia/Ib EMBER

Inluriyo (imlunestrant)

- study [published online September 06, 2024]. *J Clin Oncol*. 2024;JCO2302733. <https://doi.org/10.1200/JCO.23.02733>
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53(282):457-481. <https://www.tandfonline.com/doi/abs/10.1080/01621459.1958.10501452>
- Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612. <https://doi.org/10.7326/0003-4819-150-9-200905050-00006>
- Maurer W, Bretz F. Memory and other properties of multiple test procedures generated by entangled graphs. *Stat Med*. 2013;32(10):1739-1753. doi:10.1002/sim.5711
- Meegdes M, Geurts SM, Erdkamp FL, et al. Real-world time trends in overall survival, treatments and patient characteristics in HR+/HER2- metastatic breast cancer: an observational study of the SONABRE Registry. *Lancet Reg Health Eur*. 2023;26:100573. <https://doi.org/10.1016/j.lanepe.2022.100573>
- [NCCN] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Breast cancer. Version 4.2024. Accessed September 25, 2024. Available at: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419>
- Neven P, Stahl N, Vidal M, et al. A preoperative window-of-opportunity study of oral SERD, imlunestrant, in newly diagnosed ER-positive, HER2-negative early breast cancer: Results from EMBER-2 Study [published online October 8, 2024]. *Clin Cancer Res*. <https://doi.org/10.1158/1078-0432.CCR-24-2113>
- Patel H, Egorin MJ, Remick SC, et al. Comparison of Child-Pugh (CP) criteria and NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction (HD): implications for chemotherapy dosing. *J Clin Oncol*. 2004;22(14):6051. <https://doi.org/10.1200/jco.2004.22.90140.6051>
- Patel R, Klein P, Tiersten A, Sparano JA. An emerging generation of endocrine therapies in breast cancer: a clinical perspective. *NPJ Breast Cancer*. 2023;9(1):20. <https://doi.org/10.1038/s41523-023-00523-4>
- Waks AG, Winer EP. Breast cancer treatment: a review. *J Am Med Assoc*. 2019;321(3):288-300. <https://doi.org/10.1001/jama.2018.19323>

The FDA's References:

Surveillance, Epidemiology, and End Result Program (SEER). National Cancer Institute NIH. Cancer Stat Facts: Female Breast Cancer. September 2025. [Female Breast Cancer — Cancer Stat Facts](#)

Inluriyo (imlunestrant)

Amit O, Mannino F, Stone A, et al. Blinded independent central review of progression in cancer clinical trials: results from a meta-analysis. *Eur J Cancer*. 2011;47(12):1772-8.

Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Engl J Med*. 2022;386(10):942-950.

Shah M, Lingam H, Gao X, et al. US Food and Drug Administration Approval Summary: Elacestrant for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative, *ESR1*-Mutated Advanced or Metastatic Breast Cancer. *J Clin Oncology*. 2024;42(10):1193-1201.

19.2 Financial Disclosure

The Applicant's Position:

Financial disclosure information has been provided for all principal investigators and sub-investigators who participated at sites that enrolled patients in EMBER-3, included in the NDA submission.

Covered Clinical Study (Name and/or Number):* EMBER-3 (J2J-OX-JZLC)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>1374</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u>		

Inluriyo (implunestrant)

Significant equity interest held by investigator in study: <u>0</u>		
Sponsor of covered study: <u>1</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>1373</u>		
Is an attachment provided with the reason:	N/A ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment that there were no apparent financial conflicts that would have impacted the overall integrity of EMBER-3 and the review teams conclusions regarding the benefit: risk analysis for the intended indication. However, FDA notes that one investigator who enrolled two patients reported significant payments of other sorts between \$25000 and \$50000 in consulting and speaking honoraria.

19.3 Nonclinical Pharmacology/Toxicology

The Applicant's Position:

Please refer to Section 5 for further details.

The FDA's Assessment:

Refer to Section 5 for the Nonclinical review for this application.

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1 Population PK Analysis

19.4.1.1 Executive Summary

The FDA's Assessment:

The popPK analyses assessed the effect of covariates on PK parameters of implunestrant. Notably,

Inluriyo (implunestrant)

implunestrant disposition was not affected by multiple covariates including drug formulation, presence of abemaciclib, age, ethnicity, race, serum albumin levels, mild-to-moderate renal impairment, and mild hepatic impairment.

Body weight showed statistical significance but limited clinical impact, with exposure differences of 26-40% across the weight range. The simulation results from the final model demonstrated that 87% of patients receiving the proposed 400 mg once daily dose are expected to achieve minimum concentrations exceeding biologically effective thresholds throughout the dosing interval.

The Applicant’s dataset and analyses were reviewed and verified by the pharmacometrics reviewers. The final model was deemed adequate to characterize the PK profile of implunestrant in healthy participants and patients with ER+ breast cancer and endometrial endometroid cancer (EEC). The Applicant's popPK analysis is acceptable.

19.4.1.2 PPK Assessment Summary

The Applicant’s Position:

General Information		
Objectives of PPK Analysis		- Characterize the PK of implunestrant in patients with ER+ breast cancer and ER+ EEC - Identify patient factors, laboratory parameters, and disease characteristics that may influence implunestrant disposition in this patient population - Generate model-predicted estimates of implunestrant exposure for assessment of exposure-response relationships
Study Included		JZLA (EMBER), JZLB (EMBER-2), JZLC (EMBER-3), and JZLD
Dose(s) Included		200, 400, 600, 800, and 1200 mg
Population Included		Healthy, ITT
Population Characteristics (Table 19.1)	General	- Age – median 60 yr (28-95 yr, 36% subj >=65 yr, 10% subj >=75 yr) - Weight – median 68.2 kg (36-145 kg) 1043 (99%) female

Inluriyo (imlunestrant)

General Information		
		667 (64%) white, 50 (5%) black or African American, 240 (23%) Asian, and 93 (9%) missing or other
	Organ Impairment	Hepatic Function (NCI) - Normal – 842 (80%) - Mild – 201 (19%) - Moderate – 1 (<1%) Renal Function (eGFR) - Normal – 448 (43%) - Mild – 482 (46%) - Moderate – 108 (10%) - Severe – 2 (<1%)
	Pediatrics (if any)	Not applicable
No. of Patients, PK Samples, and BLQ		6895 evaluable imlunestrant concentrations from 1050 patients. 300 BLQ samples prior to first dose 93 BLQ samples following the start of treatment
Sampling Schedule	Rich Sampling	Patients: Predose to 48 hr postdose after first dose, predose to 24 hr postdose at steady state Healthy Participants: Predose up to 96 or 120 hr postdose
	In ITT Population	Cycle 1 Day 1: 2-4 hr postdose Cycle 2 Day 1 (± 3 days): Predose Cycle 3 Day 1 (± 3 days): Approximately 3 hr postdose and 5 ± 0.5 hr postdose Cycle 4 Day 1 (± 3 days): Predose
Covariates Evaluated	Static	Baseline body weight, age, race, ethnicity, serum albumin, hepatic function, renal function, study population, formulation, presence of abemaciclib
	Time-varying	None
Final Model		Summary Acceptability

Inluriyo (imlunestrant)

General Information		
		[FDA's comments]
Software and Version	NONMEM (Version 7.5.0) R (Version 4.3.2)	Acceptable
Model Structure	2-compartment structural model parameterized in terms of CL/F, V _c /F, V _p /F, and Q/F with 3 transit compartments for absorption	Acceptable
Model Parameter Estimates	Table 19.2	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Table 19.2 Shrinkage for interindividual ETA parameters on MTT, CL/F, and V _c /F in the final model 23.8%, 12.7%, and 22.3%, respectively.	Acceptable
BLQ for Parameter Accuracy	BLQs were treated as missing due to the small number of postdose BLQ samples	Acceptable
GOF, VPC	Figure 19.1, Figure 19.2	Acceptable
Significant Covariates and Clinical Relevance	Figure 19.3 Figure 19.4 Large overlaps in exposure range between range of body weights; no clinical significance	Acceptable
Analysis Based on Simulation (optional)	Not Applicable	N/A
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	The (b) (4) maximum concentration (C _{max}) of imlunestrant is 141 ng/mL (45%)	Acceptable

Inluriyo (imlunestrant)

General Information		
	and the area under the concentration-time curve (AUC ^{(b) (4)}) is 2400 ng*h/mL (46%) ^{(b) (4)} over a dosage range from 200 mg to 1200 mg QD(0.5 to 3 times the approved recommended dosage).	

Table 19.1. Summary of Baseline Patient Characteristics for the popPK Analysis

	Study JZLA (N = 373)	Study JZLB (N = 86)	Study JZLC (N = 527)	Study JZLD (N = 64)	Overall (N = 1050)
Age (years)					
- Range	29-95	50-83	28-87	30-65	28-95
- Median	60.0	63.5	61.0	55.5	60.0
- Mean (CV%)	59 (20.6)	64 (11.6)	60.9 (18.8)	52.3 (18.1)	60.0 (19.3)
- ≥65 years (N, %)	134 (35.9)	38 (44.2)	204 (38.7)	4 (6.2)	380 (36.2)
- ≥75 years (N, %)	36 (9.7)	9 (10.5)	63 (12.0)	0 (0)	108 (10.3)
- ≥85 years (N, %)	4 (1.1)	0 (0)	10 (1.9)	0 (0)	14 (1.3)
Body weight (kg)					
- Range	41.0-145.0	47.7-110.0	36.0-142.6	54.5-99.9	36.0-145.0
- Median	70.0	70.8	66.0	73.5	68.2
- Mean (CV%)	72.4 (25.0)	72.5 (19.5)	68.8 (23.2)	72.9 (13.9)	70.6 (23.3)
Serum albumin (g/L)					
- Range	22.0-50.0	35.0-50.0	29.0-55.0	38.0-51.0	22.0-55.0
- Median	41.0	45.0	44.0	45.0	43.5
- Mean (CV%)	40.6 (10)	44.6 (6.2)	44.2 (7.6)	44.8 (6.4)	43.0 (9.3)
- Missing	0	1	4	0	5
Absolute eGFR ^a (mL/min)					
- Range	26.3-222.2	38.6-131.4	29.0-140.2	59.4-147.6	26.3-222.2
- Median	86.2	82.9	86.1	99.1	86.5
- Mean (CV%)	86.7 (24.6)	82.3 (23.3)	85.1 (23.9)	99.2 (17.2)	86.3 (24)
- Missing	7	1	2	0	10
Sex (N, %)					
- Female	372 (99.7)	86 (100)	521 (98.9)	64 (100)	1043 (99.3)
- Male	1 (0.3)	0 (0)	6 (1.1)	0 (0)	7 (0.7)
Race (N, %)					

Inluriyo (imlunestrant)

	Study JZLA (N = 373)	Study JZLB (N = 86)	Study JZLC (N = 527)	Study JZLD (N = 64)	Overall (N = 1050)
- White	260 (69.7)	77 (89.5)	283 (53.7)	47 (73.4)	667 (63.5)
- Black or African American	14 (3.8)	1 (1.2)	19 (3.6)	16 (25.0)	50 (4.8)
- Asian	78 (20.9)	0 (0)	162 (30.7)	0 (0)	240 (22.9)
East Asian					
- Chinese	0 (0)	0 (0)	25 (4.7)	0 (0)	25 (2.4)
- Japanese	18 (4.8)	0 (0)	53 (10.1)	0 (0)	71 (6.8)
- Korean	29 (7.8)	0 (0)	40 (7.6)	0 (0)	69 (6.6)
- Taiwanese	17 (4.6)	0 (0)	29 (5.5)	0 (0)	46 (4.4)
West Asian					
- Indian	0 (0)	0 (0)	14 (2.7)	0 (0)	14 (1.3)
Other Asian	14 (3.8)	0 (0)	1 (0.2)	0 (0)	15 (1.4)
- Other ^b	7 (1.9)	0 (0)	30 (5.7)	1 (1.6)	38 (3.6)
- Missing	14 (3.8)	8 (9.3)	33 (6.3)	0 (0)	55 (5.2)
Ethnicity (N, %)					
- Hispanic or Latino	29 (7.8)	2 (2.3)	114 (21.6)	35 (54.7)	180 (17.1)
- Non-Hispanic	318 (85.3)	77 (89.5)	353 (67.0)	29 (45.3)	777 (74.0)
- Missing	26 (7.0)	7 (8.1)	60 (11.4)	0 (0)	93 (8.9)
Cancer type (N, %)					
- Healthy	0 (0)	0 (0)	0 (0)	64 (100)	64 (6.1)
- Breast	301 (80.7)	86 (100)	527 (100)	0 (0)	914 (87.0)
- Endometrial	72 (19.3)	0 (0)	0 (0)	0 (0)	72 (6.9)
Drug formulation (N, %)					
- Tablet	305 (81.8)	86 (100)	527 (100)	64 (100)	982 (93.5)
- Capsule	64 (17.2)	0 (0)	0 (0)	0 (0)	64 (6.1)
- Missing	4 (1.1)	0 (0)	0 (0)	0 (0)	4 (0.4%)
Imlunestrant dosed in presence of abemaciclib					
- No	237 (63.5)	86 (100)	321 (60.9)	64 (100)	708 (67.4)
- Yes	136 (36.5)	0 (0)	206 (39.1)	0 (0)	342 (32.6)
Renal function ^c (N, %)					
- Normal	156 (41.8)	31 (36.0)	213 (40.4)	48 (75.0)	448 (42.7)
- Mild impairment	174 (46.6)	41 (47.7)	252 (47.8)	15 (23.4)	482 (45.9)
- Moderate impairment	35 (9.4)	13 (15.1)	59 (11.2)	1 (1.6)	108 (10.3)
- Severe impairment	1 (0.3)	0 (0)	1 (0.2)	0 (0)	2 (0.2)
- Missing	7 (1.9)	1 (1.2)	2 (0.4)	0 (0)	10 (1.0)
Hepatic function ^d (N, %)					
- Normal	272 (72.9)	79 (91.9)	429 (81.4)	62 (96.9)	842 (80.2)
- Mild impairment	100 (26.8)	7 (8.1)	93 (17.6)	1 (1.6)	201 (19.1)
- Moderate impairment	1 (0.3)	0 (0)	0 (0)	0 (0)	1 (0.1)
- Missing	0 (0)	0 (0)	5 (0.9)	1 (1.6)	6 (0.6)

Inluriyo (imlunestrant)

Abbreviations: AST = aspartate aminotransferase; CKD-EPI = Chronic Kidney Disease Epidemiology

Collaboration; CV% = percent coefficient of variation; eGFR = estimated glomerular filtration rate; N = number of patients; Scr = serum creatinine; TBI = total bilirubin; ULN = upper limit of normal.

- a eGFR as calculated by CKD-EPI equation: $eGFR = 141 \times \min(Scr/\kappa, 1)^\alpha \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] or 1.159 [if Black], where $\kappa = 0.7$ if female and 0.9 if male, $\alpha = -0.329$ if female and -0.411 if male, $\min$ = the minimum of Scr/κ or 1 , and $\max$ = the maximum of Scr/κ or 1 . (Levey et al. 2009). Absolute eGFR calculated as $(eGFR/1.73 \text{ m}^2) \times \text{body surface area (kg/m}^2)$.
- b Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or Other.
- c Classified as normal ($eGFR \geq 90 \text{ mL/minute}$), mild impairment ($60 \text{ mL/minute} \leq eGFR < 90 \text{ mL/minute}$), moderate impairment ($30 \text{ mL/minute} \leq eGFR < 60 \text{ mL/minute}$), and severe impairment ($15 \text{ mL/minute} \leq eGFR < 30 \text{ mL/minute}$).
- d As determined by the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria for hepatic dysfunction (Patel et al. 2004). Classified as normal ($TBI \leq ULN$ and $AST \leq ULN$), mild impairment ($TBI \leq 1.5 \times ULN$ and $AST > ULN$) or ($ULN < TBI \leq 1.5 \times ULN$), moderate impairment ($1.5 \times ULN < TBI \leq 3 \times ULN$), or severe impairment ($TBI > 3 \times ULN$).

Table 19.2. PK and Covariate Parameters in popPK Model

Parameter	Parameter Estimates (%SEE)		Final Model Bootstrap
	Base Model	Final Model	95% CI
Bioavailability (F, fraction, Θ_1)	1 Fixed	1 Fixed	1 Fixed
Mean transit time (MTT, h, Θ_2)	1.82 (2.60)	1.84 (2.21)	(1.77, 1.93)
Clearance (CL/F, L/h, Θ_3)	165 (2.95)	166 (1.75)	(160, 172)
Intercompartmental clearance (Q/F, L/h, Θ_5)	257 (10.7)	256 (6.48)	(216, 297)
Central volume of distribution (V_c /F L, Θ_4)	4490 (5.39)	8120 (7.07)	(7161, 9227)
Effect of patient population (MBC) on V_c /F (Θ_{10}) ^a	---	-0.469 (8.38)	(-0.540, -0.389)
Effect of patient population (EEC) on V_c /F (Θ_{11}) ^a	---	-0.637 (5.86)	(-0.704, -0.562)
Peripheral volume of distribution (V_p /F, L, Θ_6)	2280 (11.1)	2280 (2.83)	(1961, 2591)
Allometry			
Effect of body weight on CL/F and Q/F (kg, Θ_8) ^b	0.864 (9.50)	0.871 (8.67)	(0.709, 1.02)
Effect of body weight on V_c /F and V_p /F (kg, Θ_9) ^c	0.992 (10.8)	0.994 (9.72)	(0.801, 1.18)
Interindividual variability CV%			
MTT	46.9% (7.99)	47.7% (7.71)	(43.7, 51.3)
CL/F	50.6% (5.97)	50.5% (5.90)	(47.1, 53.6)
V_c /F	76.9% (6.84)	69.1% (7.44)	(62.8, 75.0)
Inter-Patient Variability Correlation Coefficient (CL/F and V_c /F)	0.556 (9.17)	0.618 (8.48)	

Inluriyo (imlunestrant)

Parameter	Parameter Estimates (%SEE)		Final Model Bootstrap
	Base Model	Final Model	95% CI
Interoccasion variability CV%			
F	34.7% (9.47)	35.4% (8.98)	(31.9, 38.5)
Residual variability			
Proportional (Θ_7)	0.240 (2.35)	0.241 (2.35)	(0.229, 0.252)

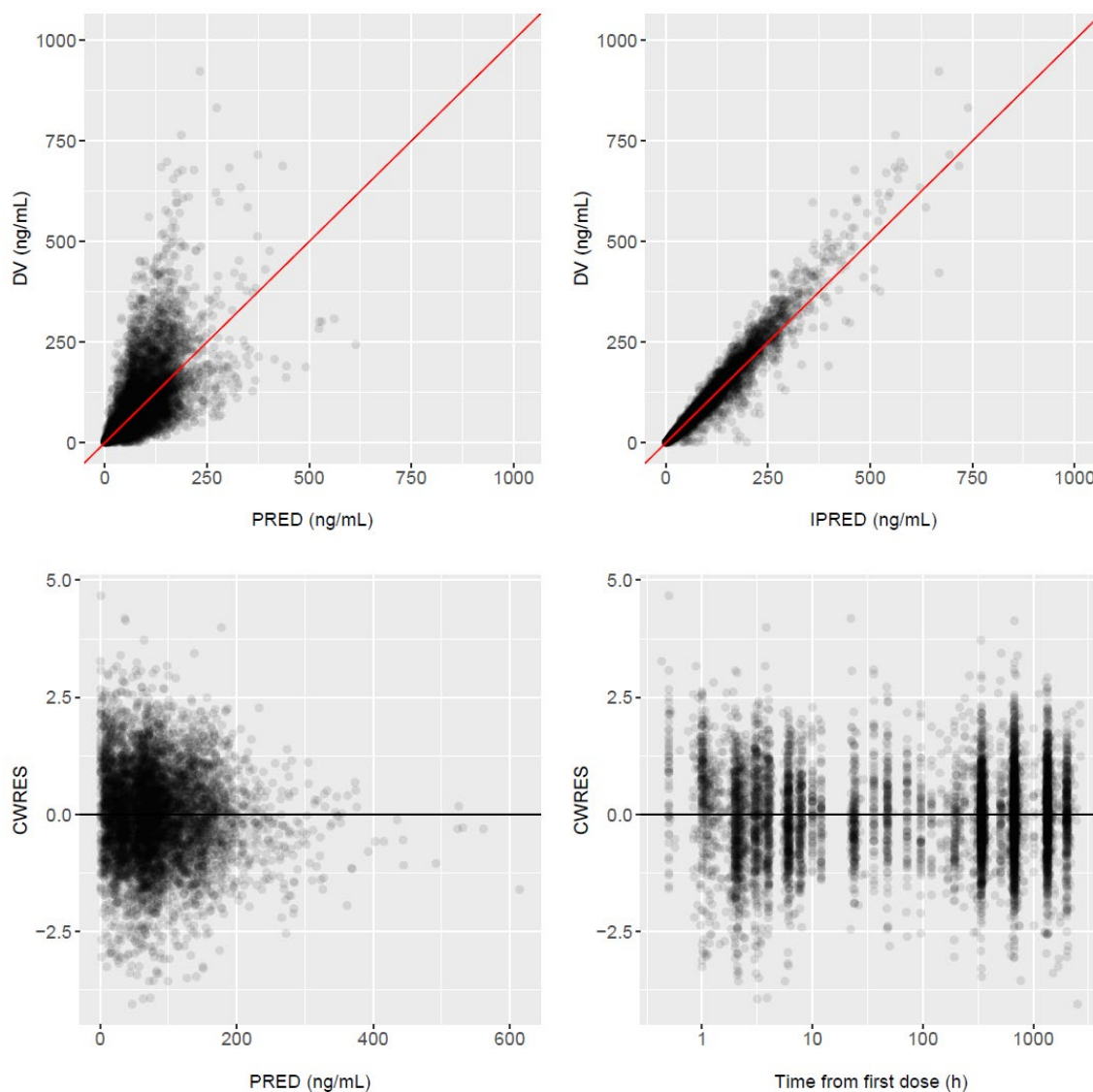
Abbreviations: CI = confidence interval; CL = total body clearance of drug calculated after intravenous administration; CL/F = apparent total body clearance of drug calculated after extravascular administration; CV% = percent coefficient of variation; EEC = endometrial endometroid cancer; F = relative bioavailability; MBC = metastatic breast cancer; MTT = mean transit time; PK = pharmacokinetic; Q = intercompartmental clearance; Q/F = intercompartmental apparent clearance; %SEE = percent standard error of the estimate; V_c = central volume of distribution; V_c/F = apparent central volume; V_p = peripheral volume of distribution; V_p/F = apparent peripheral volume; WT = body weight at entry.

a V_c/F = Population estimate of $V_c * I1 * I2$, where $I1 = (1 + \Theta_{10})$ for patients with MBC and $I2 = (1 + \Theta_{11})$ for patients with EEC.

b CL/F = Population estimate of $CL * ((WT/68.2)^{\Theta_8})$; Q/F = Population estimate of $Q * (WT/68.2)^{\Theta_8}$.

c V_c/F = Population estimate of $V_c * ((WT/68.2)^{\Theta_9})$; V_p/F = Population estimate of $V_p * ((WT/68.2)^{\Theta_9})$.

Inluriyo (implunestrant)

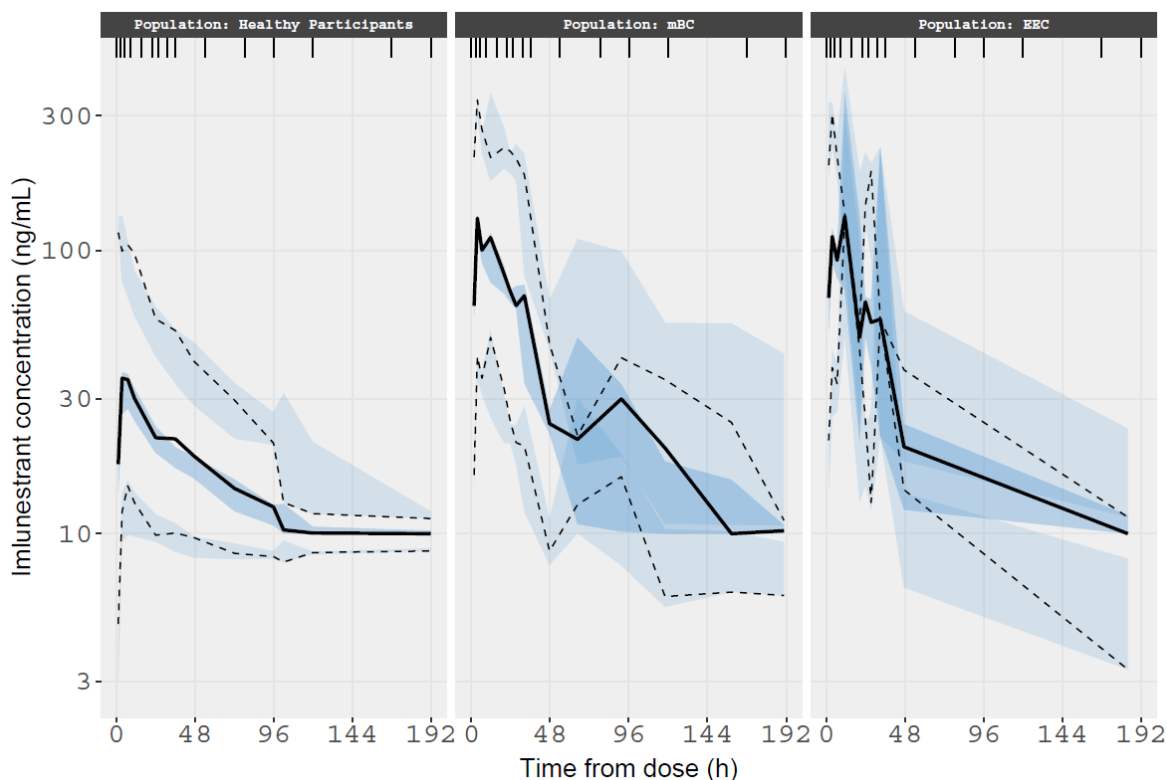


Abbreviations: CWRES = conditional weighted residual; DV = dependent variable (implunestrant concentration, ng/mL); IPRED = individual predicted implunestrant concentration (ng/mL); popPK = population pharmacokinetic; PRED = population predicted implunestrant concentration (ng/mL).

Note: Red lines represent loess fits to data.

Figure 19.1. Imlunestrant popPK final model goodness-of-fit plots.

Inluriyo (imlunestrant)

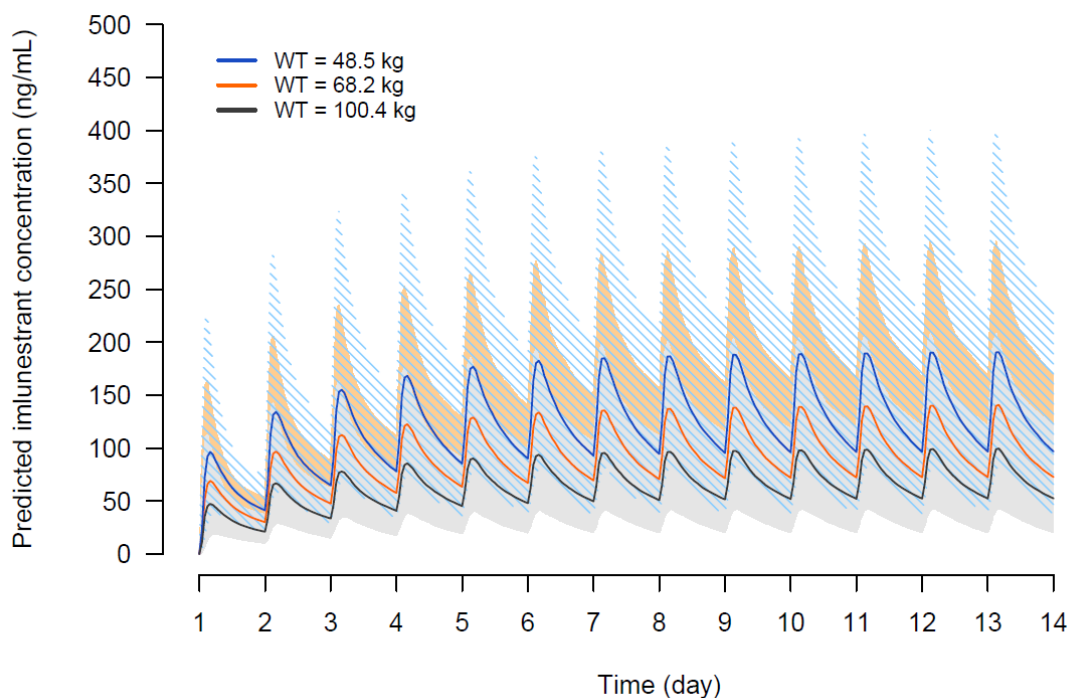


Abbreviations: EEC = endometrioid endometrial cancer; mBC = metastatic breast cancer; popPK = population pharmacokinetic.

Note: Solid black line represents median of observed data, dotted black lines represent the 5th and 95th percentiles of observed data. Shaded blue areas depict the model-predicted 95% confidence interval for the 5th, 50th (median), and 95th percentiles.

Figure 19.2. Visual predictive check of the popPK model for imlunestrant stratified by study population.

Inluriyo (imlunestrant)



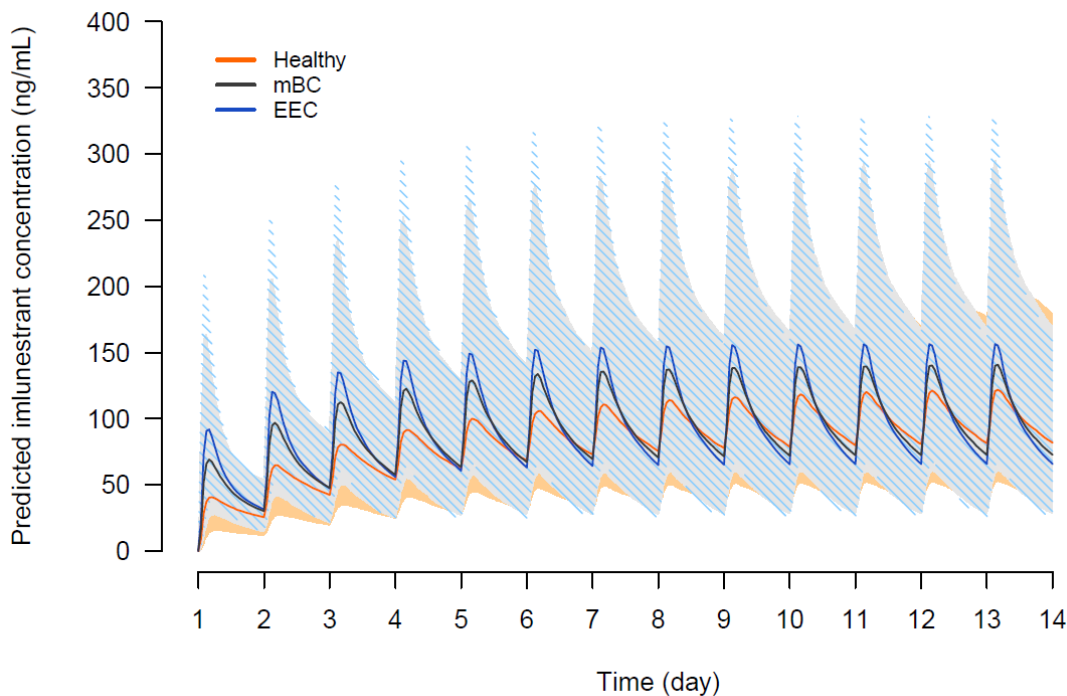
Abbreviations: PK = pharmacokinetic; QD = once daily; WT = body weight.

Note: Solid lines represent the median prediction, with shaded or hashed areas corresponding to 90th prediction intervals based on interindividual variability.

Figure 19.3.

Simulated PK profiles at 400 mg QD for patients with body weights that are 5th, 50th, and 95th percentiles of observed patient characteristics in the pooled analysis population.

Inluriyo (imlunestrant)



Abbreviations: EEC = endometrial endometroid cancer; mBC = metastatic breast cancer; PK = pharmacokinetic; QD = once daily.

Note: Solid lines represent the median prediction, with shaded or hashed areas corresponding to 90th prediction intervals based on interindividual variability.

Figure 19.4. Simulated imlunestrant PK profiles at 400 mg QD for patients and healthy participants in the pooled analysis population.

The FDA’s Assessment:

The Applicant’s popPK analysis is acceptable. The FDA Reviewer was able to repeat and verify the Applicant’s analysis with no significant discordance identified. The FDA Reviewer agrees with the Applicant’s conclusions regarding the effect of covariates (age, sex, and body weight) on imlunestrant exposure and related labeling language in labeling Section 12.3.

19.4.1.3 PPK Review Issues

The FDA’s Assessment:

Not applicable.

19.4.1.4 Reviewer’s Independent Analysis

The FDA’s Assessment:

Not applicable.

19.4.2 Exposure-Response Analysis

19.4.2.1 ER (efficacy) Executive Summary

The FDA’s Assessment:

The Applicant conducted an exposure–response (E-R) analysis for efficacy using data from Study J2J-OX-JZLC (EMBER-3). Initially, the Applicant concluded that higher imlunestrant exposures were associated with longer progression-free survival (PFS). This conclusion was found to be incorrect as the Applicant identified a mistake in unit conversion during the review. After correcting the errors and updating the exposure-PFS analysis, no significant exposure-PFS relationship was identified. The corrected analysis is acceptable.

In general, the E-R relationship for efficacy was considered not fully characterized because the analysis included data from only one dose level (400 mg QD) evaluated in the pivotal EMBER-3 study. Labeling language in Section 12.2 (Pharmacodynamics) was updated to reflect this limitation.

19.4.2.2 ER (efficacy) Assessment Summary

The Applicant’s Position:

General Information		
Goal of ER analysis		Characterize the relationship between imlunestrant systemic exposure and selected efficacy outcomes (PFS and CBR) in patients with ER+, HER2– locally advanced or MBC
Study Included		JZLC (EMBER-3)
Endpoint		Primary: PFS Secondary: CBR
No. of Patients (total, and with individual PK)		527
Population Characteristics (Table 19.1)	General	See Table 19.1
	Pediatrics (if any)	Not applicable
Dose(s) Included		400 mg QD

Inluriyo (imlunestrant)

Exposure Metrics Explored (range)	Average concentration, C_{avg} (range: 18.1 – 389.8 ng/mL)	
Covariates Evaluated	<i>ESR1</i> mutation status, Presence of abemaciclib, Prior CDK4/6 therapy, Number of prior lines of treatment, Presence of visceral metastases	
Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	PFS: Time-to-event model with concentration effects on baseline hazard and Gompertz shape parameter CBR: logistic regression model with concentration effects on CBR	Acceptable
Model Parameter Estimates	Table 19.3 , Table 19.4	See below
Model Evaluation	Figure 19.5	See below
Covariates and Clinical Relevance	Significant factors leading to increase CBR included: - Presence of abemaciclib - Prior CDK4/6 therapy - Presence of visceral metastases	FDA disagrees with the positive relationship between imlunestrant exposure and PFS. During the review process, the Applicant identified an error in the description of the exposure–PFS analysis presented in the EMBER-3 population PK/PD report. Specifically, an incorrect unit conversion in the dataset used for the exposure–PFS analysis was discovered, which altered the interpretation of the results. The previously reported positive relationship between exposure and PFS

Inluriyo (imlunestrant)

		based on EMBER-3 data was incorrect; no exposure–PFS relationship was observed. In other words, variations in imlunestrant exposure at the 400 mg once-daily dose in the EMBER-3 trial did not affect PFS.
Simulation for Specific Population	Figure 19.5	Updated based on Applicant’s addendum analysis submitted on May 5, 2025
Visualization of E-R relationships	Figure 19.6	Updated based on Applicant’s addendum analysis submitted on May 5, 2025
Overall Clinical Relevance for ER	Exposures up to 2-fold below that of 400 mg are still expected to have some therapeutic benefit	See below
Labeling Language	Description	Acceptability [FDA’s comments]
12.2 Pharmacodynamics	Not applicable	FDA modified language in this section and the Applicant accepted the modifications.

Table 19.3. Parameter Estimates from Time-to-Event Model for PFS

Parameter Description	Estimate (%SEE)
Baseline Hazard (Θ_1)	-0.107 (34)
Gompertz Shape Parameter (Θ_3)	-0.0746 (28)
Effect of average concentration on baseline hazard (Θ_4) ^a	0.652 (11)
Effect of average concentration Gompertz shape parameter (Θ_5) ^b	-0.0109 (13)
Effect of CDK4/6i prior therapy on baseline hazard (Θ_6) ^c	-0.408 (17)
Effect of visceral metastases on baseline hazard (Θ_7) ^d	-0.368 (19)
Effect of abemaciclib on baseline hazard (Θ_8) ^e	-0.366 (21)

Abbreviations: CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; EXP = exponential; PFS = progression-free survival; %SEE = percent standard error of the estimate

a Baseline hazard = $\text{EXP}(\Theta_1 * \text{average concentration} ** \Theta_4)$.

b Gompertz shape parameter = $\Theta_3 * (1 + \text{average concentration} * \Theta_5)$.

c Baseline hazard = $\Theta_1 * I$, where $I = (1 + \Theta_6)$ for patients without prior CDK4/6i therapy (with visceral metastases and without abemaciclib).

d Baseline hazard = $\Theta_1 * I$, where $I = (1 + \Theta_7)$ for patients without visceral metastases (with CDK4/6i prior therapy and without abemaciclib).

e Baseline hazard = $\Theta_1 * I$, where $I = (1 + \Theta_8)$ for patients with abemaciclib (with visceral metastases and CDK4/6i prior therapy).

Table 19.4. Parameter Estimates from Logistic Regression Model for CBR

Parameter Description	Estimate (%SEE)
Intercept (Θ_1)	0.975 (20)
Effect of abemaciclib (Θ_2)	0.841 (23)
Effect of visceral metastases (Θ_3)	-0.699 (27)
Effect of CDK4/6i prior therapy (Θ_4)	-1.15 (17)

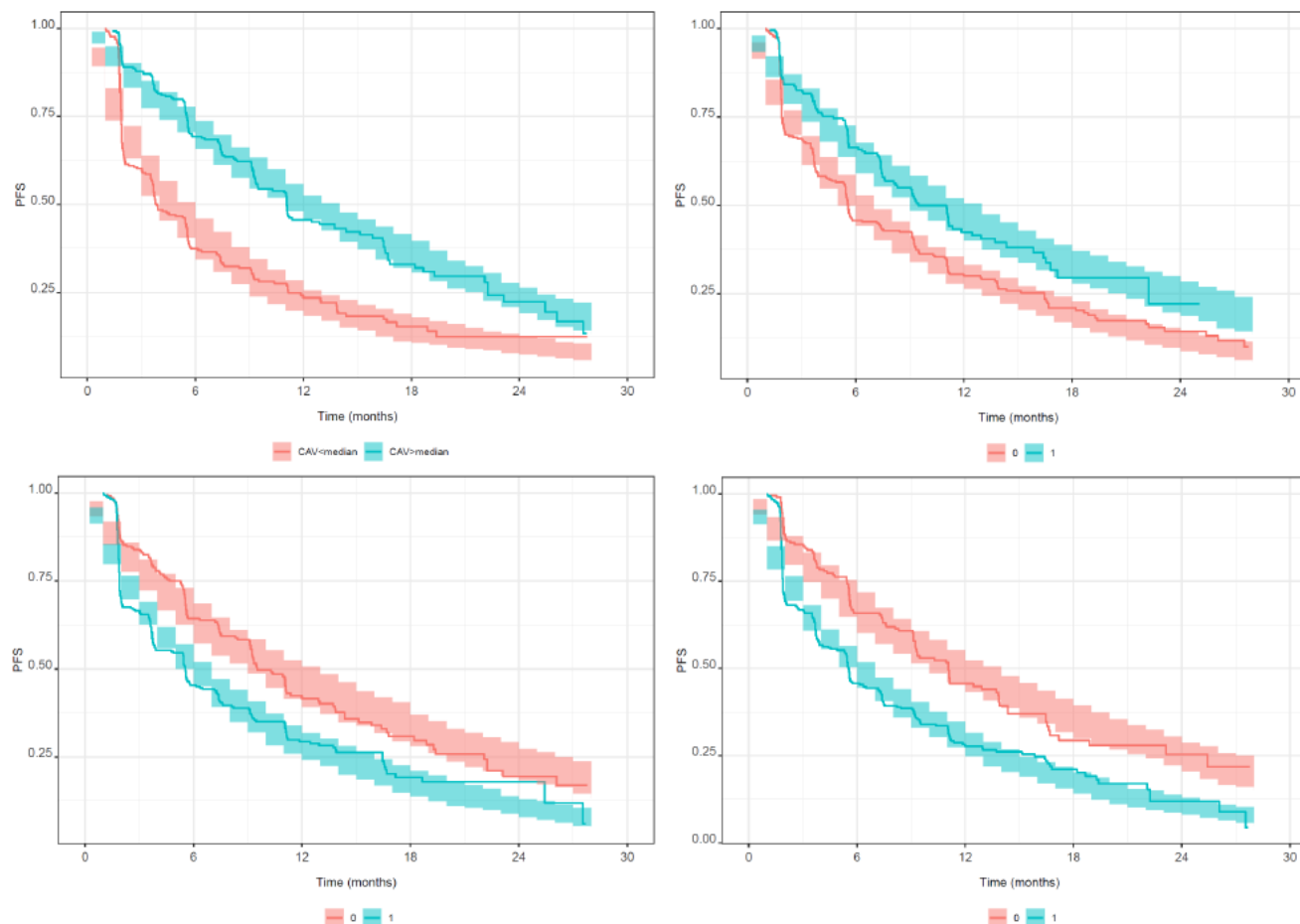
Abbreviations: CBR = clinical benefit rate; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; EXP = exponential; %SEE = percent standard error of the estimate.

Note: Clinical Benefit Rate = $\text{EXP}(\text{LOGIT}) / (1 + \text{EXP}(\text{LOGIT}))$, where $\text{LOGIT} = \Theta_1 + \Theta_2 * I1 + \Theta_3 * I2 + \Theta_4 * I3$

I1 = binary indicator for abemaciclib presence with 1 = present and 0 = absent,

I2 = binary indicator for visceral metastases with 1 = present and 0 = absent, and

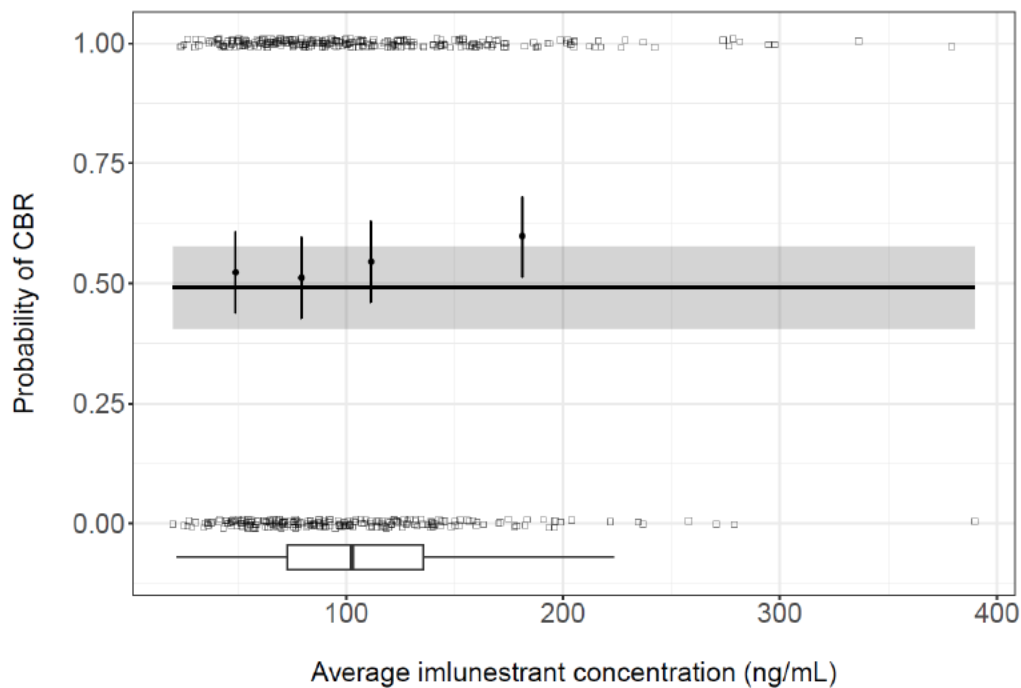
I3 = binary indicator for prior CDK4/6i therapy where 1 = prior and 0 = no prior.



Abbreviations: CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; PFS = progression-free survival.

Note: The lines represent the Kaplan-Meier plots of the observed data and the shaded areas represent 95% prediction intervals of the simulated data. Categories of 0 represent “no” or “absence” and 1 represent “yes” or “presence.”

Figure 19.5. **Visual predictive check graphs for time-to-event model of PFS. Clockwise from top-left: average concentrations below/above median, presence/absence of abemaciclib, prior/no prior CDK4/6i therapy, presence/absence of visceral metastases.**



Abbreviations: CI = confidence interval; CBR = clinical benefit rate.
Note: Solid black line and grey shaded area are the logistic regressions and 95% CIs of the predicted probability of CBR. Black open squares reflect the individual observed CBR in imlunestrant-treated patients. The observed CBR (black circles) and 95% CI (error bars) of each exposure quartile are plotted versus concentration. Box plot represents the 25th, 50th, and 75th percentiles of predicted average imlunestrant concentration for a 400-mg dose. Whiskers represent 1.5 times the interquartile range.

Figure 19.6. Logistic regression model for CBR.

The FDA’s Assessment:

The Applicant updated the exposure-PFS analyses in their addendum PK/PD report submitted on May 5th, 2025. (b) (4)

They are updated with Table 19.3 (addendum), Figure 19.5 (addendum) and Figure 19.6 (addendum) below, respectively. FDA agrees with the corrected exposure-PFS analysis in the Applicant’s addendum PK/PD report. No significant relationship between imlunestrant exposure and PFS was identified within the therapeutic exposure range at the 400 mg QD dosage.

FDA agrees with the Applicant’s conclusion from the corrected analysis that there is no

significant relationship between imlunestrant exposure and PFS. The initial statement—that patients with 2-fold higher exposures experienced approximately 5 months longer median PFS compared to the mean exposure at 400 mg once daily, while patients with 2-fold lower exposures had approximately 2 months shorter median PFS—^{(b) (4)} and should be discarded based on the corrected exposure-PFS analysis presented in the addendum PK/PD report.

Table 19.3 (addendum). Parameter Estimates from Logistic Regression Model for PFS

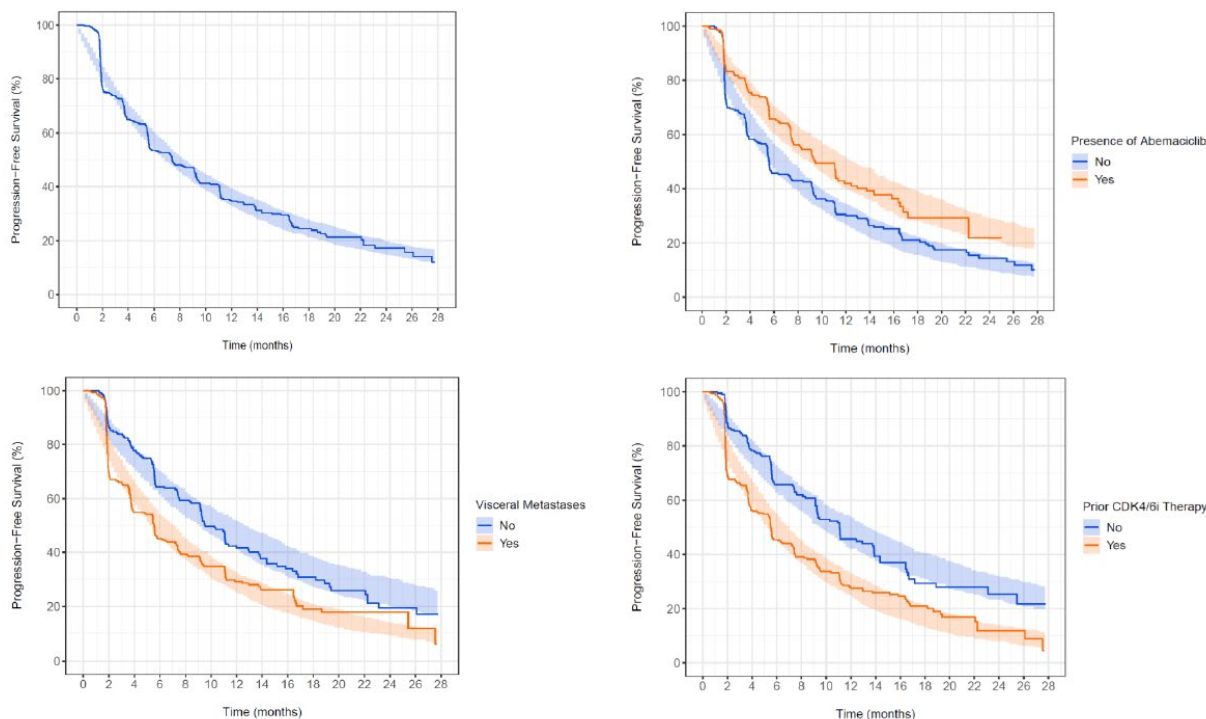
Parameter Description	Estimate (%SEE)
Baseline Hazard (Θ_1) ^a	-3.19 (3.32)
Gompertz Shape Parameter (Θ_3)	-0.00329 (65.7)
Effect of CDK4/6i prior therapy on baseline hazard (Θ_4) ^b	-0.461 (13.7)
Effect of abemaciclib on baseline hazard (Θ_5) ^c	-0.405 (17.5)
Effect of visceral metastases on baseline hazard (Θ_6) ^d	-0.386 (17.9)

Abbreviations: %SEE = percent standard error of the estimate; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; EXP = exponential; PFS = progression-free survival.

- ^a Baseline hazard = $\text{EXP}(\Theta_1)$.
- ^b Baseline hazard = $\Theta_1 * I$ where $I = (1 + \Theta_4)$ for patients without prior CDK4/6i therapy (with visceral metastases and without abemaciclib).
- ^c Baseline hazard = $\Theta_1 * I$ where $I = (1 + \Theta_5)$ for patients with abemaciclib (with visceral metastases and CDK4/6i prior therapy).
- ^d Baseline hazard = $\Theta_1 * I$ where $I = (1 + \Theta_6)$ for patients without visceral metastases (with CDK4/6i prior therapy and without abemaciclib).

Source: Applicant's Population PK and PD Report Addendum, page 47, Table 9.4.

Figure 19.7. (addendum) Visual predictive check graphs for time-to-event model of PFS. Clockwise from top-left: average concentrations below/above median, presence/absence of abemaciclib, prior/no prior CDK4/6i therapy, presence/absence of visceral metastases

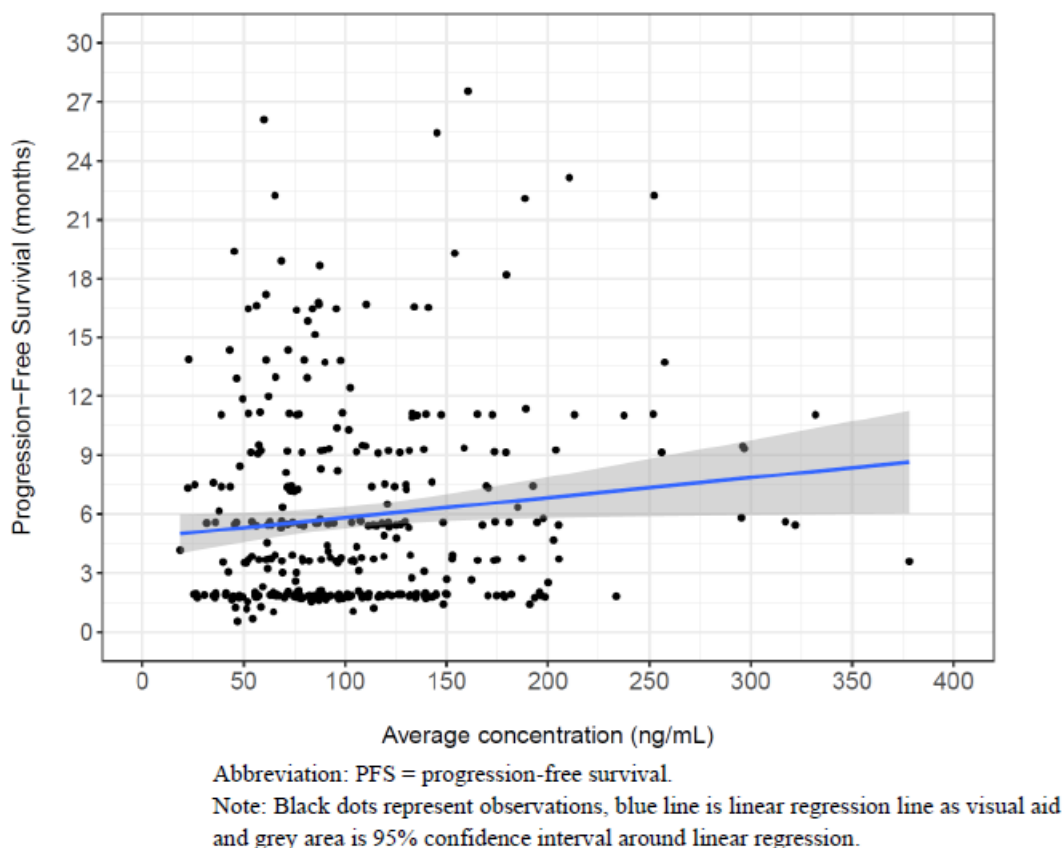


Abbreviations: CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; PFS = progression-free survival

Note: The lines represent the Kaplan-Meier plots of the observed data and the shaded areas represent 95% prediction intervals of the simulated data.

Source: Applicant's Population PK and PD Report Addendum, page 46, Figure 9.5.

Figure 19.8.(addendum) Exposure-Response plot of PFS against average imlunestrant concentration.



Source: Applicant's Population PK and PD Report Addendum, page 46, Figure 9.4.

As noted above, the exposure-response relationship for efficacy should be interpreted with caution as this relationship was characterized from a single dose level (400 mg QD) in the pivotal EMBER-3 study, which limits the ability to fully characterize the E-R relationship across a broader range of therapeutic exposures.

19.4.2.3 ER (safety) Executive Summary

The FDA's Assessment:

The Applicant conducted E-R analysis for safety of imlunestrant by evaluating the relationship between drug exposure and adverse events in patients with estrogen receptor positive (ER+) breast cancer and EEC.

The safety analysis included 473 patients from monotherapy arms of Studies EMBER and EMBER-3. Four key safety endpoints of interest were evaluated: serious adverse events (SAEs), nausea, diarrhea, and fatigue. These endpoints were selected based on their frequency and clinical importance.

There were no significant relationships between imlunestrant exposure and selected safety endpoints. The Applicant's E-R analysis for safety is acceptable.

19.4.2.4 ER (safety) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		Characterize the relationship between imlunestrant exposure and TEAEs (SAEs, nausea, diarrhea, and fatigue) in patients with ER+ breast cancer and ER+ EEC
Study Included		Studies JZLA (EMBER) and JZLC (EMBER-3)
Population Included		Patients with MBC and EEC who received imlunestrant monotherapy
Endpoint		SAEs, nausea, diarrhea, and fatigue
No. of Patients (total, and with individual PK)		473
Population Characteristics (Table 19.1)	General	See Table 19.1
	Organ impairment	See Table 19.1
	Pediatrics (if any)	Not applicable
	Geriatrics (if any)	See Table 19.1
Dose(s) Included		200, 400, 600, 800, and 1200 mg
Exposure Metrics Explored (range)		Average concentration, C _{av} (range: 11.6 to 531.3 ng/mL) Maximum concentration, C _{max} (range: 13.5 to 1167.1 ng/mL)
Covariates Evaluated		Prior CDK4/6i therapy, Number of prior lines of treatment, Presence of visceral metastases

Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	Logistic regression models with concentration effects on SAE, nausea, diarrhea, and fatigue	Acceptable
Model Parameter Estimates	Table 19.5	Acceptable
Model Evaluation	Figure 19.7	Acceptable
Covariates and Clinical Relevance	Increase in imlunestrant exposures were not associated with increases in treatment-emergent AEs (SAEs, nausea, diarrhea, and fatigue). Prior CDK4/6 therapy was a significant covariate on nausea.	Acceptable
Simulation for Specific Population	Not applicable	Acceptable
Visualization of E-R relationships	Figure 19.7	Acceptable
Overall Clinical Relevance for ER	Changes in exposure from 400 mg QD that increase imlunestrant exposure by 2.5-fold are not expected to have a major impact on safety.	Acceptable
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	Not applicable	Acceptable

Table 19.5. Parameter Estimates from Logistic Regression Models for Safety

TEAE Endpoint	Parameter Description	Estimate (%SEE)	Probability of TEAE Incidence at 400-mg Average Concentration ^a
Nausea ^b	Intercept (Θ_1)	2.82 (34.2)	0.25 0.09
	Effect of average imlunestrant concentration (Θ_2)	-0.734 (27.8)	
	Effect of CDK4/6i prior therapy (Θ_3)	-0.627 (53.9)	
	Effect of no CDK4/6i prior therapy (Θ_4)	-1.82 (23.9)	
Diarrhea ^c	Intercept (Θ_5)	2.11 (46.2)	0.20
	Effect of average imlunestrant concentration (Θ_6)	-0.770 (29.0)	
Fatigued ^d	Intercept (Θ_7)	1.72 (54.5)	0.21
	Effect of average imlunestrant concentration (Θ_8)	-0.668 (31.7)	
Serious adverse events ^e	Intercept (Θ_9)	-2.83 (7.28)	0.06

Abbreviations: CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; EXP =exponential; %SEE = percent standard error of the estimate; TEAE = treatment-emergent adverse event.

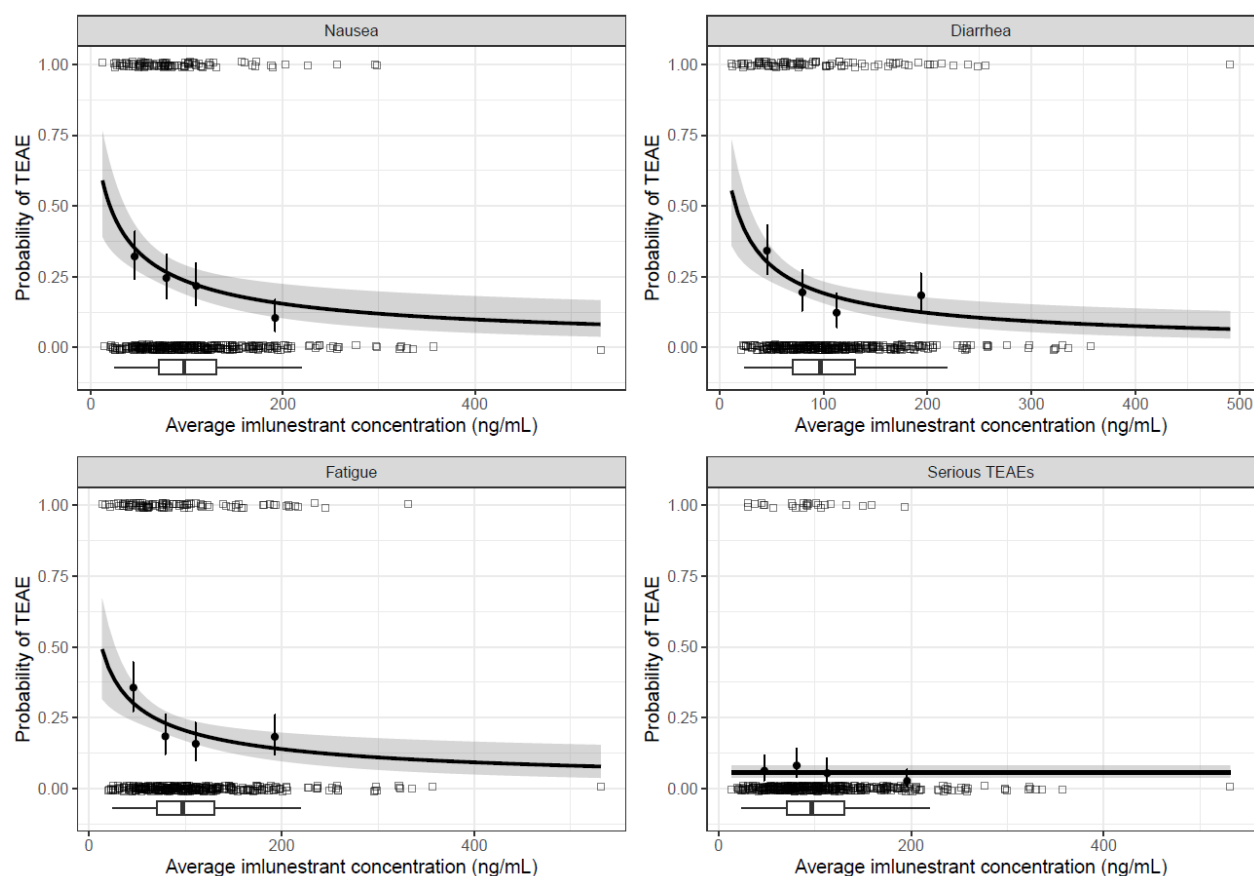
^a Average imlunestrant concentration at 400 mg = 102 ng/mL.

^b Probability of TEAE = $\text{EXP}(\text{LOGIT})/(1+\text{EXP}(\text{LOGIT}))$, where $\text{LOGIT} = \Theta_1 + \Theta_2 \cdot \log(\text{CAV}) + \Theta_3$ in patients with prior CDK4/6i therapy, and $\text{LOGIT} = \Theta_1 + \Theta_2 \cdot \log(\text{CAV}) + \Theta_4$ in patients without prior CDK4/6i therapy and CAV = average imlunestrant concentration.

^c Probability of TEAE = $\text{EXP}(\text{LOGIT})/(1+\text{EXP}(\text{LOGIT}))$, where $\text{LOGIT} = \Theta_5 + \Theta_6 \cdot \log(\text{CAV})$ and CAV = average imlunestrant concentration.

^d Probability of TEAE = $\text{EXP}(\text{LOGIT})/(1+\text{EXP}(\text{LOGIT}))$, where $\text{LOGIT} = \Theta_7 + \Theta_8 \cdot \log(\text{CAV})$ and CAV = average imlunestrant concentration

^e Probability of TEAE = $\text{EXP}(\text{LOGIT})/(1+\text{EXP}(\text{LOGIT}))$, where $\text{LOGIT} = \Theta_9$.



Abbreviations: CI = confidence interval; TEAE = treatment-emergent adverse event.
 Note: Solid black lines and grey shaded area are the logistic regressions and 95% CIs of the predicted probability of TEAE. Black open squares reflect the individual observed TEAEs in imlunestrant-treated patients. The observed response rate (black circles) and 95% CI (black error bars) of each exposure quartile are plotted versus imlunestrant concentration. Box plots represent the 25th, 50th, and 75th percentiles of predicted average imlunestrant concentration for a 400-mg dose. Whiskers represent 1.5 times the interquartile range.

Figure 19.9.

Exposure-response relationships for safety endpoints using the average concentration of imlunestrant up to the day of TEAE for participants in monotherapy arms of Studies JZLA (EMBER) and JZLC (EMBER-3).

The FDA's Assessment:

No significant relationships between imlunestrant exposure and serious TEAEs were identified. Higher exposure to imlunestrant was associated with lower incidence of other AEs of interest (nausea, diarrhea, and fatigue) in the E-R analysis. Such reverse E-R relationships for safety

should be interpreted with caution. In Study EMBER-2, higher doses of imlunestrant were associated with higher rates of GI adverse events which conflicts with the E-R finding.

19.4.2.5 ER Review Issues

The FDA's Assessment:
See **Section 19.4.2.2.**

19.4.2.6 Reviewer's Independent Analysis

The FDA's Assessment:
Not applicable.

19.4.2.7 Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

The proposed imlunestrant dose of 400 mg QD is associated with meaningful benefit and an acceptable safety profile. A 2.5-fold increase in exposure from 400 mg QD is not expected to have a major impact on safety. Dose reductions for tolerability from 400 mg QD to 200 mg QD are expected to maintain sufficient benefit to warrant continued treatment. Overall, the totality of data from EMBER-3 demonstrates a favorable benefit-risk profile for Imlunestrant 400mg QD and a reduced dose of 200mg QD when needed to maintain tolerability.

The FDA's Assessment:
FDA disagrees with the Applicant's initial statement that there was a significant relationship between imlunestrant exposure and PFS due to the error in the initial analysis as described above. There were no clear E-R relationships for efficacy or safety of imlunestrant. However, the proposed dosage of 400 mg QD is supported by the totality of data including the E-R analyses. The Applicant's position regarding overall benefit-risk is stated in **Section 8.4**. See FDA's Assessment in **Section 1** and **Section 8.4**.

19.4.3 Bioanalytical Methods

19.4.3.1 Summary of Bioanalytical Validation Used for Quantitation of Imlunestrant in Human Plasma

The FDA's Assessment:
FDA finds the Applicant's bioanalytical method validation and performance acceptable to determine the concentration of imlunestrant.

The Applicant submitted the following method validation reports:

- 1) Validation Used for Quantitation of Imlunestrant in Human Plasma (#8415876)

2) Validation Used for Quantification of Imlunestrant in Human K2EDTA Plasma
 (#400008-213865-PMV_1)

The method validation results are summarized in Tables below (**Table 19.6** and **Table 19.7**).

Table 19.6: Summary of Bioanalytical Validation Used for Quantitation of Imlunestrant in Human Plasma

Bioanalytical method validation report name, amendments, and hyperlinks	Bioanalytical Validation Report 8415876 and 8415876 Addendum 4		
Method description	Validation of a Method for the Determination of Imlunestrant in Human Plasma by HPLC with MS/MS Detection		
Materials used for standard calibration curve and concentration	Imlunestrant Lot RS1313 LSN3514100 Lot AKF-A15934-142 Dry powder		
Validated assay range	0.500 ng/mL to 500 ng/mL		
Material used for QCs and concentration	Imlunestrant Lot RS1313 LSN3514100 Lot AKF-A15934-142 Dry powder		
Minimum required dilutions (MRDs)	Not applicable		
Source and lot of reagents	Not applicable		
Regression model and weighting	Linear 1/x ² weighted		
Validation parameters	Method validation summary		Acceptability
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.8% to 3.0%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤7.4% CV	Yes
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs	-1.1% to 0.7%	Yes
	Interbatch %CV QCs:	≤4.6% CV	Yes
	Total Error (TE) QCs:	Not applicable	Yes
Selectivity & matrix effect	Six lots of blank plasma were tested. Response was ≤5.4% of		Yes

NDA/BLA Multi-disciplinary Review and Evaluation {Insert Application Type and Number}
 {Insert Product Trade and Generic Name}

	LLOQ.	
Interference & specificity	No significant interference in the quantification of imlunestrant was observed in the presence of LY2835219, LSN2839567, LSN3106726, anastrozole, alpelisib, everolimus, exemestane, letrozole, itraconazole, rifampicin, omeprazole, 5-hydroxyomeprazole, carbamazepine, carbamazepine-10,11-epoxide, midazolam, 1-OH midazolam, repaglinide, dextromethorphan, dextrophan, digoxin, quinidine, or rosuvastatin.	Yes
Hemolysis effect	Six replicates of 2 concentrations in 2% lysed plasma were tested. Response was $\leq 8.0\%$ of the theoretical value.	Yes
Lipemic effect	Six replicates of 2 concentrations in hyperlipidemic (≥ 300 mg/dL) plasma were tested. Response was $\leq 3.3\%$ of the theoretical value.	Yes
Dilution linearity & hook effect	200-fold dilution validated. Hook effect not applicable.	Yes
Bench-top/process stability	Plasma: 24 ours on wet ice Processed sample: 118 hours at 4°C	Yes
Freeze-thaw stability	8 cycles at -20°C and -70°C	Yes
Long-term storage	364 days at -20°C and 1393 days at -70°C	Yes
Parallelism	Not applicable	NA
Carry over	There was no significant carry over.	Yes
Method performance in Studies		
Assay passing rate	JZLA: 90 out of 91 runs passed (99%) JZLB: 9 out of 9 runs passed (100%) JZLC: 25 out of 26 runs passed (96%) JZLD: 27 out of 27 runs passed (100%) JZLE: 11 out of 11 runs passed (100%) JZLG: 17 out of 19 runs passed (89%) JZLI: 26 out of 32 runs passed (81%) JZLK: 9 out of 11 runs passed (82%)	Yes

NDA/BLA Multi-disciplinary Review and Evaluation {Insert Application Type and Number}
{Insert Product Trade and Generic Name}

Standard curve performance	- Cumulative bias range: JZLA: -2.5% to 1.8% JZLB: -3.2% to 2.9% JZLC: -3.7% to 3.1% JZLD: -3.8% to 2.7% JZLE: -6.3% to 3.7% JZLG: -2.2% to 1.5% JZLI: -5.2% to 3.3% JZLK: -5.5% to 3.1% - Cumulative precision: JZLA: ≤5.2% CV JZLB: ≤6.2% CV JZLC: ≤6.1% CV JZLD: ≤4.6% CV JZLE: ≤3.5% CV JZLG: ≤5.0% CV JZLI: ≤4.4% CV JZLK: ≤5.9% CV	Yes
QC performance	- Cumulative bias range: JZLA: -1.0% to 1.3% JZLB: -0.2% to 2.9% JZLC: -3.9% to 0.8% JZLD: -1.5% to 1.6% JZLE: -3.8% to 3.9% JZLG: -3.4% to 0.3% JZLI: -4.4% to 3.6% JZLK: -1.8% to 3.0% - Cumulative precision: JZLA: ≤5.1% CV JZLB: ≤4.5% CV JZLC: ≤8.9% CV JZLD: ≤4.2% CV JZLE: ≤4.5% CV JZLG: ≤4.5% CV JZLI: ≤3.9% CV JZLK: ≤6.7% CV	Yes
Method reproducibility	JZLA: 6% of samples run in ISR and 93% passed criteria JZLB: 11% of samples run in ISR and 100% passed criteria JZLC: 8% of samples run in ISR and 96% passed criteria JZLD: 8% of samples run in ISR and 94% passed criteria JZLE: 12% of samples run in ISR and 88% passed criteria JZLG: 10% of samples run in ISR and 100% passed criteria JZLI: 8% of samples run in ISR and 96% passed criteria JZLK: 11% of samples run in ISR and 96% passed criteria.	Yes
Study sample analysis/stability	Samples were stored at -70°C for up to 1226 days. Stability was established for 1393 days at -70°C.	

NDA/BLA Multi-disciplinary Review and Evaluation {Insert Application Type and Number}
 {Insert Product Trade and Generic Name}

		Yes
--	--	-----

Abbreviations: CV = coefficient of variation; HPLC = high performance liquid chromatography; ISR = incurred sample reanalysis; LLOQ = lower limit of quantitation; MS/MS = tandem mass spectrometry; QC = quality control; ULOQ = upper limit of quantitation.

Table 19.7: Summary of Bioanalytical Validation Used for Quantification of Imlunestrant in Human K₂EDTA Plasma

Bioanalytical method validation report name, amendments, and hyperlinks	Bioanalytical Report 400008-213865-PMV_1 and 400008-213865-PMV Amendment 02		
Method description	Validation of an LC-MS/MS method for the determination of LY3484356 in human K ₂ EDTA plasma		
Materials used for standard calibration curve and concentration	Imlunestrant Lots RS1313 and RS1339 LSN3514100 Lot CAZ-ELC1-21-1		
Validated assay range	0.500 ng/mL to 500.000 ng/mL		
Material used for QCs and concentration	Imlunestrant Lots RS1313 and RS1339 LSN3514100 Lot CAZ-ELC1-21-1		
Minimum required dilutions (MRDs)	Not applicable		
Source and lot of reagents	Not applicable		
Regression model and weighting	Linear 1/x ² weighted		
Validation parameters	Method validation summary		Acceptability
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.4% to 1.2%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤4.4% CV	Yes
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 3 QCs	2.3% to 4.8%	Yes
	Interbatch %CV QCs:	≤3.6% CV	Yes
	Total Error (TE) QCs:	Not applicable	Yes
Selectivity & matrix effect	Six lots of blank plasma were tested. Response was ≤2.6% of LLOQ.		Yes
Interference & specificity	No significant interference was seen.		Yes
Hemolysis effect	One lot of lysed plasma was tested. Response was 0.0% of LLOQ.		Yes
Lipemic effect	One lot of hyperlipidemic plasma was tested. Response was 0.0% of LLOQ.		Yes
Dilution linearity & hook effect	200-fold dilution validated. Hook effect not applicable.		Yes

Bench-top/process stability	Plasma: 25 hours on wet ice	Yes
Freeze-thaw stability	5 cycles at -20°C and -70°C	Yes
Long-term storage	372 days at -20°C and 960 days at -70°C	Yes
Parallelism	Not applicable	NA
Carry over	There was no significant carry over.	Yes
Method performance in Studies		
Assay passing rate	JZLC: 5 out of 7 runs passed (71%)	Yes
Standard curve performance	- Cumulative bias range: JZLC: -3.3% to 1.5% - Cumulative precision: JZLC: ≤4.6% CV	Yes
QC performance	- Cumulative bias range: JZLC: -2.5% to 2.5% - Cumulative precision: JZLC: ≤4.8% CV	Yes
Method reproducibility	JZLC: 12% of samples run in ISR and 100% passed criteria	Yes
Study sample analysis/stability	Samples were stored at -70°C for up to 441 days. Stability was established for 960 days at -70°C.	Yes

Abbreviations: CV = coefficient of variation; ISR = incurred sample reanalysis; K₂EDTA = dipotassium ethylenediaminetetraacetic acid; LC-MS/MS = liquid chromatography with tandem mass spectrometry; LLOQ = lower limit of quantitation; QC = quality control; ULOQ = upper limit of quantitation.

Assessment Conclusions

The Applicant has sufficiently validated bioanalytical methods for determination of imlunestrant concentration in human plasma by HPLC with MS/MS detection (8415876) as well as in K₂EDTA plasma by LC-MS/MS (400008-213865-PMV_1).

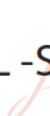
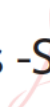
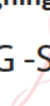
The precision and accuracy of quality control (QC) were within the prespecified acceptance limits. The Applicant validated the selectivity, matrix effect, hemolysis effect, lipemic effect, dilution linearity, bench-top and process stability, and freeze-thaw stability. The long term stability was established for concentration control was 1393 days at -70°C and 960 days at -70°C for methods 8415876 and 400008-213865-PMV_1, respectively.

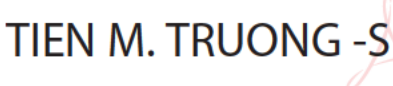
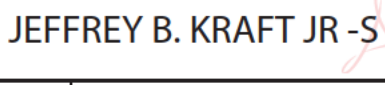
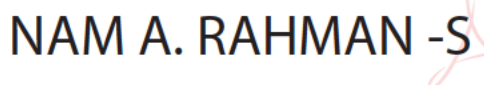
19.5 Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

Refer to the FDA analysis for Safety in Section 8.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Wimolnut Manheng, PhD	DHOT	Sections: 5	Select one: ☒ _ Authored ☒ _ Approved
	Signature: WIMOLNUT MANHENG -S  Digitally signed by WIMOLNUT MANHENG -S Date: 2025.09.15 11:53:05 -04'00'			
Acting Nonclinical Team Leader	Nikolett Biel, PhD	DHOT	Sections: 5	Select one: ☐ _ Authored ☒ _ Approved
	Signature: NIKOLETT M. BIEL -S  Digitally signed by NIKOLETT M. BIEL -S Date: 2025.09.15 11:57:39 -04'00'			
Acting Nonclinical Deputy Director	Tiffany Ricks, PhD	DHOT	Section: 5	☐ _ Authored ☒ _ Approved
	Signature: Tiffany K. Ricks -S  Digitally signed by Tiffany K. Ricks -S Date: 2025.09.15 12:44:17 -04'00'			
Clinical Pharmacology Reviewer	Banu Zolnik, PhD	DCPII	Sections: 6, 19.4	Select one: ☒ _ Authored ☐ _ Approved
	Signature: Ruby Leong is signing on behalf of Dr. Zolnik RUBY LEONG -S  Digitally signed by RUBY LEONG -S Date: 2025.09.15 14:23:32 -04'00'			
Pharmacometrics Reviewer	Frank Fang Li, PhD	DPM	Sections: 6, 19.4	Select one: ☒ _ Authored ☐ _ Approved
	Signature: Frank Li -S  Digitally signed by Frank Li -S Date: 2025.09.15 14:48:26 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	DISCIPLINE
Pharmacometrics Team Leader	Jingyu Yu, PhD	DPM	Sections: 6, 19.4	Select one: ☐ _Authored ☐ _Approved
	Signature:	 Digitally signed by JINGYU YU -S Date: 2025.09.15 15:08:20 -04'00'		
Genomics Reviewer	Tien Truong, PharmD	DTPM	Sections: 6	Select one: ☐ _Authored ☐ _Approved
	Signature:	 Digitally signed by TIEN M. TRUONG -S Date: 2025.09.15 09:23:43 -10'00'		
Genomics Team Lead	Jeffrey Kraft, PhD	DTPM	Sections: 6	Select one: ☐ _Authored ☐ _Approved
	Signature:	 Digitally signed by JEFFREY B. KRAFT JR -S Date: 2025.09.16 09:37:21 -04'00'		
Clinical Pharmacology Team Leader	Lauren Price, PharmD	DCPII	Sections: 6, 19.4	Select one: ☒ _Authored ☐ _Approved
	Signature:	 Digitally signed by LAUREN PRICE -S Date: 2025.09.16 09:55:46 -04'00'		
Clinical Pharmacology Division Director	Nam Atiqur Rahman, PhD	DCPII	Sections: 6, 19.4	Select one: ☐ _Authored ☒ _Approved
	Signature:	 Digitally signed by NAM A. RAHMAN -S Date: 2025.09.16 10:47:41 -04'00'		
Clinical Reviewer	Joshua Donaldson, MD, PhD	DO1	Sections: 2, 3, 4, 7, 8.1, 8.4, 11, 19	Select one: ☒ _Authored ☐ _Approved
	Signature:	 Digitally signed by JOSHUA M. DONALDSON -S Date: 2025.09.16 11:38:56 -04'00'		

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	DISCIPLINE
Clinical Reviewer	Maria Garcia-Jimenez, MD, MHS	DO1	Sections: 8.2, 11	Select one: ☒ Authored ☐ Approved
	Signature: MARIA D. GARCIA-JIMENEZ -S Digitally signed by MARIA D. GARCIA-JIMENEZ -S Date: 2025.09.16 12:22:41 -04'00'			
Statistical Reviewer	Hui Zhang, PhD	DBV	Sections: 8.1, 8.3	Select one: ☒ Authored ☐ Approved
	Signature: Hui Zhang -S Digitally signed by Hui Zhang -S Date: 2025.09.16 13:09:02 -04'00'			
Statistical Team Leader	Xin Gao, PhD	DBV	Sections: 8.1, 8.3	Select one: ☐ Authored ☒ Approved
	Signature: XIN GAO -S Digitally signed by XIN GAO -S Date: 2025.09.16 13:44:57 -04'00'			
Statistical Division Director	Shenghui Tang, PhD	DBV	Sections: 8.1, 8.3	Select one: ☐ Authored ☒ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2025.09.16 14:42:41 -04'00'			
Associate Director for Labeling (ADL)	William Pierce, PharmD	DO1	Sections: Section 11, Prescribing Information, Patient Labeling	Select one: ☒ Authored ☒ Approved
	Signature: William F. Pierce -S Digitally signed by William F. Pierce -S Date: 2025.09.18 10:01:37 -04'00'			
Clinical Team Leader and Cross-Disciplinary Team Leader (CDTL)	Preeti Narayan, MD	DO1	Sections: All	Select one: ☒ Authored ☒ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONSAUTHORED/ APPROVED	DISCIPLINE
Division Director (Clinical)	Laleh Amiri- Kordestani, MD	DO1	Sections: All	Select one: _Authored X_Approved
	Signature:			
Director- Office Signatory (OOD)	Richard Pazdur, MD	OOD	Sections: All	Select one: _Authored _X Approved
	Signature:			

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

/s/

PREETI NARAYAN
09/24/2025 06:46:36 PM

LALEH AMIRI KORDESTANI
09/24/2025 06:57:15 PM

ROMEO A DE CLARO
09/25/2025 09:55:29 AM