CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218881Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 145311

MEETING MINUTES

Eli Lilly and Company
Attention: Brandon Lane
Global Regulatory Affairs - NA
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Brandon Lane:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for imlunestrant (LY3484356).

We also refer to the video conference between representatives of your firm and the FDA on September 23, 2024. The purpose of the meeting was to review the results of EMBER-3 and attain agreement on the data package to support filing of an NDA for the proposed indications, the content and format of the NDA, the overall content of a 4-month safety update, and various administrative items including Project Orbis review (b) (4).

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

If you have any questions, contact Rashida Redd, Senior Regulatory Project Manager, at 301-796-5489 or Rashida.Redd@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rashida Redd, BA
Senior Regulatory Health Project Manager
Oncology 1 Group
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

{See appended electronic signature page}

Elaine Chang, MD
Clinical Team Lead (Acting)
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 23, 2024, 2:00 – 3:00 pm EST
Meeting Location: Videoconference

Application Number: IND 145311
Product Name: imlunestrant (LY3484356)
Indication: Breast cancer

Sponsor Name: Eli Lilly and Company
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Elaine Chang, MD
Meeting Recorder: Rashida Redd

FDA ATTENDEES

Laleh Amiri-Kordestani, MD, Division Director
Christy Osgood, MD, Associate Division Director
Elaine Chang, MD, Clinical Team Lead
Mirat Shah, MD, Clinical Team Lead
Preeti Narayan, MD, Clinical Team Lead
Joshua Buturla, MD, Clinical Reviewer
Suparna Wedam, MD, Clinical Reviewer
James Buturla, MD, Clinical Reviewer
Wimolnut Manheng, PhD, Pharmacology Toxicology Reviewer
Xin (Cindy) Gao, PhD, Biostatistics Team Lead
Hee-Koung Joeng, PhD, Biostatistics Reviewer
Lauren Price, PhD, Clinical Pharmacology Team Lead
Liuya Tang, PhD, CDRH Reviewer
Rashida Redd, Senior Regulatory Project Manager

SPONSOR ATTENDEES

Name	Title
Jake Van Naarden	Executive Vice President and President, Loxo@Lilly
David Hyman, MD	Chief Medical Officer
Lillian Smyth, MD	Senior VP, Global Clinical Development
Holly Knoderer, MD	Associate VP, Senior Medical Director, Oncology

Stacy Moulder, MD	VP, Medical Professional Development and Breast Cancer Franchise
Naji Gehchan, MD	Head of Development - SERD
Bhardwaj Desai, MD	Executive Director, Medical, Oncology
Kamnesh Pradhan,	MD Executive Director, CRP-SERD
Emily Barrett, MSc	Senior Advisor, GPS
Xuejing Aimee Wang, PhD	Director, Statistics
Valerie Andre, MD	Executive Director, Statistics
Janice Evans, BS	VP, Regulatory Affairs
Brian Wagner, PharmD	Senior Director, Regulatory Affairs
Yolanda Villabos del Fresno, BSPharm, MBA	Executive Director, Regulatory Affairs
Jillian Fuhs, PharmD, JD	Associate VP, Regulatory Affairs
Brandon Lane, PhD	Associate Director, Regulatory Affairs

1.0 BACKGROUND

Eli Lilly and Company (Lilly) requested a Type B meeting to discuss the results of the phase 3 EMBER-3 trial of imlunestrant in adult patients with ER-positive (ER+), HER2-negative (HER2-), locally advanced or metastatic breast cancer previously treated with endocrine therapy to support the following indication (b) (4)

> *imlunestrant as monotherapy for the treatment of patients with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, ESR1-mutated, locally advanced or metastatic breast cancer, previously treated with endocrine therapy*

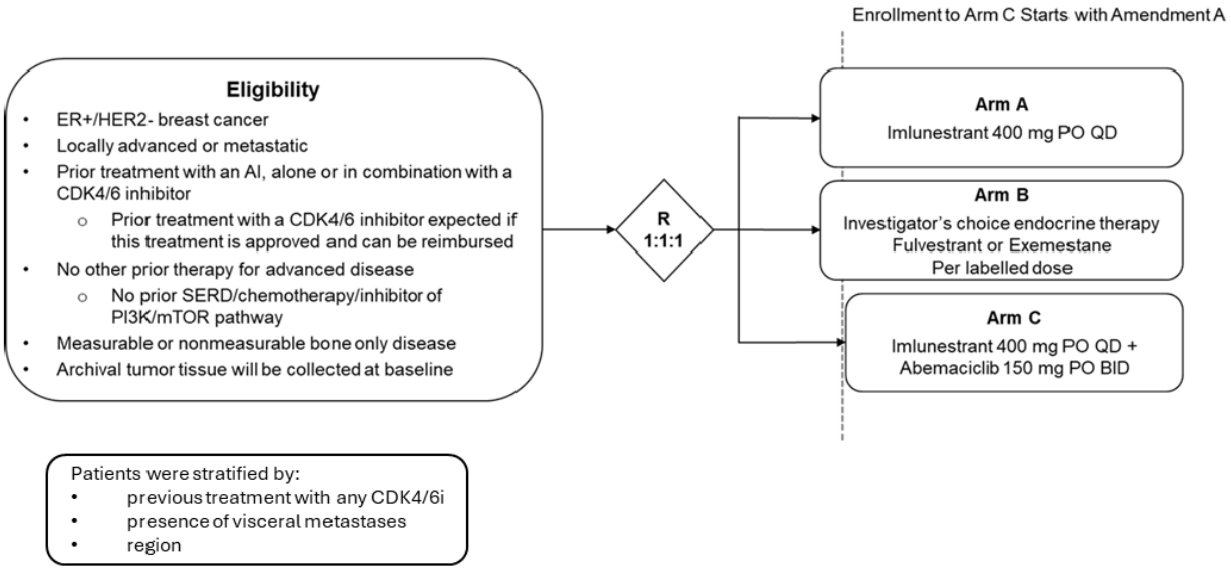
(b) (4)

Imlunestrant (LY3484356) is an orally bioavailable selective estrogen receptor degrader (SERD). (b) (4)

Imlunestrant received Fast Track Designation on November 9, 2021, for the treatment of patients with ER+, HER2- locally advanced or metastatic breast cancer, previously treated with endocrine therapy. Lilly met with the FDA on February 11, 2021, for a Type B EOP1 meeting to discuss EMBER-3 (Figure 1, except (b) (4) in the initial proposal, instead of region). FDA recommended that the patient population represent the US population including PARPi for germline BRCA

mutated tumors and prior CDK4/6i in first-line. A protocol amendment was submitted to exclude known BRCA mutated patients. First-line CDK4/6i was not required. On June 16, 2022, the FDA provided written responses to a Type C meeting and recommended against [redacted] (b) (4). FDA also warned Lilly that the efficacy of the combination for patients being retreated with a CDK4/6i would be a review issue. On September 1, 2022, Lilly submitted an updated SAP that added a new primary objective and endpoint for PFS and new secondary objective and endpoint for OS in the *ESR1*m detected population. On August 22, 2023, SAP v5 modified the initial alpha allocation for PFS between Arm A and Arm B in the ITT population (H1) and PFS between Arm A and Arm B in the ESR1-mutation detected population (H2) from 0.02 and 0.005 to 0.005 and 0.02, respectively, based on external data for oral SERDs in patients with recurrent ER+ HER2- breast cancer where clinically and statistically meaningful improvement in PFS has been primarily driven by the *ESR1*m detected population. Of note, elacestrant was approved for *ESR1*m ER+, HER2-, metastatic breast cancer on January 27, 2023.

Figure 1. Study Schema



Source: Briefing Document

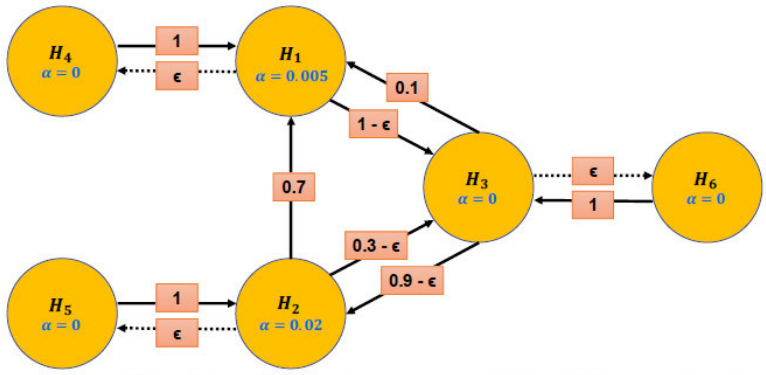
EMBER-3 is an ongoing open-label, global, phase 3, randomized trial of hormone therapy with or without a CDK4/6i in patients with ER+, HER2- locally advanced or metastatic breast cancer after progression on an aromatase inhibitor (AI) with or without a CDK4/6i (Figure 1). A total of 874 patients were randomized to three arms:

- Arm A: imlunestrant 400 mg PO daily
- Arm B: SOC ET (fulvestrant IM or exemestane PO)
- Arm C: imlunestrant 400 mg PO daily with abemaciclib 150 mg PO twice daily

Patients could not have received prior SERD, chemotherapy, or targeted therapy to the PI3K/mTOR pathway. Stratification factors included prior therapy with a CDK4/6i (yes or no), presence of visceral metastasis (yes or no), and region (East Asia or North America/Western Europe or other). Estrogen receptor (*ESR1*) mutation testing was performed using the Guardant 360 CDx or OncoCompass Plus test for patients in China. ESR1m (detected or not detected) was not a stratification factor.

The primary endpoints of the trial were 3 investigator-assessed progression free survival (PFS) comparisons as shown in Figure 2. To control the overall type I error rate at 0.025 (1-sided), PFS hypotheses were tested hierarchically using a graphical approach. Initially, the overall 1-sided alpha level of 0.025 was split into hypothesis 1 (H1) (PFS for Arm A vs. Arm B in ITT) and hypothesis 2 (H2) (PFS for Arm A vs. Arm B in ESR1m). If either of H1 or H2 was rejected, it was planned to test hypothesis 3 (H3) (PFS for Arm C vs. Arm A in ITT) using the recycled alpha shown in Figure 2. The key secondary OS hypotheses (H4, H5, and H6) would be tested only if the corresponding primary PFS hypotheses were rejected.

Figure 2. Hierarchical Testing Schema



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 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 ITT population; ITT = intent to treat; OS = overall survival; PFS = progression-free survival.
Small edge weights are represented by dotted lines. ϵ denotes an infinitesimally small number ($\epsilon = 10^{-4}$).

Source: Briefing Document

Patient demographics and baseline characteristics with the exception of *ESR1*m status were fairly well balanced between arms for both the *ESR1*m and ITT populations. In total, 37% of patients in the trial had a detectable *ESR1*m (42% in Arm A, 32% in Arm B, 36% in Arm C). Slightly less than 60% of patients had prior CDK4/6i.
The study met 2 out of 3 primary PFS endpoints. Investigator assessed PFS improvement for imlunestrant monotherapy (Arm A) versus SOC ET (Arm B) in the *ESR1*m population with a HR 0.62 (95% CI 0.46, 0.82) (Table 1) was statistically significant. However, the Arm A vs. Arm B PFS comparison in the ITT population was

not significant with a HR 0.87 (95% CI 0.72, 1.04). Blinded independent central review (BICR) results were similar (Table 7.2 in the Briefing Document). OS for Arm A vs. Arm B in the *ESR1*m population demonstrated a favorable trend that was immature at a 52% information fraction and not significant with a HR 0.55 (95% CI 0.35, 0.86). Despite the HR of 0.55, the Kaplan-Meier curves are unfavorable for imlunestrant from about 3 to 7 months.

Table 1. Efficacy Results for Imlunestrant versus SOC ET in *ESR1*m and ITT Populations

Statistic	Primary Analysis Populations				Exploratory Analysis Population	
	*ESR1*m N=256		ITT N=661		*ESR1*m-ND (ITT) N=405	
	Arm A: Imlunestrant	Arm B: SOC ET	Arm A: Imlunestrant	Arm B: SOC ET	Arm A: Imlunestrant	Arm B: SOC ET
	N=138	N=118	N=331	N=330	N=193	N=212
Primary Analysis: Investigator-Assessed PFS[a]						
Events, n (%)	109 (79.0)	102 (86.4)	237 (71.6)	253 (76.7)	128 (66.3)	151 (71.2)
Median PFS, months (95% CI)	5.5 (3.9, 7.4)	3.8 (3.7, 5.5)	5.6 (5.3, 7.3)	5.5 (4.6, 5.6)	5.6 (4.4, 9.1)	5.7 (5.5, 7.4)
HR (95% CI) stratified	0.62 (0.46, 0.82)		0.87 (0.72, 1.04)		1.00 (0.79, 1.27)	
6-month PFS rate (95% CI)	44.1 (35.5, 52.4)	32.1 (23.4, 41.1)	45.3 (39.7, 50.8)	42.6 (37.0, 48.2)	46.2 (38.7, 53.4)	48.4 (41.2, 55.2)
12-month PFS rate (95% CI)	24.5 (16.9, 32.9)	6.6 (2.7, 13.0)	29.5 (24.2, 34.9)	21.5 (16.9, 26.5)	33.0 (25.9, 40.3)	29.6 (23.2, 36.4)
Secondary Endpoint: BIRC-Assessed PFS[a]						
Events, n (%)	74 (53.6)	71 (60.2)	160 (48.3)	159 (48.2)	86 (44.6)	88 (41.5)
Median PFS, months (95% CI)	7.4 (4.8, 11.1)	5.5 (3.8, 6.7)	9.2 (7.3, 11.1)	7.4 (5.6, 9.4)	10.9 (7.4, 22.2)	11.0 (9.0, 18.3)
HR (95% CI) stratified	0.657 (0.469, 0.920)		0.928 (0.742, 1.160)		1.173 (0.869, 1.583)	
6-month PFS rate (95% CI)	53.4 (44.0, 62.0)	40.0 (29.6, 50.1)	57.6 (51.6, 63.2)	53.3 (47.0, 59.2)	60.7 (52.7, 67.8)	60.5 (52.7, 67.5)
12-month PFS rate (95% CI)	37.2 (27.2, 47.2)	12.8 (5.0, 24.4)	43.6 (37.0, 50.0)	38.3 (31.6, 44.9)	48.1 (39.5, 56.2)	49.9 (41.5, 57.8)

Statistic	Primary Analysis Populations				Exploratory Analysis Population	
	*ESR1*m N=256		ITT N=661		*ESR1*m-ND (ITT) N=405	
	Arm A: Imlunestrant	Arm B: SOC ET	Arm A: Imlunestrant	Arm B: SOC ET	Arm A: Imlunestrant	Arm B: SOC ET
	N=138	N=118	N=331	N=330	N=193	N=212
Secondary Endpoint: Interim OS[a]						
Events, n (%)	32 (23.2)	48 (40.7)	62 (18.7)	90 (27.3)	30 (15.5)	42 (19.8)
Median OS, months (95% CI)	NR (23.2, NR)	21.22 (16.2, 26.8)	NR (NR, NR)	26.84 (25.8, NR)	NR (NR, NR)	NR (26.3, NR)
HR (95% CI) stratified	0.546 (0.348, 0.856)		0.690 (0.498, 0.956)		0.867 (0.539, 1.395)	
Median follow-up time, months (95% CI)	16.4 (14.4, 18.2)	17.4 (16.0, 19.4)	16.1 (14.4, 17.0)	16.9 (15.4, 17.8)	15.4 (13.8, 17.1)	16.2 (14.8, 17.8)
Secondary Endpoint: ORR[a]						
ORR by Investigator, n/N_e (%)	16/112 (14.3)	7/91 (7.7)	32/262 (12.2)	21/251 (8.4)	16/150 (10.7)	14/160 (8.8)
ORR by BIRC, n/N_e (%)	17/104 (16.3)	4/77 (5.2)	41/241 (17.0)	19/205 (9.3)	24/137 (17.5)	15/128 (11.7)

Source: Briefing Document

(b) (4)

(b) (4) (b) (4)

(b) (4)

The safety profile of imlunestrant compared to SOC ET was similar including all TEAEs, Grade ≥3 TEAEs, SAEs (Table 3). Treatment discontinuations were higher for imlunestrant (4.3% versus 1.2%). Death rates were similar in both arms. (b) (4)

All Grade TEAEs for imlunestrant that were ≥5% higher than SOC ET were fatigue (23% vs. 13%) and diarrhea (21% vs. 12%). Rates of SAEs were balanced between arms. Imlunestrant had a similar impact on hypercholesterolemia and hypertriglyceridemia as SOC ET.

(b) (4)

Table 3. Summary of Safety Results by Arm

Number of Patients, n (%)	Arm A Imlunestrant N=327	Arm B SOC ET N=324	Arm C Imlun+Abema (b) (4)
Patients with ≥1 TEAE	270 (82.6)	273 (84.3)	
Related to Study Treatment	160 (48.9)	104 (32.1)	
Patients with ≥1 Grade ≥3 TEAE	56 (17.1)	67 (20.7)	
Related to Study Treatment	15 (4.6)	6 (1.9)	
Patients with ≥1 SAE	34 (10.4)	38 (11.7)	
Related to Study Treatment	6 (1.8)	1 (0.3)	
Patients with AE leading to:			
Dose Reduction	8 (2.4)	0	
Treatment Discontinuation	14 (4.3)	4 (1.2)	
Death on Study Treatment	5 (1.5)	4 (1.2)	
Death within 30 days of discontinuation from study treatment[a]	0	2 (0.6)	

Source: Briefing Document

FDA sent Preliminary Comments to Eli Lilly on September 12, 2024.

2.0 DISCUSSION

Question 1: Does FDA agree the EMBER-3 results provide adequate evidence to support filing (b) (4) for:

a) imlunestrant as monotherapy for the treatment of patients with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, ESR1-mutated, locally advanced or metastatic breast cancer, previously treated with endocrine therapy; AND

(b) (4)

FDA Response to Question 1:

a) Yes. The results of the EMBER-3 trial support filing an NDA for imlunestrant as monotherapy for ER+, HER2-, ESR1m, locally advanced or metastatic breast cancer, previously treated with endocrine therapy. Whether the results can support the approval will be a review issue.

Preliminarily, we note the following concerns about the imlunestrant as monotherapy results which will be review issues and should be addressed in your NDA submission:

i. *ESR1m* status was not a stratification factor. Although major imbalances in the *ESR1*m population are not evident in baseline characteristics provided, potential imbalances of unknown prognostic and predictive factors make the results difficult to interpret and this will be a review issue.

ii. The Kaplan-Meier curve for OS in the *ESR1*m population demonstrates that imlunestrant is inferior to SOC ET from about 3 to 7 months. Provide a rationale for why the early OS results appear to favor SOC ET.

iii. The median PFS benefit for imlunestrant in the *ESR1*m population is approximately 1.7 months which is shorter than the 8-week or 12-week imaging interval which increases uncertainty about the clinical meaningfulness of the results.

iv. Patients were not required to have a prior CDK4/6i for eligibility and less than 60% of patients in the trial had a prior CDK4/6i which is lower than what is observed in the intended US patient population.

v. The selection of first-line CDK4/6i agent has changed in the US since this trial enrolled as some CDK4/6 inhibitors have demonstrated an overall survival benefit.

Sponsor's Response to FDA Response to Question 1a: Lilly acknowledges FDA's overall agreement on the filing of an ESR1m monotherapy NDA and, in addition to responses here, will address FDA's preliminary concerns within the application.

Lilly does not require further discussion on Question 1a during the meeting.

(i): Balanced Baseline Characteristics

EMBER-3 was designed before the impact of oral selective estrogen receptor degraders on *ESR1*m was known. At the time of EMBER-3 design, Lilly reasoned that the alterations were of high enough natural prevalence in ET-pretreated ABC that significant imbalance of *ESR1*m across treatment arms was unlikely. Additionally, the (b) (4) selected stratification factors, specifically prior CDK4/6i therapy (yes or no) and visceral metastasis (yes or no), were likely to maintain balance of important clinical prognostic factors across the study.
Lilly agrees, as noted by FDA, that baseline characteristics appear to be balanced across treatment arms, and is completing multiple sensitivity analyses to demonstrate the results are robust. The NDA will include

- a prespecified sensitivity analysis from a Cox model adjusting for baseline prognostic factors, and

- comparisons of baseline characteristics among *ESR1*m patients between treatment arms within the

    - EMBER-3 clinical study report, and
    - study report prepared in collaboration with Guardant for clinical validation of the *ESR1*m assay.

(ii): The Kaplan-Meier Curve for OS in the *ESR1*m Population

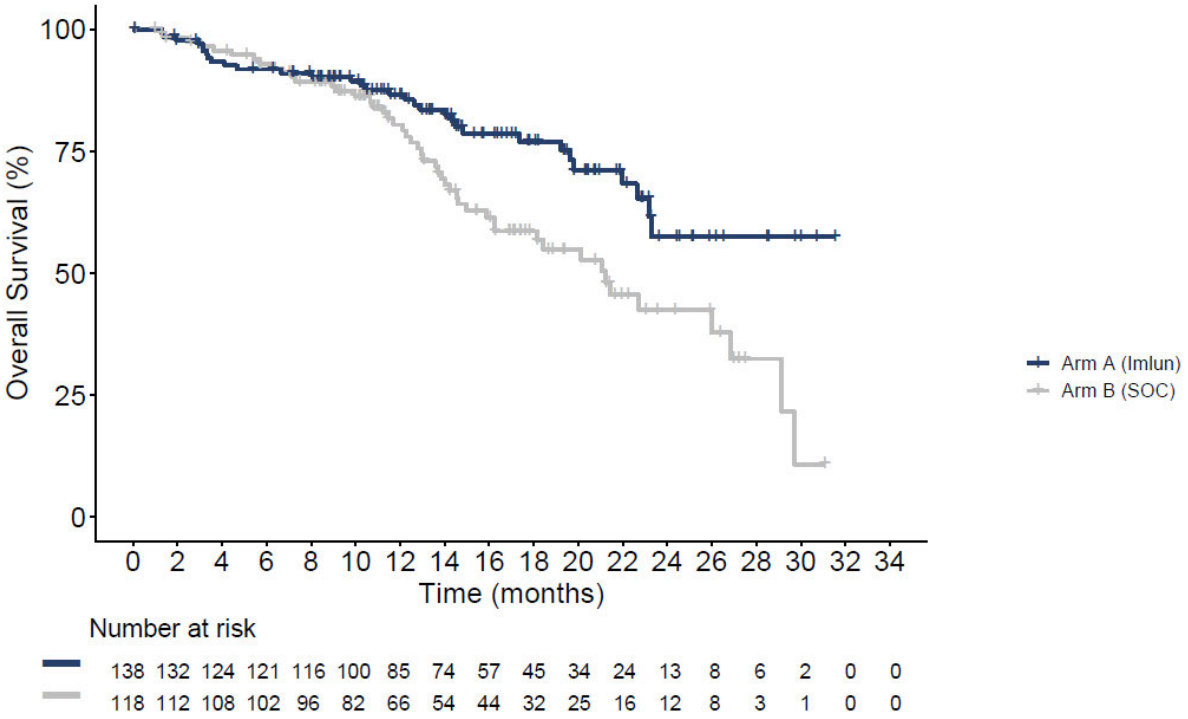
Lilly does not believe the data support the FDA's comment that the OS curves demonstrate imlunestrant was inferior from Months 3 to 7. Between Month 3 and Month 7, a total of only 15 OS events occurred (8 in the imlunestrant arm and 7 in the SOC arm, Table 4.1). Conclusions from a post hoc inferential analysis of a very small number of events occurring during this segment of the Kaplan-Meier curve are likely to be unreliable. From Month 7 onward, the information fraction begins to increase and the curves (Figure 4.1) begin to separate in favor of imlunestrant. While the overall analysis remains immature, with the information fraction equaling 52%, the overall trend is clearly in favor of imlunestrant and provides no evidence of detriment.

These results will be provided in the NDA.

Table 0.1. Overall Survival Events by Time Interval *ESR1*m Population Arm A versus Arm B

Time Interval	Number of OS Events Within Time Interval	
	Arm A Imlunestrant	Arm B SOC
0-3 months	4	3
3-7 months	8	7
>7 months	20	38

Abbreviations: *ESR1*m = estrogen receptor 1-mutation; OS = overall survival; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane.



Abbreviations: *ESR1*m = estrogen receptor 1-mutation; Imlun = imlunestrant; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane.

Figure 0.1. Kaplan-Meier plot of overall survival for imlunestrant versus SOC in the *ESR1*m-detected population.

(iii): PFS Benefit for Imlunestrant in the *ESR1*m Population

While median PFS focuses on only 1 point on the Kaplan-Meier curve, HR summarizes the treatment effect over the entire curve. Imlunestrant demonstrated a statistically significant improvement in PFS compared with SOC, with HR = 0.617 (95% CI 0.464, 0.821). Higher PFS rates were observed at both 6 months and 12

months, suggesting a sustained PFS benefit. The magnitude of benefit was further supported by multiple prespecified sensitivity analyses with consistent treatment effect. In addition to meeting the investigator-assessed PFS primary endpoint, all prespecified secondary efficacy endpoints, including

- ORR
- Duration of Response
- Clinical Benefit Rate
- Blinded independent committee review-assessed PFS, and
- OS

favored imlunestrant over SOC in the *ESR1*m population. Therefore, the totality of efficacy data suggests consistency with the primary analysis and clinically meaningful efficacy favoring imlunestrant compared with SOC in *ESR1*m patients. To further explore the robustness of the primary analysis results of investigator-assessed PFS with respect to the imaging assessment interval, Lilly is conducting an exploratory interval censoring analysis for PFS. The results of the analysis will be provided in the NDA.

(iv): Alignment of Prior Treatment in EMBER-3 with US Medical Practice

The population enrolled in the EMBER-3 program closely matches US medical practice with regard to prior treatment with CDK4/6i. Recent published reports estimate approximately 50% to 65% of US patients receive CDK4/6i as first-line therapy for hormone receptor-positive, HER2- MBC (Brufsky et al. 2024; Hanson et al. 2022). These estimates are consistent with a real-world evidence analysis using (b) (4) databases (2024, data on file). The analysis shows that between 2021 and 2023, approximately 60% of patients with hormone receptor-positive, HER2- MBC received 1L CDK4/6i with any ET. When filtered to CDK4/6i with aromatase inhibitor to match the EMBER-3 population, the use rate decreases to 45% of patients. As such, the population enrolled in the EMBER-3 program is representative of the prior CDK4/6i experience of US patients who would be eligible to receive imlunestrant under the proposed monotherapy indication. The NDA will provide further details on the CDK4/6i utilization rate and the adequacy to the US population.

(v): Selection of First-Line CDK4/6i Agent from Approved Agents

The global EMBER-3 study allowed multiple prior CDK4/6i as consistent with the FDA's ongoing traditional approval of all 3 agents. The NDA will provide further details on the mix of prior 1L CDK4/6i use and the adequacy to the US population.

Meeting Discussion of Question 1a: *None.*

b) (b) (4)

Sponsor's Response to FDA Response to Question 1b:

(b) (4)

5 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Question 3: Does the FDA have any comment or feedback on the format and content of the proposed NDA?

FDA Response to Question 3: No. See Additional Comments.

Sponsor's Response to FDA Response: See responses below regarding FDA Additional Comments.

Meeting Discussion of Question 3: *None.*

Question 4: Does FDA agree with the proposed approach for [redacted] (b) (4) ?

FDA Response to Question 4: No. See FDA Response to Question 1.

Sponsor's Response to FDA Response: No further comments.

Meeting Discussion of Question 4: *None.*

Additional Comments

1. **Please refer to Pilot OCE/OOD Safety Team Standard Data Requests for best practices around dataset preparation to support FDA safety analyses.**

2. **You should provide a breakdown of patient demographics and disease characteristics by age (≥65 and ≥75), ethnicity (Hispanic or Latino and not Hispanic or Latino), stage at diagnosis, histology, and specific ESR1 mutation (e.g., D538G) for ESR1m patients in Arm A and Arm B.**

3. **Based on the information provided in the clinical protocol, it appears that ESR1 mutational status was not a stratification factor for randomization. This may be a review issue if the number of patients harboring ESR1 mutations and critical baseline characteristics are not balanced between Arm A and Arm B.**

4. **You indicated that "ESR1m status was centrally determined at baseline in plasma by Guardant 360 ctDNA assay and Burning Rock Biotech OncoCompass Plus assay for patients from China (n=40)". We do not object to your proposal to work with Guardant Health to develop Guardant 360 ctDNA assay as a CDx device to aid in the selection of patients with ER+/HER2- BC positive for an ESR1 mutation for the proposed treatment. Please note that the clinical validation of the CDx(s) should be based on the same primary efficacy population that is intended to support the drug's**

approval. As ESR1m status was not determined by Guardant 360 ctDNA assay for patients from China, Guardant Health should re-test all the biomarker-positive samples and an adequate number of biomarker-negative samples (mutation not detected/screen failures), which were originally tested with the OncoCompass Plus assay, with the Guardant360 CDx assay. Although you indicated that "A concordance study demonstrated that the OncoCompass Plus results predict Guardant 360 results with high confidence", it does not obviate the need of re-testing the clinical samples that were not originally tested with the final CDx. However, if it is not feasible to re-test the subset of original clinical samples that were not screened by the CDx device (e.g., samples from Chinese population that are not available for re-testing with the final CDx), CDRH will evaluate the device safety and effectiveness based on the data submitted for review, which will also include subjects that were not screened by the final CDx due to non-availability, and be considered missing subjects. Based on the limited information provided in the meeting background package, it appears that the percentage of the missing patients would be ~6% (40/661), therefore, appropriate sensitivity analysis should be done to evaluate any impact on the clinical validation of the CDx. In addition, we recommend performing a sensitivity analysis by excluding the patients in China for each of the primary and key secondary efficacy endpoints (i.e., PFS and OS) in the NDA.

5. **If it is determined that a biomarker selected population is required for the safe and effective use of the drug, then it is expected that the CDx will be approved at the same time as drug approval. Therefore, the device sponsor should submit the sPMA to CDRH concurrently with the NDA submission to CDER for review and regulatory action.**

Sponsor's Response to FDA Response: Lilly acknowledges FDA's feedback and will address the concerns within the NDA. As recommended in Additional Comment 5, the Sponsor and Guardant are prepared and planning to file the ESR1m CDx supplemental application in parallel with the imlunestrant NDA submission.

Meeting Discussion of Additional Comments: *None.*

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the

Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

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

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[1]

[1] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

FDARA REQUIREMENTS

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

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

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

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

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

REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to*

FDA for Drug and Biological Products.[5] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

None.

[5] https://www.fda.gov/media/124795/download

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