CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208855Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	208,855
Priority or Standard	Priority
Submit Date(s)	August 15, 2017
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PDUFA Goal Date	April 15, 2018
Division/Office	DOP1/OHOP/OND
Review Completion Date	February 27, 2018
Established Name	abemaciclib
(Proposed) Trade Name	VERZENIO™
Pharmacologic Class	Kinase Inhibitor
Code name	LY2835219
Applicant	Eli Lilly
Formulation(s)	50 mg, 100 mg, 150 mg, 200 mg tablet
Dosing Regimen	150 mg orally twice daily in combination with endocrine therapy
Applicant Proposed Indication(s)/Population(s)	VERZENIO™ (b) (4) is a kinase inhibitor indicated (b) (4) • In combination with an aromatase inhibitor as initial endocrine-based therapy • In combination with fulvestrant (b) (4) following endocrine therapy • as (b) (4) women with disease progression following endocrine therapy and (b) (4) prior chemotherapy regimens in the metastatic setting.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	VERZENIO™ is a kinase inhibitor indicated: • in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

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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

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Abemaciclib (VERZENIO) is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6 that is currently approved in combination with fulvestrant for women with locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2) negative breast cancer and as monotherapy for treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. CDK 4 and 6 are activated upon binding to D-cyclins and play a key role in signaling pathways which lead to cell cycle progression and cellular proliferation.

This is a Type 9 New Drug Application (NDA) for VERZENIO in patients with advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor (HER2)-negative breast cancer.

The applicant proposed the following indications for the VERZENIO label at the time of NDA submission:

"VERZENIO™ (b) (4) is a kinase inhibitor indicated (b) (4) :

- *in combination with an aromatase inhibitor as initial endocrine-based therapy*
- *in combination with fulvestrant (b) (4) following endocrine therapy*
- *as (b) (4) for women with disease progression following endocrine therapy (b) (4) prior chemotherapy regimens in the metastatic setting"*

At the time of this NDA submission (NDA208855), NDA 208716 for abemaciclib was under review and was not yet approved. The proposed indication above merged indications for both NDAs. The proposed indications not covered under NDA 208716 are as follows:

VERZENIO™ (b) (4) is a kinase inhibitor indicated (b) (4) :

- *in combination with an aromatase inhibitor as initial endocrine-based therapy*
- *in combination with fulvestrant (b) (4)*

The proposed dose is 150 mg orally Q12H when used in combination with endocrine therapy such as aromatase inhibitors and fulvestrant.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends approval of VERZENIO (abemaciclib), according to 21 Code of Federal Regulations (CFR) 314.126(a)(b), for the following indications:

"*VERZENIO™ is a kinase inhibitor indicated:*

- *in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. "*

The basis for the recommendation for indication in combination with an aromatase inhibitor for initial endocrine based therapy is a favorable benefit-risk profile for abemaciclib when added to aromatase inhibitors in women with HR-positive, HER2-negative advanced or metastatic breast cancer. In the randomized, double-blind, placebo-controlled phase 3 study, MONARCH 3 (I3Y-MC-JPBM), there was a statistically significant and clinically meaningful improvement in progression free survival (PFS) that favored the abemaciclib plus non-steroidal aromatase inhibitor (NSAI) treatment arm. The estimated median PFS in the abemaciclib plus NSAI arm was 28.18 months compared to 14.76 months in the placebo plus NSAI arm (HR 0.540, p <0.0001). Results of blinded independent central review (BICR), subgroup analyses, and sensitivity analyses all support the results of the primary efficacy endpoint.

Overall, abemaciclib was generally tolerable with adverse reactions managed with dose reductions, temporary treatment discontinuations, supportive therapies, and/or standard medical care. The most common adverse event across the clinical program was diarrhea, which occurred in 81% of patients in the MONARCH 3 trial. Like MONARCH 1 and 2, there were few cases of Grade 3 diarrhea and this was generally treated with supportive care therapies, temporary treatment discontinuations, and dose reductions when persistent or severe. Like other cyclin dependent kinase 4/6 inhibitors in this class, neutropenia was also a common adverse reaction that occurred in 41% patients in the MONARCH 3 trial. The rate of neutropenic fever and neutropenic sepsis was low. Additional common adverse reactions were fatigue, nausea, infections, abdominal pain, alopecia, anemia, leukopenia, decreased appetite, vomiting, and headache.

The number of venous thromboembolic events was higher in patients receiving abemaciclib plus NSAI compared with those receiving placebo plus NSAI. This imbalance was apparent in other trials in the abemaciclib program as well and is currently labelled as a Warning and Precaution. With the exception of diarrhea and hematological toxicities, most adverse reactions were Grade 1 or 2, and rates of treatment discontinuation due to adverse reactions were low. The safety profile of this agent is acceptable for this patient population with a serious and life-threatening disease.

Additional supportive data from patients treated with abemaciclib in combination with exemestane from Study I3Y-MC-JPBH including clinical pharmacology review of data assessing the interaction of abemaciclib with exemestane, a steroidal aromatase inhibitor, demonstrated no clinically relevant effect on abemaciclib pharmacokinetics or vice versa. The indication for abemaciclib in combination with any aromatase inhibitor (AI) is supported by these data.

Based on MONARCH 1 and 2 study results, abemaciclib tablets received first regulatory approval under NDA 208716 on September 28, 2017, for the following indications:

- in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy; and
- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

In summary, abemaciclib in combination with an AI for the initial treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer demonstrates a favorable benefit-risk profile with adequate evidence to recommend approval. All disciplines agreed with approval of abemaciclib for this indication and did not identify any outstanding issues that precluded approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Breast cancer is the most common cancer diagnosed in women and the second leading cause of cancer related death in women in the US. Metastatic breast cancer (MBC) is estimated to affect over 150,000 women in the US in 2017, with approximately 75% of patients experiencing a relapse after initial diagnosis of stage I-III disease (Mariotto, Etzioni et al. 2017). It is projected that there will be more than 165,000 women living with MBC in the year 2020. Breast cancer in male patients is rare, with fewer than 1% of breast cancer diagnoses in male patients. In 2017, there are approximately 2400 males who are expected to be diagnosed with this disease (2002).

Metastatic breast cancer is categorized into different histopathological subtypes based on the expression of the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2). Hormone receptor (HR)-positive, HER2-negative breast cancer is the most common subtype of breast cancer in both females and males. Many patients are diagnosed and treated at an early stage with a combination of surgery and endocrine therapy, with or without radiation and/or chemotherapy.

Despite treatment of early-stage disease, approximately one-third of patients develop recurrent disease, including metastatic disease (Metzger-Filho, Sun et al. 2013). The initial therapy for HR-positive metastatic disease is endocrine based, typically with an aromatase inhibitor with or without a CDK4/6 inhibitor, tamoxifen for premenopausal women, or fulvestrant. However, not all patients respond to first-line therapy due to primary or *de novo* resistance. Metastatic breast cancer is incurable and has a 5-year survival rate of approximately 25% (American Cancer Society 2017). Improving the outcomes of patients with metastatic disease is an unmet medical need.

The applicant submitted a new drug application (NDA) for abemaciclib for a proposed indication in combination with a non-steroidal aromatase inhibitor (NSAI) for the initial endocrine-based treatment of postmenopausal women with HR-positive, HER2-negative advanced or MBC. Abemaciclib is an oral selective small molecule inhibitor of cyclin dependent kinase 4 (CDK4) and cyclin dependent kinase 6 (CDK6) and is most active against CDK4 in enzymatic assays (Ki=0.6 nM). In breast cancer cell lines, CDK4 has been shown to promote phosphorylation of the retinoblastoma protein (Rb), cellular proliferation, and growth of the tumor. Abemaciclib inhibits Rb phosphorylation and blocks the progression from G1 to the S phase in the cell cycle leading to inhibition of tumor growth in preclinical models in the short term and with sustained target inhibition, the rebound of Rb phosphorylation is inhibited preventing cell cycle re-entry and leads to tumor senescence and

apoptosis.

The benefit-risk assessment in this NDA is primarily based on the phase 3 trial MONARCH 3 of abemaciclib in combination with NSAI. MONARCH 3 was a randomized, double-blind, placebo-controlled trial in postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer with no prior systemic therapy in this disease setting. This was a well-designed trial with an appropriate comparator arm. The primary endpoint was investigator-assessed progression-free survival (PFS) using RECIST 1.1 criteria. The estimated median PFS in the abemaciclib plus NSAI arm was 21.18 months compared with 14.76 months in the placebo plus NSAI arm (HR=0.540, 95% CI: 0.418, 0.698, p<0.0001). Abemaciclib plus NSAI demonstrated a 7.1-month improvement in the estimated median PFS when compared with placebo plus NSAI. Results from a BICR audit, subgroup analyses, and sensitivity analyses all supported the primary efficacy endpoint results. Overall survival (OS) data are immature.

The applicant requested (b) (4) abemaciclib in combination with fulvestrant for (b) (4) setting based on the 44 endocrine-naïve patients that enrolled in the MONARCH 2 study, as well as the recent updating of the fulvestrant label to include the initial endocrine therapy setting for postmenopausal patients. Due to the small numbers of patients enrolled and the inclusion of both pre- and postmenopausal women in the MONARCH 2 endocrine-naïve cohort, (b) (4)

Overall, abemaciclib was generally tolerable with adverse reactions that were managed by dose reductions, temporary treatment discontinuations, and/or supportive medications and standard medical care. Diarrhea was the most common adverse event across the clinical program with 81% of patients experiencing this in MONARCH 3. This rate is similar to that across the MONARCH 2 and MONARCH 1 trial populations and is currently listed in Warnings and Precautions in the USPI. Neutropenia was additionally common as seen in other agents in this class with 41% of patients having an AE of neutropenia in MONARCH 3. Neutropenia is similarly listed in Warnings and Precautions in the USPI.

Additional adverse effects seen at increased incidence with the use of this agent include venous thromboembolic events. This was identified in the initial review with safety data from multiple trials within the abemaciclib clinical development program. A similar higher incidence of VTE events was seen in the study therapy arm and deaths due to VTE were seen in other studies. This is currently listed in Warnings and Precautions and data regarding the incidence of VTE in the USPI are included for the MONARCH 3 study.

In conclusion, abemaciclib in combination with NSAI demonstrated a statistically significant improvement in PFS in a large, randomized, double blind study. The indication was broadened to include the class of aromatase inhibitor agents as these agents are used interchangeably in clinical

practice and did not demonstrate any new safety signal or drug interaction when used with abemaciclib. Therefore, the benefit-risk profile is favorable to support approval of:
VERZENIO™ in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In 2017 it is estimated that there are over 150,000 women in the US with metastatic breast cancer. MBC is incurable and has a 5-year survival of approximately 25%.	**Locally advanced and metastatic breast cancer are serious and life-threatening conditions**
Current Treatment Options	• The goals of treating MBC and locally advanced unresectable breast cancer are palliative in nature with the aim to prolong survival and to reduce cancer-related symptoms. Endocrine therapy options for postmenopausal women with HR-positive, HER2-negative MBC include aromatase inhibitors such as anastrozole, letrozole, and exemestane and the estrogen receptor downregulator fulvestrant. Endocrine therapies in combination with CDK4/6 inhibitors is another first line treatment option.	**There is an unmet medical need to improve the outcomes of patients with HR-positive, HER2-negative advanced or metastatic breast cancer.**
Benefit	• The clinical data from the randomized, double-blind, placebo controlled, phase 3 trial (MONARCH 3) in postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer who have not had systemic therapy in this disease setting presented in this NDA demonstrates an improvement in PFS for abemaciclib plus NSAI compared to placebo plus NSAI. The estimated median PFS in the abemaciclib plus NSAI arm was 21.18 months as compared to o 14.76 months in the placebo plus NSAI arm (HR 0.540, p <0.0001). OS results were immature at the time of the final PFS analysis with a total of 63 deaths (19.2%) in the	**Evidence of effectiveness was supported by a statistically significant and clinically meaningful PFS improvement with the addition of abemaciclib to NSAI therapy. MONARCH 3 was a large, double-blind, randomized, placebo-controlled trial. Additionally, abemaciclib demonstrated a statistically significant and clinically meaningful improvement in PFS in the MONARCH 2 trial as well, further supporting**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	abemaciclib plus NSAI arm and 30 deaths (18.2%) in the placebo plus NSAI arm as of November 3, 2017. Confirmed overall response rate (ORR) for patients with measurable disease was 55.4% (95% CI 49.5, 61.4) in the abemaciclib plus NSAI arm and 40.2% (95% CI 31.8, 48.5) for the placebo plus NSAI arm. Estimated median duration of response (based upon confirmed responses) was not estimable (95% CI = 25.7 months, not estimable) in the abemaciclib + NSAI arm and 17.5 months (95% CI = 11.6 months, 22.2 months) in the placebo + NSAI arm.	**the evidence of benefit of the addition of this agent to endocrine based therapy. Supportive ORR, blinded independent central review (BICR)-assessed PFS, and subgroup analyses further substantiate the evidence of abemaciclib benefit. Despite immature OS, in this population, the substantial improvement in PFS represents a clinically meaningful benefit due to the delay of progression and postponement of subsequent toxic therapies. A PMC was agreed upon to submit OS analysis updates, including the final OS analysis.**
Risk and Risk Management	• Diarrhea was reported in >80% of patients in the MONARCH 3 study who received abemaciclib plus NSAI. This was similar to other studies within the development program. Diarrhea was the most common reason for treatment interruption and/or dose reduction. There were few Grade 3 events and no Grade 4 or Grade 5 events attributed to diarrhea. • Neutropenia was reported as an AE in 41% of patients who received abemaciclib plus NSAI on the MONARCH 3 study. • There is no proposal for a risk management plan. • Clinical and pharmacokinetic data from the use of abemaciclib in combination with exemestane showed no evidence of drug-drug interactions or new safety signals	**The safety profile of abemaciclib is acceptable for the intended population. Toxicities were manageable with appropriate treatment interruption and/or dose modifications which are clearly delineated in labeling. Warnings and Precautions in labeling detail the serious risks of the drug.** **Additional data regarding the combination of abemaciclib with exemestane support the indication of abemaciclib in combination with the entire class of aromatase inhibitors.** **The safe use of abemaciclib can be managed through accurate labeling and routine oncology care. No REMS is indicated.**

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
	√	Clinical outcome assessment (COA) data, such as			[e.g., Section 6.1 Study endpoints]
			√	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)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X

Laleh Amiri-Kordestani, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

In the US and Europe, breast cancer is the most common cancer affecting women and is the second leading cause of cancer related death in females (National Cancer Institute 2017). In 2017, metastatic breast cancer (MBC) is estimated to affect over 150,000 women in the US with most of these patients experiencing relapse after an initial diagnosis of stage I-III disease (Mariotto, Etzioni et al. 2017). It is projected that in the year 2020, there will be more than 165,000 living with metastatic breast cancer.

Unlike early stage breast cancer, metastatic breast cancer is incurable and treatments that extend progression free and overall survival are used until evidence of disease progression or lack of tolerability. The median overall survival for patients with metastatic disease is currently 2-3 years with a five-year survival rate of approximately 25% (Cardoso, Costa et al. 2017). The natural history of metastatic disease differs by sites of disease (visceral vs. bone only vs. other) as well as the breast cancer subtype (hormone receptor positive, HER2-positive, and triple negative breast cancer) (Kobayashi, Ito et al. 2016, Wedam, Beaver et al. 2016). According to observational data, HR-positive, HER2-negative MBC has an estimated median survival of 24.8 months (95% CI 21.3-30.3 months). The estimated median survival for those with bone only disease in this same population was 39.3 months while those with visceral disease had an estimated survival of 15.7 months (Lobbezoo 2013). Similar data were found in the SEER database and an analysis demonstrated that breast cancer subtype was also associated with metastatic disease pattern (Wu 2017).

Symptoms associated with metastatic breast cancer are dependent on the site(s) of metastatic disease and may include pain, fatigue, and shortness of breath. Surveys of patients with advanced breast cancer indicate that these patients often feel social isolation and effects on their personal and professional relationships, including issues with employment, income, and household duties (Cardoso, Harbeck et al. 2016).

2.2. Analysis of Current Treatment Options

Initial treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative metastatic breast cancer is often endocrine based therapy such as an aromatase inhibitor (anastrozole, letrozole, exemestane) or tamoxifen. Cyclin-dependent kinase inhibitors, including palbociclib and ribociclib, can be used in combination with aromatase inhibitors and have been shown to improve progression-free survival in the initial endocrine-

based therapy setting. Data have also demonstrated that fulvestrant has improved progression-free survival compared with anastrozole in the initial endocrine-based therapy setting.

In the PALOMA-2 trial, postmenopausal women treated with palbociclib and letrozole had an estimated PFS of 24.8 months as compared to the estimated PFS for those treated with placebo and letrozole being 14.5 months (HR 0.576, 95% CI 0.463, 0.718, p<0.0001). In the MONALEESA 2 study, the combination of ribociclib with letrozole demonstrated an estimated PFS that was not yet reached as compared to an estimated PFS of 14.7 months in the placebo plus letrozole arm (HR 0.556, 95% CI 0.429, 0.720, p<0.0001).

For initial endocrine-based therapy for locally advanced or metastatic HR-positive, HER2-negative breast cancer, aromatase inhibitors, tamoxifen, or fulvestrant are typically used. Initial therapy may be in combination with a CDK 4/6 inhibitor. Depending on the patient's disease burden and other characteristics, chemotherapy may be used as well. Table 1 includes a summary of initial current therapies for HR-positive, HER2-negative metastatic breast cancer.

Table 1. Current Initial Treatments Available for HR-positive, HER2-negative MBC

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Endocrine Therapies						
Aromatase Inhibitors (letrozole, anastrazole, exemestane)	For the treatment of postmenopausal women with hormone receptor positive advanced breast cancer	Anastrozole 1995 Letrozole 1997 Exemestane 1999	One tablet taken daily	Anastrozole HR of 1.42, 95% CI 1.11, 1.82 with an estimated median TTP of 11.1 months in the anastrozole arm compared to 5.6 months in the tamoxifen arm Letrozole HR of 0.72, 95% CI 0.62, 0.83 with an estimated PFS of 9.4 months in the letrozole arm and 6.0 months in the tamoxifen arm Exemestane HR of 0.84, 95% CI 0.72, 0.99, with an estimated median TTP of 20.3 weeks in the exemestane arm and 16.6 weeks in the	Reduction in bone mineral density, increase in risk of ischemic cardiovascular events, increases in cholesterol, fatigue, dizziness, somnolence	

				megestrol acetate arm		
Fulvestrant	For the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy	2002, 2017	500 mg IM injection monthly after an initial loading dose of 500 mg IM on days 1 and 15 of month one	Results from the FALCON study, a randomized controlled trial of fulvestrant compared to anastrozole demonstrated an estimated median PFS of 16.6 months for fulvestrant vs. 13.8 months for anastrozole (HR 0.797, p=0.049). The ORR of fulvestrant was 46.1% (95% CI 38.9, 53.4) and anastrozole was 44.9% (95% CI 37.8, 52.1). Median DoR was 20.0 months for fulvestrant vs. 13.3 months for anastrozole	Hot flashes, nausea, arthralgia, myalgia, fatigue, back pain, injection site pain, embryo-fetal toxicity, increased hepatic enzymes	
Tamoxifen	For the treatment of metastatic breast cancer in women and men. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from tamoxifen therapy.	1998	20 mg tablet taken orally daily	ORR of 50% in male patients. Data from the Ingle, Pritchard and Buchanan studies demonstrated similar ORR, TTF and survival when compared to ovarian ablation in premenopausal patients.	Hot flashes, arthralgias, fatigue, uterine carcinoma, increased thromboembolic risk	

Toremifene	For the treatment of metastatic breast cancer in postmenopausal women with estrogen-receptor positive or unknown tumors	2011	60 mg tablet once daily orally	ORR ranged from 20.4% to 31.3%. Estimated median TTP in Nordic study was 10.2 months as compared to 7.3 months for tamoxifen 40 mg.		Hot flashes, sweating, nausea, dizziness, vomiting, edema. Increased risk of hypercalcemia when used in combination with drugs that decrease urine calcium excretion. Electrolyte abnormalities including hypokalemia and hypomagnesemia. QT prolongation.
Endocrine Therapy with CDK 4/6 inhibitor						
Palbociclib (Ibrance)	For the treatment of hormone receptor (HR) positive, human epidermal growth factor 2 (HER2)-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial	2015, 2016	125 mg by mouth daily with food for 21 days followed by 7 days off treatment	Estimated median PFS of palbociclib and NSAI was 24.8 months (22.1, NE) and 14.5 months (12.9, 17.1) (HR 0.576, p<0.0001), ORR for palbociclib and letrozole was 55.3% (49.9, 60.7) and placebo plus letrozole was 44.4% (36.9, 52.2)	Neutropenia, Embryo-fetal toxicity, fatigue	There was initial concern for increase in VTE events, however this did not appear to be significant at the safety update in 2017

	endocrine based therapy in postmenopausal women					
Ribociclib (Kisqali)	In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer	2017	Three (3) 200 mg tablets taken once daily with or without food for 21 consecutive days followed by 7 days off treatment	Ribociclib + letrozole estimated median PFS not reached (19.3, NR) vs. placebo and letrozole 14.7 months, HR 0.556 (0.429, 0.720), p <0.0001 ORR ribociclib and letrozole 52.7% (46.6, 58.9) vs. placebo and letrozole 37.1% (31.1, 43.2)	QT prolongation, neutropenia, hepatotoxicity, embryo fetal toxicity	

Source: *FDA reviewer analysis using information from Drugs @ FDA*

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Abemaciclib tablets received regulatory approval under NDA 208716 on September 28, 2017, for the following indications:

- in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy; and

- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

3.2. Summary of Presubmission/Submission Regulatory Activity

September 15, 2009: IND 106100 for LY2835219 (abemaciclib) was submitted in the United States for the treatment of advanced cancer to the Division of Oncology Products 1.

October 16, 2009: The First in Human dose study, I3Y-M0JPBA was initiated.

December 18, 2013: A type B Pre-Phase 3 meeting was conducted to discuss MONARCH 1, 2, and 3 studies. FDA recommended to the applicant to conduct a randomized trial with a time-to event endpoint for JPBN (MONARCH 1) single agent study.

February 24, 2014: MONARCH 1 original protocol submitted to IND 106100.

April 1, 2014: MONARCH 2 original protocol submitted to IND 106100.

July 8, 2014: The FDA acknowledged Eli Lilly's plan to request a full waiver from Pediatric Research Equity Act requirements based on their agreed upon Initial Pediatric Study Plan (iPSP)

September 8, 2017: MONARCH 3 original protocol submitted to IND 106100.

October 5, 2015: FDA granted Breakthrough Therapy Designation as metastatic breast cancer is a serious or life-threating disease and preliminary clinical evidence generated by FIH Phase 1 Study JPBA appeared to demonstrate improvement in ORR in patients with HR-positive, HER2 negative metastatic breast cancer who had been treated with previous chemotherapies.

November 12, 2015: FDA granted Fast Track Designation for the investigation of abemaciclib for patients with refractory hormone receptor positive advanced or metastatic breast cancer.

December 16, 2015: Type B comprehensive multidisciplinary initial breakthrough meeting held to discuss the clinical development program and manufacturing development strategy of abemaciclib.

May 5, 2017: NDA 208716 was submitted electronically to FDA.

July 7, 2017: A Type B Pre-NDA meeting was conducted for MONARCH 3.

August 15, 2017: NDA 208855 was submitted electronically to FDA.

September 28, 2017: NDA 208716 was approved.

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

4.1. Office of Scientific Investigations (OSI)

The Clinical Inspection Summary was provided by Lauren Iacono-Connors, Good Clinical Practice Assessment Branch, Division of Good Clinical Practice Compliance, Office of Scientific Investigations (OSI). The OSI inspected the CRO and three of the highest-accruing sites in France, Canada, and Israel.

Table 2. Summary of OSI Findings

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI #1: Mario Campone, MD (Site 356) Bd Jacques Monod Saint Herblain Cedex, 44805 FRANCE	Protocol: I3Y-MC-JPBM Subjects: 14	December 18-22, 2017	NAI
CI #2: Orit Freedman, MD (Site 203) R. S. McLaughlin Durham, Regional Cancer Centre One Hospital Court Oshawa, Ontario	Protocol: I3Y-MC-JPBM Subjects: 8	December 18-21, 2017	NAI

CANADA			
CI #3: Shani Paluch-Shimon, MD (Site 754) 2 Sheba Road Tel Hashomer Ramat Gan, Israel 5266202 ISRAEL	Protocol: I3Y-MC-JPBM Subjects: 10	December 10-12, 2017	NAI
CRO: Performed as the Independent Review Committee (IRC) for (b) (4)	Protocol: I3Y-MC-JPBM Randomly selected subjects: 26	October 10-12, 2017	NAI

The inspection of the clinical sites and the CRO revealed no significant deficiencies. For the clinical sites, the primary endpoint data were verifiable with source records maintained at the site. There was no evidence of under-reporting of AEs. The CRO inspection of randomly selected subjects were compared to the data listings submitted to the application and no discrepancies were noted.

See Clinical Inspection Summary written by Sharon Gershon, PharmD, Good Clinical Practice Assessment Branch, Division of Good Clinical Practice Compliance, OSI, for full details.

Reviewer Comments: *There were no findings in the inspection that would affect the results of the primary endpoint or safety data analysis.*

4.2. Product Quality

Please see review from Xiao Hong Chen, PhD. The final evaluation deemed the provided data and justifications acceptable to support the applicant's categorical exclusion per 21 CFR25.31 (b). Additionally, refer to NDA 208716 CMC review.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

No device or companion diagnostic is included in this application.

APPEARS THIS WAY ON ORIGINAL

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Pharmacology and toxicology data were previously reviewed under NDA 208716. The applicant did not submit changes to nonclinical sections of the prescribing information. From the nonclinical perspective, VERZENIO™ (abemaciclib) is recommended for approval for the proposed indication.

X	X
Tiffany Ricks, PhD Primary Reviewer	Todd Palmby, PhD Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

Abemaciclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). VERZENIO™ (abemaciclib tablet) was initially approved on September 28, 2017, under NDA 208716, in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy, and as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. The approved dosing regimens are 200 mg BID in the monotherapy and 150 mg BID in the combination therapy.

In the current submission, the applicant seeks regular approval of VERZENIO™ in combination with an aromatase inhibitor as an initial endocrine-based therapy for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer, and in combination with fulvestrant (b) (4) for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer. The proposed dosing regimen is 150 mg administered orally twice daily (BID), for both proposed indications.

Clinical Pharmacology section of the current NDA is supported by data from two clinical studies, JPBM (MONARCH 3) and JPBH, as well as the content of population pharmacokinetics (popPK) analysis, exposure-response (E-R) analysis, and assessment of the QT/QTc prolongation potential, which cross-referenced corresponding evaluations under NDA 208716.

The efficacy and safety of abemaciclib with aromatase inhibitors (i.e. anastrozole or letrozole) was demonstrated in Study MONARCH 3. E-R analysis suggested positive relationships on efficacy (tumor shrinkage and PFS) and safety (risks of diarrhea and neutropenia). The efficacy and safety of abemaciclib with fulvestrant as the initial endocrine therapy was evaluated in a subgroup of patient in Study MONARCH 2. The E-R relationships in MONARCH 3 are generally consistent with those in original NDA 208716. Available data does not suggest PK interactions between abemaciclib and endocrine therapies including fulvestrant, anastrozole, letrozole, tamoxifen, or exemestane. The proposed dosing regimen is acceptable from a Clinical Pharmacology perspective.

6.1.1. Recommendations

The Office of Clinical Pharmacology recommends the approval of NDA 208855 from a Clinical Pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Evidence of effectiveness is supported by data submitted in this NDA.
General dosing instructions	Acceptable. Positive ER relationships were observed on safety and efficacy endpoints. A lower starting dose is expected to compromise efficacy. A higher starting dose is expected to increase the risks of neutropenia and dose interruption.
Dosing in patient subgroups	No changes based on data submitted in this NDA.
Labeling	Acceptable.
Bridge between the to-be-marketed and clinical trial formulations	Not Applicable. Bridge between the to-be-marketed and clinical trial formulation was evaluated in NDA 208716.
Other (specify)	Not Applicable.

6.1.1. Post-Marketing Requirements and Commitments

Not Applicable.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacology and Clinical Pharmacokinetics characteristics of abemaciclib are summarized in Section 6.2.1 of the Multidisciplinary Review of NDA 208716. NDA 208855 does not contain new pharmacology or PK data that warrants substantial revision of the Clinical Pharmacology section in the product label.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Based on PK and E-R analyses of abemaciclib in NDA 208716 and NDA 208855 submissions, the proposed dosing regimen of 150 mg BID is acceptable for use with aromatase inhibitors or fulvestrant in the general population for which the indication is being sought.

Therapeutic Individualization

Data submitted in this NDA does not suggest changes to therapeutic individualization as approved in NDA 208716 (refer to Section 6 of the Multidisciplinary Review of NDA 208716).

Outstanding Issues

Data submitted in this NDA does not present outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology and Clinical Pharmacokinetics characteristics of abemaciclib are summarized in Section 6.3.1 of the Multidisciplinary Review of NDA 208716. In brief, abemaciclib has an absolute bioavailability of 0.45 (19% CV) and a median Tmax of 8 hours. Abemaciclib is mainly eliminated by hepatic metabolism and demonstrates approximate linearity between 50 to 200 mg dose levels. Based on popPK analysis, geometric mean systemic volume of distribution is approximately 690.3 L (49% CV), the estimated geometric mean hepatic clearance in patients was 26.0 L/h (51% CV), and the mean plasma elimination half-life for abemaciclib in patients was 18.3 hours (72% CV). Food does not have a clinically meaningful effect on abemaciclib PK. NDA 208855 does not contain new pharmacology or PK data that warrants substantial revision of the Clinical Pharmacology section in the product label.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program support the proposed starting doses in the general patient population for which the indications are being sought?

Yes. Clinical, PK, and E-R analysis supported the 150 mg BID dosing regimens for the proposed indications.

Dose selection rationale

Dose selection for MONARCH 3 was based on findings from phase 1 Studies JPBA and JPBH. In Study JPBA (reviewed in NDA 208716), the maximum tolerated dose was determined to be 200 mg BID and clinical activity was evident at both 150 mg and 200 mg BID. In addition, the range of steady-state exposures was comparable for abemaciclib at 150 mg and 200 mg BID. Study JPBH revealed a higher incidence of treatment-emergent Grade 3 diarrhea at the 200 mg dose level when abemaciclib was given in combination with NSAI than when abemaciclib was administered alone. Therefore, 150 mg BID was recommended for MONARCH 3.

Dose selection rationale for endocrine therapy-naïve patient with fulvestrant was identical to that for MONARCH 2 study (reviewed in NDA 208716).

Exposure-response analysis

In study MONARCH 3, E-R analyses on efficacy indicated that higher abemaciclib concentrations were associated with higher tumor shrinkage rate and lower hazard for disease progression. With the 150 mg BID starting dose and the current dose reduction scheme, the actual average dose in MONARCH 3 is 132 mg BID. The next lower level of starting dose, 100 mg BID, is expected to compromise efficacy. E-R analyses on safety identified positive relationship between abemaciclib exposure and the inhibitory effect on neutrophil production and hence the risks of neutropenia. The next higher level of starting dose, 200 mg BID, is expected to increase the risks of neutropenia. In addition, prior experience with abemaciclib suggested that abemaciclib at the 200 mg BID dose is associated with shorter time to diarrhea event and higher risks of diarrhea than the 150 mg BID. There is no evidence to suggest comparable of diarrhea in the MONARCH 3 population at a higher starting dose than 150 mg BID.

Consistent with E-R analyses for Study JPBL (MONARCH 2, reviewed in NDA 208716), post hoc analyses in the endocrine therapy-naïve patients suggested that the higher abemaciclib exposures were associated with higher risks of neutropenia.

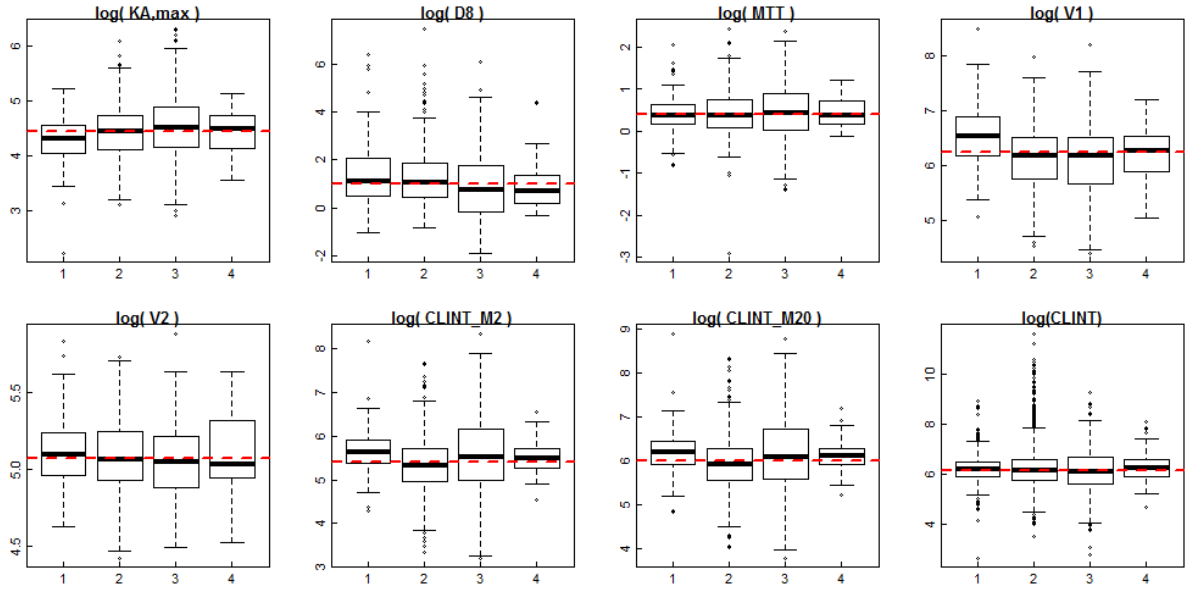
Overall, there is no evidence to suggest an alternative starting dose for the proposed indications.

Are there clinically meaningful drug-drug interactions between abemaciclib and anastrozole, letrozole, or fulvestrant, in the study population?

No. There is no evidence to suggest a clinically meaningful impact of fulvestrant, anastrozole, letrozole, tamoxifen, or exemestane, on abemaciclib PK, and vice versa.

In the proportion of patients who provided evaluable PK samples in MONARCH 3 (excluding 4 patients with extreme parameter estimates) and in the subgroup of MONARCH 2 patients who received abemaciclib as the initial endocrine based therapy, the post hoc estimates of PK parameters were comparable to those in the general patient population, suggesting a lack of apparent effect of anastrozole, letrozole, or fulvestrant in the target populations (Figure 1). In Study JPBH, abemaciclib exposures were comparable across treatment arms in patients taking anastrozole, letrozole, tamoxifen, or exemestane, suggesting a lack of effect of tamoxifen and exemestane on abemaciclib PK (Figure 11 in Appendix).

Figure 1. Comparison of PK parameter distribution based on popPK analysis.

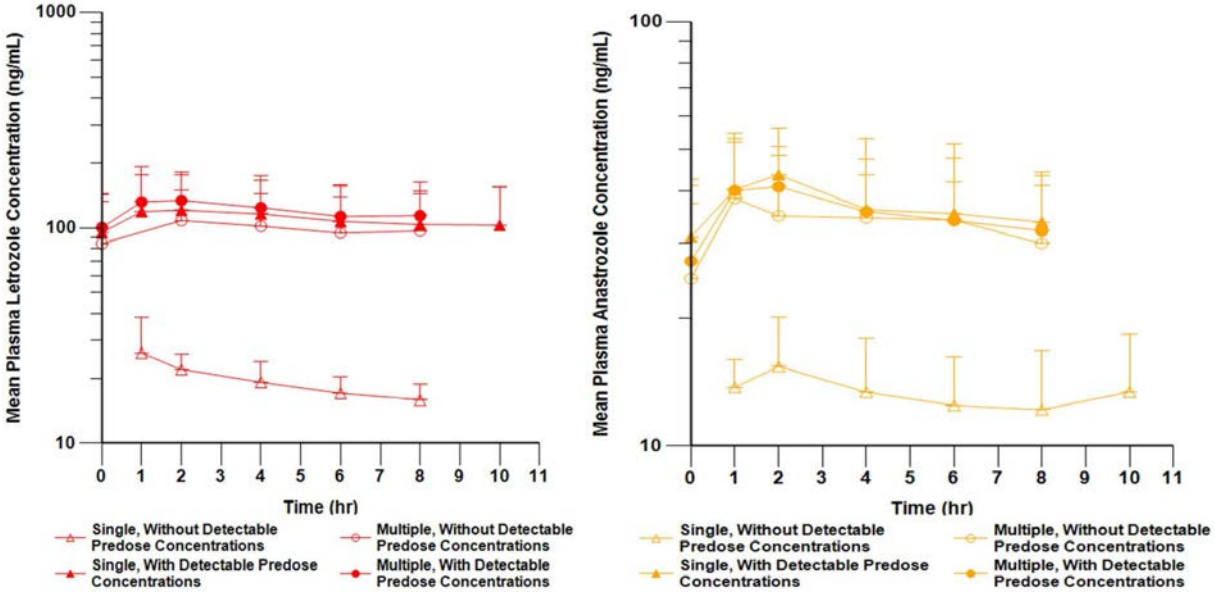


Group 1: MONARCH 1. Group 2: MONARCH 2. Group 3: MONARCH 3. Group 4: in the endocrine treatment naïve subgroup in MONARCH 2. Red dotted line: median value in the combined MONARCH 1-3 studies.
Source: Reviewer's analysis

In Study JPBH, the steady-state plasma letrozole or anastrozole levels observed after once-daily dosing in the patients who initiated letrozole or anastrozole with abemaciclib were similar to those observed on the first day of combination dosing of those who may have previously been taking letrozole or anastrozole (Figure 2). In the patients with quantifiable pre-dose letrozole or anastrozole levels, letrozole or anastrozole C_{max} and $AUC_{0\text{-last}}$ were similar on Day 1 after a single abemaciclib dose and on Day 28 after multiple twice-daily doses of abemaciclib. Therefore, abemaciclib does not appear to influence letrozole or anastrozole PK. Similar analysis in tamoxifen and exemestane treatment arms suggested a lack of effect from abemaciclib on tamoxifen and exemestane PK (Figure 10 in Appendix).

In MONARCH 2 study, fulvestrant plasma concentrations were similar between the abemaciclib and placebo arms, in both the overall population and in the subgroup of patients who take abemaciclib as initial endocrine based therapy (Table 3). The trough plasma levels of fulvestrant observed on Cycle 2 Day 1 were similar to those previously reported in patients receiving fulvestrant 500 mg as a single agent [Pritchard et al. Breast Cancer Res Treat. 2010 Sep;123(2):453-61.]. Therefore, abemaciclib did not appear to influence fulvestrant PK.

Figure 2. Mean (Std Dev) plasma concentrations versus time profiles of letrozole (Left) or anastrozole (Right) following administration of abemaciclib in combination with 2.5 mg of letrozole or 1 mg of anastrozole every 24 hours.



Source: JPBH clinical study report, Figure 7.12 and 7.13.

Table 3. Summary of fulvestrant plasma concentrations in Study MONARCH 2.

Cycle (C) / Day (D)	Sampling Time	Group	Fulvestrant Concentration (ng/mL)[a]		
			Abemaciclib 150 mg + Fulvestrant 500 mg	Abemaciclib 200 mg + Fulvestrant 500 mg	Placebo + Fulvestrant 500 mg
C1D1	2 to 4 h after fulvestrant dose	All	1.42 (100%), n=165	1.89 (112%), n=75	1.35 (105%), n=87
		EN naïve	1.77 (99%), n=10		1.40 (122%), n=10
C1D15	Pre fulvestrant dose	All	10.3 (44%), n=294	10.7 (54%), n=126	10.8 (50%), n=140
		EN naïve	NA		NA
C2D1	Pre fulvestrant dose	All	14.7 (39%), n=266	14.1 (39%), n=108	14.3 (41%), n=132
		EN naïve	11.6 (46%), n=27		13.1 (49%), n=14
C3D1	Pre fulvestrant dose	All	12.2 (34%), n=223	11.8 (33%), n=79	12.0 (35%), n=114
		EN naïve	9.90 (41%), n=24		10.6 (43%), n=14

[a] Geometric mean (CV%).

Source: Adapted from JPBL clinical study report, Table 11.26, with reviewer's analysis on endocrine naïve data.

X X

Nan Zheng, PhD
Primary Reviewer

Jingyu (Jerry) Yu, PhD
Team Leader

X

Qi Liu, PhD
Team Leader

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Data from two clinical studies were submitted to this supplemental NDA. This includes the phase 3 randomized, double-blind, placebo-controlled, multicenter MONARCH 3 study (I3Y-MC-JPBM) of a nonsteroidal aromatase inhibitor (anastrozole or letrozole) with or without abemaciclib for postmenopausal women with hormone receptor positive, HER2 negative, locally advanced or metastatic breast cancer. Additionally, I3Y-MC-JPBH, the phase 1b study of LY2835219 in combination with endocrine therapies for patients with HR-positive, HER2-negative metastatic breast cancer was submitted.

The primary evidence to support this sNDA is derived from the MONARCH 3 trial.

Table 4. Listing of Clinical Trials Relevant to sNDA 208855

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
MONARCH 3 I3Y-MC-JPBM	02246621	Randomized, double-blind, placebo-controlled Phase 3 trial	150 mg orally BID with letrozole 2.5 mg orally daily or anastrozole 1 mg orally daily	Investigator assessed PFS	Until disease progression or lack of tolerability	579 patients were screened and 493 patients were randomized to the ITT population	Postmenopausal women with HR positive, HER2-negative metastatic breast cancer	158 sites in 22 countries
I3Y-MC-JPBH	02057133	Phase 1b, nonrandomized, open-label study	200 mg abemaciclib orally BID with letrozole, anastrozole, tamoxifen, or exemestane	ORR	Until disease progression or lack of tolerability	67 patients	Women with HR positive, HER2-negative metastatic breast cancer	15 sites in the US
		Studies to Support Safety						
MONARCH 2 I3Y-MC-JPBL	02107703	Randomized, double-blind, placebo-controlled Phase 3 trial	150 mg orally BID with fulvestrant 500 mg IM on days 1 and 15 of Cycle 1 and then Day 1 of each cycle	PFS	Until disease progression or lack of tolerability	855 patients entered 669 patients were randomized/enrolled into the ITT population	Women with HR positive, HER2-negative metastatic breast cancer	145 sites in 19 countries

							after progression on endocrine therapy	
MONARCH 1 I3Y-MC-JPBN	021024 90		200 mg orally BID	ORR	Until disease progression or lack of tolerability	184 patients entered 132 patients enrolled and received at least one dose of treatment	Female patients with HR positive, HER2-negative metastatic breast cancer that has spread	35 sites in 4 countries

7.2. Review Strategy

The clinical and statistical review is based on the clinical study report and datasets from the randomized phase 3 MONARCH 3 trial, I3Y-MC-JPBM. Dr. Lynn Howie conducted the efficacy and safety reviews. Dr. Erik Bloomquist conducted the statistical review.

Data Sources

The review included the following:

1. Literature review of hormone receptor-positive, HER2-negative metastatic breast cancer in postmenopausal women, data regarding the use and indication of fulvestrant in the initial therapy setting for postmenopausal women with HR-positive, HER2-negative MBC, and the cyclin D1 CDK 4/6 pathway.
2. Research of the FDA database to characterize the regulatory history of abemaciclib IND 106100 including review of meeting minutes during drug development.
3. Review of submitted CSRs, protocols, protocol amendments, and selected datasets for MONARCH 3 (I3Y-MC-JPBM) and MONARCH 2 (I3Y-MC-JPBL).
4. Review of selected case report forms (CRFs) for MONARCH 3.
5. Review of patient narratives for serious adverse events and deaths in MONARCH 3.
6. Review of responses to clinical and biostatistical queries sent to the applicant.
7. Review of consultation reports from the Office of Scientific Investigation (OSI).
8. Consultation with the multidisciplinary review team including Biostatistics and Clinical Pharmacology.
9. EDR for electronic data sources is: \\CDSESUB1\evsprod\NDA208855\0001
10. SDTM and ADaM datasets were submitted along with software code for data analyses.

Data Analysis and Quality

The data submitted with this application were in ADaM and SDTM formats. The data were of good quality and the applicant's analyses were reproducible. Requests for additional information from the applicant through the review process were addressed in a timely fashion. Randomization could be verified through the datasets. The applicant submitted information about their data quality assurance plan including their site inspections, the use of a central laboratory for hematology and serum chemistry labs, and provided site audit summaries.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. MONARCH 3

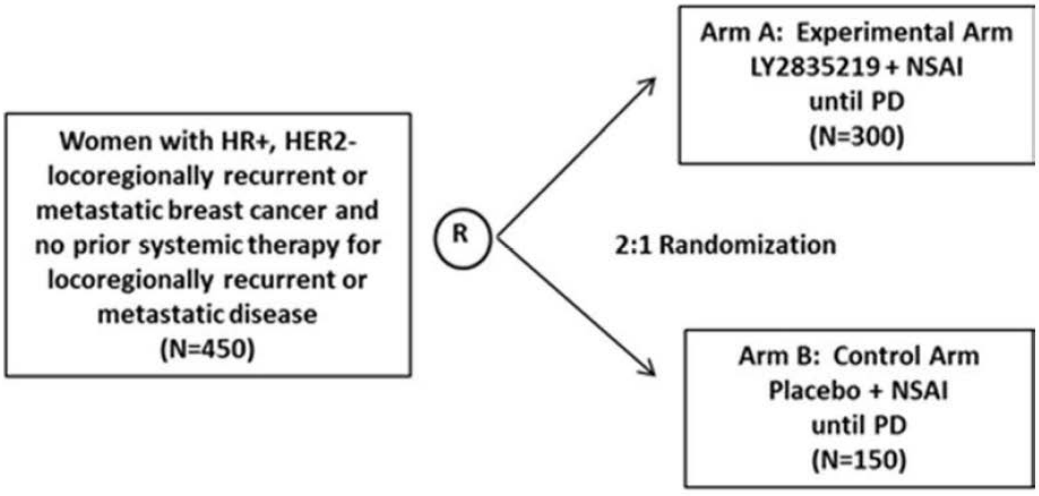
Trial Design

MONARCH 3 (I3Y-MC-JPBM) was a phase 3, double-blind, randomized trial of an NSAI (letrozole or anastrozole) with or without abemaciclib in postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer with no previous systemic therapy in this disease setting.

The primary objective was to evaluate the efficacy of abemaciclib plus NSAI compared to NSAI alone based on investigator-assessed progression-free survival (PFS) using RECIST 1.1.

Patients were randomized in a 2:1 ratio to the treatment arm using the stratification factors of nature of disease (visceral vs. bone-only vs. other) and prior (neo)adjuvant therapy. Patients were instructed to take abemaciclib at 150 mg twice-daily or placebo orally twice daily continuously over a 28-day cycle. The NSAI agent was to be taken once daily as well (letrozole 2.5 mg daily, anastrozole 1 mg daily). Figure 3 demonstrates the MONARCH 3 trial schema.

Figure 3. MONARCH 3 Study Schema



Abbreviations: HER2- = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; N = number; NSAI = nonsteroidal aromatase inhibitor; PD = progressive disease; R = randomized.

Source MONARCH 3 CSR, page 38

After completing study screening, follow up visits occurred on day 1 of each 28-day cycle. Radiological tumor assessment (breast MRI, CT scan or MRI of the chest, abdomen, and pelvis) occurred on days 21-28 of cycle 2 and every second cycle continuing through cycle 18 and on days 21-28 of every third cycle thereafter. If there was evidence of clinical progression, imaging was to be performed within 14 days of this. Bone scintigraphy was performed on day 21-28 of every sixth cycle beginning with cycle 6. X-ray, CT scan with bone windows, or MRI was to be performed on day 21-28 of every second cycle beginning with cycle 2 through cycle 18 and every third cycle thereafter for patients with bone lesions identified at baseline. If there was evidence of clinical progression, imaging was to be performed within 14 days of this. For patients with new lesions identified by post-baseline scintigraphy, targeted assessment with x-ray, CT scan with bone windows, or MRI was to be performed to confirm findings. Patients were discontinued from study drugs in the event of progressive disease (PD) as defined by RECIST 1.1, enrollment in any other clinical trial involving an investigational drug or other research deemed to not be scientifically or medically compatible with this study, or based on investigator, patient, or sponsor decision.

Patient-reported outcomes (PRO data) were collected using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), EORTC QLQ-BR23 (breast) questionnaire, and the health status score from the EuroQol 5-Dimension 5-Level (EQ-5D-5L). PRO data were collected on day 1 cycle 1 and then day 1 of every second cycle beginning with cycle 3 through cycle 19 and on day 1 of every third cycle after cycle 19.

Study Design and Choice of Control Group

The study design was randomized, controlled, and double-blinded to minimize systematic bias in the selection and assignment of patients to study therapy. Non-steroidal aromatase inhibitors are considered standard of care in patients with HR-positive, HER2-negative metastatic breast cancer per clinical practice guidelines and this choice of control allowed for direct statistical estimation of benefits and harms of this therapy and minimized bias in assessing and interpreting treatment effects. Patients were stratified by factors thought be associated with clinical outcomes to further reduce the potential for bias.

Reviewer Comments: *The choices of study design and control arm are appropriate in this patient setting. It is appropriate to stratify randomization based on nature of disease given the known differences in the natural history of patients with visceral and bone only disease. Additionally, it is notable that PRO measures were not collected frequently and that these measures may not be as sensitive to capturing patient experienced toxicities given that they were captured every other visit and supportive care measures may have been implemented in the interim.*

Diagnostic Criteria

To be included, patients were required to have a diagnosis of HR-positive, HER2-negative breast cancer. Though not required as a protocol procedure, metastatic disease should have been considered for biopsy to reassess HR and HER2 status as clinically indicated. To fulfill the criteria for HR-positive, a breast cancer must have expressed by immunohistochemistry (IHC) at least one of the hormone receptors, estrogen receptor (ER) or progesterone receptor (PgR) as defined by American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guidelines. To fulfill the criteria of HER2-negative, a breast cancer must not have demonstrated either at initial diagnosis or subsequent biopsy overexpression of HER2 by IHC or in situ hybridization by ASCO/CAP Guidelines.

Reviewer Comments: *The Agency agrees with the use of ASCO/CAP guidelines in defining HR and HER2 status.*

Inclusion/Exclusion Criteria
Inclusion Criteria

- Have a diagnosis of HR positive, HER2 negative breast cancer. While not required by protocol, metastatic disease should have been considered for biopsy when possible to reassess HR and HER2 status as clinically indicated
    - HR positive disease is defined as IHC expression of at least one of the hormone receptors (ER, progesterone receptor [PgR]) as defined by relevant ASCO/CAP guidelines
    - To fulfill the requirement of HER2 negative disease, a breast cancer must not demonstrate on initial diagnosis or subsequent biopsy overexpression of HER2 either by IHC or in situ hybridization as defined in the relevant ASCO/CAP guidelines.
- Have locoregionally recurrent disease not amenable to resection or radiation therapy with curative intent or metastatic disease
- Postmenopausal status as defined by:
    - Prior bilateral oophorectomy
    - Age ≥60 years
    - Age <60 years and amenorrheic (not treatment induced) for at least 12 months with FSH and estradiol in the postmenopausal range
- Have one of the following as defined by RECIST v1.1
    - Measurable disease
    - Nonmeasurable bone-only disease
- ECOG PS ≤1
- Adequate organ function including
    - Hematologic: ANC ≥1.5 x 10^9/L, platelets ≥100,000 x 10^9/L, and hemoglobin ≥8 g/dL. Patients may receive RBC transfusion to achieve this hemoglobin level

however study treatment must not begin earlier than the day after the transfusion
    - Hepatic: bilirubin ≤1.5 times the upper limit of normal and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 times ULN (or ALT and AST ≤5 times ULN if liver metasteses are present)
    - Renal: Serum creatinine ≤1.5 times ULN
- Have discontinued previous localized radiotherapy for palliative purposes or for a lytic lesion at risk of fracture at least 2 weeks prior to randomization and recovered from the acute effects of therapy (until the toxicity resolves to either baseline or at least Grade 1) except for residual alopecia or peripheral neuropathy.
- Female and ≥18 years of age
- Able to swallow capsules
- Given written informed consent prior to study procedures
- Reliable, willing to be available for the duration of the study, and are willing to follow study procedures

Exclusion Criteria

- Visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis. Visceral crisis is severe organ dysfunction as assessed by signs/symptoms, laboratory studies, and rapid disease progression
- Inflammatory breast cancer
- Clinical evidence of history of CNS metastasis. Screening not required for enrollment.
- Currently or previously received endocrine therapy for locoregionally recurrent or metastatic breast cancer. A patient may be enrolled if she received (neo)adjuvant endocrine therapy for localized disease. Additionally, a patient may be enrolled if she received ≤2 weeks of NSAI in this disease setting immediately prior to screening and agrees to discontinue NSAI until study treatment initiation
- Have received prior (neo)adjuvant endocrine therapy with a disease-free interval ≤12 months from completion of treatment
- Currently receiving or have previously received chemotherapy for locally recurrent or metastatic breast cancer
- Prior treatment with everolimus
- Prior treatment with any CDK 4/6 inhibitor
- Have initiated bisphosphonates or an approved RANK ligand (RANK-L) targeted agent <7 days prior to randomization
- Currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study
- Received treatment with a drug that has not received regulatory approval for any indication within 14-21 days of randomization
- Had major surgery within 14 days prior to randomization

- Have received the yellow fever vaccine within 28 days of randomization
- Have serious preexisting medical conditions that would preclude participation in the study in the judgement of the investigator
- Personal history within the last 12 months of syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest
- Personal history of cancer (except non-melanoma skin cancer or carcinoma in situ of the cervix) unless in complete remission with no therapy for at least 3 years.
- Have received an autologous or allogenic stem cell transplant
- Have an active bacterial or fungal infection or a detectable viral infection (for example HIV or viral hepatitis). Screening is not required for enrollment.

Reviewer Comments: *The above inclusion/exclusion criteria appear generally acceptable. We currently recommend that patients with stable CNS disease be included in clinical studies. Of note, patients with inflammatory breast cancer were not excluded from other CDK 4/6 inhibitor trials and this may bias the population to have more favorable features than those in other trials as a result. Males are excluded based on the limited data for the use of aromatase inhibitors in this population due to biological differences in sex hormone physiology.*

Concomitant Radiotherapy or Surgery
Patients with locoregionally recurrent breast cancer may receive surgery and/or radiotherapy if study treatment renders the tumor operable. However, such a patient should not receive study therapy at least 7 days prior to surgery and for at least 14 days after surgery and/or radiotherapy. There is no restriction on the duration of this period without study treatment and after this period ends study treatment may resume.

Except as above, radiotherapy is not permitted without permanent discontinuation from study treatment. Other than patients with locoregional disease rendered operable, all other patients requiring radiotherapy should discontinue permanently from study treatment and have tumor assessment of lesion(s) prior to radiotherapy.

Reviewer Comments: *It appears acceptable to permit locally advanced patients to remain on trial should study therapy render their disease surgically resectable. Additionally, it appears acceptable that patients who receive palliative radiation therapy should be discontinued from study therapy as these patients would have evidence of clinical progression as study therapy was unable to control signs or symptoms.*

Dose Selection
The applicant chose the dose of 150 mg of abemaciclib orally twice daily in combination with non-steroidal aromatase inhibitors based on data from study I3Y-MC-JPBH, a Phase 1b study evaluating abemaciclib in combination with letrozole or anastrozole. While the initial phase 1 study, I3Y-MC-JPBA, had identified a maximum tolerated dose of abemaciclib as a single agent of 200 mg orally twice daily, data from JPBH demonstrated increase in early diarrhea and most patients did not complete their first cycle of abemaciclib 200 mg twice daily in combination

with letrozole or anastrozole. Clinical and PK findings from JPBA demonstrated that there was evidence of activity at both the 150 and 200 mg twice daily dosing. Preliminary safety data from JPBH supported the recommended dose of abemaciclib 150 mg orally twice daily in combination with letrozole or anastrozole.

The dose of letrozole or anastrozole was based on current standard USPI dosing recommendations.

Reviewer Comments: *Based on the review of this protocol and MONARCH 2, the recommended dose of abemaciclib in combination with endocrine based therapies is 150 mg orally twice daily. Based on the review of MONARCH 1, the recommended dose of abemaciclib as a single agent is 200 mg orally twice daily.*

Study Treatments

- Experimental Arm A: abemaciclib 150 mg orally Q12H on days 1-28 of a 28 day cycle with either anastrozole 1 mg orally daily or letrozole 2.5 mg orally daily on days 1-28 of a 28 day cycle.
- Control (Placebo) Arm B: placebo orally Q12H on days 1-28 of a 28 day cycle with either anastrozole 1 mg orally daily or letrozole 2.5 mg orally daily on days 1-28 of a 28 day cycle.

The choice of NSAI (anastrozole or letrozole) administered to patients was determined by the investigator and patients were to remain on the same NSAI throughout the study. In exceptional cases the investigator may discuss a change in NSAI with the Lilly CRP in the absence of PD.

Reviewer Comments: *The dose and schedule of the NSAI was appropriate. The dosing of abemaciclib at 150 mg twice daily in combination with NSAI appears appropriate.*

Assignment to Treatment

After obtaining informed consent, patients were randomized using an interactive web response system (IWRS) that assigned a patient number. Patients meeting all criteria for enrollment were randomly assigned to receive either abemaciclib plus NSAI or placebo plus NSAI. Assignment to treatment group was determined by a computer-generated random sequence using the IWRS.

Patients were randomized in a 2:1 ratio to the treatment arm using the stratification factors of nature of disease (visceral vs. bone-only vs. other) and prior (neo)adjuvant therapy. Patients were instructed to take abemaciclib at 150mg twice-daily or placebo orally twice daily continuously over a 28-day cycle.

Blinding

Abemaciclib and placebo were provided by the Applicant and supplied as capsules for oral administration. When required, letrozole and anastrozole were supplied by Lilly and labeled according to product label.

To preserve the blinding of the study, a minimum number of Lilly personnel were able to see the randomization table and study assignments prior to study completion. On study completion, investigators may unblind patients to study treatment assignment.

Interim analyses for safety and efficacy were conducted using unblinded data under the guidance of the independent data monitoring committee (DMC).

Blinding codes were broken in case of need to know the information for the patient's acute well-being or if the patient discontinued treatment due to disease progression based on RECIST criteria and knowledge of the patient's therapy assignment was deemed necessary to select the patient's next treatment regimen. The investigator must have consulted with the Lilly clinical research physician (CRP) prior to unblinding. If the investigator or patient became unblinded, the patient was to transition to post discontinuation follow up.

Reviewer Comments: *Based on the incidence and frequency of diarrhea and neutropenia that were associated with abemaciclib and not seen on the placebo arm, it is likely that both patients and investigators were not fully blinded.*

Dose Modifications

In the event of significant treatment-related toxicities, dose adjustments were recommended for abemaciclib/placebo. Based on the USPI for letrozole and anastrozole, only a single dose strength is approved. In special circumstances with no evidence of PD and in conjunction with the applicant's CRP, a change in NSAI agent could be made. When treatment interruption was deemed necessary for one of the study drugs in the combination, treatment with the other agent was continued as planned. Dose reductions for abemaciclib/placebo are contained in Table 5 below.

Table 5. Abemaciclib Dose Levels

Dose Adjustment	Oral Dose	Frequency
0	150 mg	Q12H
1	100 mg	Q12H
2	50 mg	Q12H

Source: Adapted from MONARCH 3 protocol, page 38.

For patients requiring dose reductions, re-escalation to a previous dose was permitted only after consultation with a Lilly clinical research physician (CRP). The pre-specified dose reductions for treatment associated toxicities are demonstrated in Table 6 below.

Table 6. Dose Modification and Reduction Instructions

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity	Grade 3	Dose MUST be suspended until toxicity resolves to at least Grade 2	Dose MAY be reduced by 1 dose level-investigator's discretion
Hematologic Toxicity	Recurrent Grade 3	Dose MUST be suspended until toxicity resolves to at least Grade 2	Dose MUST be reduced by 1 dose level-investigator's discretion
Hematologic Toxicity	Grade 4	Dose MUST be suspended until toxicity resolves to at least Grade 2	Dose MUST be reduced by 1 dose level-investigator's discretion
Hematologic Toxicity: Patient requires administration of blood cell growth factors	Regardless of severity	Dose MUST be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to ≤ Grade 2	Dose MUST be reduced by 1 dose level-investigator's discretion
Nonhematologic Toxicity (except diarrhea)	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose MAY be suspended until toxicity resolves to either baseline or Grade 1	Dose MAY be reduced by 1 dose level-investigator's discretion
Nonhematologic Toxicity (except diarrhea)	Grade 3 or 4	Dose MUST be suspended until toxicity resolves to either baseline or Grade 1	Dose MUST be reduced by 1 dose level
Diarrhea	Requires hospitalization or Grade 3 or 4	Dose MUST be suspended until toxicity resolves to either baseline or Grade 1	Dose MUST be reduced by 1 dose level

Diarrhea	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 24 hours to at least Grade 1	Dose SHOULD be suspended until toxicity resolves to at least Grade 1	Dose MAY be reduced by 1 dose level-investigator's discretion
Diarrhea	Diarrhea recurs despite maximal supportive measures after resuming the same dose level after initial Grade 2 diarrhea	Dose MUST be suspended until toxicity resolves to either baseline or Grade 1	Dose MUST be reduced by 1 dose level

Source: MONARCH 3 protocol, pages 37-38.

Administrative Structure

The applicant used an external data monitoring committee (DM) to provide patient safety oversight for the MONARCH 3 study independent of the Lilly Study Team and Lilly Global Patient Safety. Safety analyses were performed every 3 months and the first interim safety analysis was triggered by the 90th patient enrolling with the data cutoff for this analysis occurring one month after this trigger. Safety interim analyses were conducted to evaluate the overall safety profile of abemaciclib when given in combination with NSAIs.

Blinded independent central review (BICR) of the primary endpoint was performed as an auditing tool to corroborate the results of the investigator assessed PFS analysis and evaluate for potential bias.

Procedures and Schedule

The key assessments and procedures for this study were:

Screening

- Informed Consent
- Eligibility Assessment
- Medical History and Physical Examination
- Baseline tumor assessment
- Adverse event collection
- Laboratory testing
- Concomitant medications
- ECG
- Health outcomes assessment including PROs

- PK analysis
- Archived tumor sample where available

On Treatment Visits

- Physical Examination
- Adverse event collection
- Concomitant medications
- Laboratory testing
- Tumor assessment (every 2 cycles for Cycle 3-19 and every 3rd cycle after cycle 19 or within 14 days of clinical progression)
- Health outcomes including PROs (every 2 cycles for Cycle 3-19 and every 3rd cycle after cycle 19)
- ECG
- PK analysis

Follow-up

- Physical Examination (short term follow-up)
- Tumor measurement
- Survival information
- AE Collection and CTCAE grading
- Concomitant medications (short term follow-up)
- Laboratory testing (short term follow-up)
- ECG (short term follow-up)
- Health outcomes including PROs (short term follow-up)

The schedule of study activities is shown in Table 7 below.

Table 7. MONARCH 3 Study Schedule

Protocol I3Y-MC-JPBM

Baseline Schedule		Study Period	Baseline (BL)		
		Visit	0		
		Approximate Visit Duration (days)	Up to 28		
		Relative day to C1D1	≤28	≤14	
Procedure Category	**Procedure**	**Protocol Reference**			**Comments**
Study Entry /Enrollment	Informed Consent Form signed	Section 13.1	X		Prior to conducting any protocol-specific tests / procedures
	Inclusion/Exclusion evaluation	Section 7		X	
Medical History	Initial medical history/preexisting conditions			X	
	Historical illnesses			X	Include habits assessment of alcohol and tobacco use
Physical Examination	Physical examination			X	Include but not limited to height and weight
	Vital Signs			X	Include blood pressure, pulse, respiratory rate, and temperature
	ECOG performance status	Attachment 4		X	
Tumor Assessment	Tumor measurement (palpable or visible)	Section 10.1.1	X		Photography of skin lesions with ruler required, if applicable
	Radiologic imaging according to RECIST 1.1	Section 10.1.1 Attachment 5	X		Performed locally. For patients with locoregionally recurrent breast cancer, MRI scan of the breast; additionally, for all patients, CT or MRI scan of the chest, abdomen, and pelvis. CT scan is the best currently available and reproducible method to measure lesions selected for response assessment; it is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast whenever possible. MRI may be used instead of CT in selected instances. Gadolinium-enhanced MRI is preferred if hypersensitivity to contrast.
	Bone Scintigraphy	Section 10.1.1 Attachment 5	X		Performed locally. Bone scintigraphy performed as part of routine clinical care within 45 days before Cycle 1 Day 1 is also acceptable.
	X-ray, or CT scan with bone windows, or MRI	Section 10.1.1 Attachment 5	X		Performed locally. *For only those patients with bone lesions identified by bone scintigraphy at baseline*, all bone lesions will be evaluated at baseline by focused studies to enable serial assessment.

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Baseline Schedule

		Study Period	Baseline (BL)		
		Visit	0		
		Approximate Visit Duration (days)	Up to 28		
		Relative day to C1D1	≤28	≤14	
Procedure Category	**Procedure**	**Protocol Reference**			**Comments**
Adverse Event Collection/CTCAE Grading		Section 10.3	X		CTCAE = Common Terminology Criteria for Adverse Events
Concomitant Medication Notation		Section 9.6	X		Note: RANK-L or bisphosphonate agents should be initiated ≥7 days prior to randomization, if applicable.
Lab/ Diagnostic Tests	Central hematology	Attachment 2		X	Enrollment and treatment decisions may be based upon results of tests performed locally. If local laboratory tests are used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Discrepancies between local and central laboratory that may have an impact on eligibility or treatment decisions will not be considered protocol deviations
	Central chemistry	Attachment 2		X	Enrollment and treatment decisions may be based upon results of tests performed locally. If local laboratory tests are used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Discrepancies between local and central laboratory that may have an impact on eligibility or treatment decisions will not be considered protocol deviations.
	Local FSH and estradiol level	Attachment 2		X	Required only for women < 60 years with amenorrhea for at least 12 months to confirm post-menopausal status
	Local ECG	Section 10.3.2.1		X	Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Abbreviations: CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle stimulating hormone; IV = intravenous; MRI = magnetic resonance imaging; RANK-L = RANK ligand; RECIST = Response Evaluation Criteria in Solid Tumors.

Protocol I3Y-MC-JPBM During Treatment Study Schedule			Study Treatment Period						
		Cycle / Visit	1	2		3	4-X		
		Approximate Visit Duration (days)	28	28		28	28		
		Relative day within a cycle	1	1	21-28	1	1	21-28	
Procedure Category	Procedure	Protocol Reference							Comments
Physical Examination	Physical Exam		X	X		X	X		Include but not limited to weight
	Vital Signs		X	X		X	X		Include blood pressure, pulse, respiratory rate, and temperature.
	ECOG performance status	Attachment 4	X	X		X	X		
Archived Tumor Tissue		Section 10.4.2.1	X						Whole or partial block or 15 – 20 slides should be provided upon patient randomization.
Adverse Event Collection/CTCAE Grading		Section 10.3	X	X		X	X		
Concomitant Medication Notation		Section 9.6	X	X		X	X		
Lab/ Diagnostic Tests	Central hematology	Attachment 2	X	X		X	X		Central hematology labs may be drawn up to 3 days prior to Day 1 of each cycle. Additional local hematology labs may be drawn for treatment adjustment and patient management purposes.
	Central chemistry	Attachment 2	X	X		X	X		Central chemistry labs may be drawn up to 3 days prior to Day 1 of each cycle. Additional local chemistry labs may be drawn for treatment adjustment and patient management purposes.
	Pharmacokinetic (PK) sampling	Attachment 7	X	X		X			See Attachment 7 for specific timing.
	Pharmacogenetic blood sample	Section 10.4.2.2	X						Draw sample before patient is dosed on C1D1.
	Biomarker plasma sample	Section 10.4.2	X	X					Draw sample before patient is dosed on C1D1 and upon arrival at site on C2D1.
	Local ECG	Section 10.3.2.1	X	X			X		2 to 4 hours after the LY dose on Cycle 1 Day 1, upon arrival at site on Cycle 2 Day 1, 2 to 4 hours after the LY dose on Cycle 4 Day 1. Following C4D1, no additional ECGs are required while the patient is on treatment (only subsequently for short-term follow-up). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Protocol I3Y-MC-JPBM During Treatment Study Schedule			Study Treatment Period							
		Cycle / Visit	1	2		3	4-X			
		Approximate Visit Duration (days)	28	28		28	28			
		Relative day within a cycle	1	1	21-28	1	1	21-28		
Procedure Category	**Procedure**	**Protocol Reference**								**Comments**
Tumor Assessment	Tumor measurement (palpable or visible)	Section 10.1.1				X	X			Skin lesions identified at baseline require repeat photographic images on Day 1of every second cycle beginning with Cycle 3 and continuing through Cycle 19 (inclusive), on Day 1of every third cycle after Cycle 19, and within 14 days of clinical progression. Photographic images may be taken more frequently based upon the discretion of the investigator or following the identification of new skin lesions post-baseline.
	Radiological imaging according to RECIST (CT scan/MRI)	Section 10.1.1 Attachment 5			X			X		Performed locally. For patients with locoregionally recurrent breast cancer not amenable to curative treatment, MRI scan of the breast is performed, if applicable, in addition to other scans. Imaging studies (Breast MRI and CT scan or MRI of the chest, abdomen, and pelvis) will be repeated on Day 21 to Day 28 of every second cycle beginning with Cycle 2 and continuing through Cycle 18 (inclusive), on Day 21 to Day 28 of every third cycle after Cycle 18, and within 14 days of clinical progression. The same method of imaging used at baseline should be used for each subsequent assessment.
	Bone Scintigraphy	Section 10.1.1 Attachment 5						X		Performed locally. Repeat for all patients on Day 21 to Day 28 of every sixth cycle beginning with Cycle 6. In addition, bone scans should be repeated even if a complete response is identified in target disease or progression in bone is suspected. Importantly, RECIST v1.1 emphasizes that bone scintigraphy is not adequate to measure bone lesions; however, bone scintigraphy can be used to confirm the presence or disappearance of bone lesions.
	X-ray, CT scan with bone windows, or MRI	Section 10.1.1 Attachment 5			X			X		Performed locally for patients with bone lesions identified by bone scintigraphy at baseline. Repeat on Day 21 to Day 28 of every second cycle beginning with Cycle 2 and continuing through Cycle 18 (inclusive), on Day 21 to Day 28 of every third cycle after Cycle 18, and within 14 days of clinical progression. For patients with new lesions identified by post-baseline bone scintigraphy, targeted assessment by X-ray, CT scan with bone windows, or MRI will be performed to confirm findings.

Protocol I3Y-MC-JPBM During Treatment Study Schedule			Study Treatment Period							
		Cycle / Visit	1	2		3	4-X			
		Approximate Visit Duration (days)	28	28		28	28			
		Relative day within a cycle	1	1	21-28	1	1	21-28		
Procedure Category	**Procedure**	**Protocol Reference**								**Comments**
Health Outcomes	EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D 5L	Section 10.2	X			X	X			Patients complete prior to extensive interaction with site staff. On Cycle 1 Day 1, questionnaires must be administered prior to the first dose of study treatment. Questionnaires should be administered on Cycle1 Day 1, and then Day 1 of every second cycle beginning with Cycle 3 through Cycle 19, and on Day 1of every third cycle after Cycle 19.
Study Drug	LY2835219 or Placebo (blinded randomization)	Section 9.1	Take 150 mg or prescribed dose orally every 12 hours on Days 1 through 28 of every cycle, with the exception that the second dose on C1D1 should be omitted to allow for adequate study drug for at home dosing on C2D1.							On Cycle 1 Day 1 only, patients should take one single dose of blinded study drug and initiate chronic every 12 hour dosing on Cycle 1 Day 2. On Cycle 2 Day 1, patients will take medication at home at least 4 hours prior to arrival at the clinic. On Cycle 4 Day 1, patients will take morning dose of blinded study drug in the clinic.
Co-Administered Drug (per investigator selection)	anastrozole	Section 9.1	Take 1mg tablet orally every 24 hours on Days 1 through 28							For PK and ECG purposes, should be taken at the same time as, or up to 20 minutes after the morning dose of blinded study drug. Adjustment to timing of dose administration may be made at the discretion of the investigator after Cycle 4 Day 1.
	letrozole	Section 9.1	Take 2.5mg tablet orally every 24 hours on Days 1 through 28							For PK and ECG purposes, should be taken at the same time as, or up to 20 minutes after the morning dose of blinded study drug. Adjustment to timing of dose administration may be made at the discretion of the investigator after Cycle 4 Day 1.

Abbreviations: C4D1 = Cycle 4 Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-BR23 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast cancer; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D 5L = EuroQol 5-Dimension 5 Level; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors.

Protocol I3Y-MC-JPBM Post Treatment Discontinuation Study Schedule		Study Period	Post-Discontinuation Short Term Follow-Up	Postdiscontinuation Long Term Follow-Up	
		Visit	801	802-X	
		Approximate Visit Duration (days)	30±5	Variable	
		Relative day	30		
Procedure Category	**Procedure**	**Protocol Reference**			**Comments**
Physical Examination	Physical Exam		X		Includes but not limited to weight
	Vitals		X		Includes blood pressure, pulse, respiratory rate, and temperature.
	ECOG Performance Status	Attachment 4	X		
Tumor Assessment	Tumor measurement (palpable or visible)	Section 10.1.1	X	X	**ONLY For patients who discontinue study treatment without objectively measured progressive disease (PD),** continue to conduct tumor assessments approximately every 8 weeks for the first 18 months following randomization and thereafter approximately every 12 weeks until the patient has objective disease progression or until study completion. After the patient has objective disease progression, photographic images are no longer required and the patient will continue with post-discontinuation follow-up approximately every 12 weeks until the patient's death or overall study completion.
	Bone Scintigraphy	Section 10.1.1 Attachment 5	X	X	**ONLY For patients who discontinue study treatment without objectively measured progressive disease (PD),** continue to evaluate repeat bone scans approximately every 6 months until objective disease progression or study completion.
	Radiologic imaging according to RECIST	Section 10.1.1 Attachment 5	X	X	The same method of imaging used at baseline should be used for each subsequent assessment. **ONLY For patients who discontinue study treatment without objectively measured progressive disease (PD),** continue to conduct tumor assessment approximately every 8 weeks for the first 18 months following randomization and thereafter approximately every 12 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression or until study completion. After the patient has objective disease progression, radiologic tests are no longer required and the patient will continue with post-discontinuation follow-up approximately every 12 weeks until the patient's death or overall study completion

Protocol I3Y-MC-JPBM Post Treatment Discontinuation Study Schedule		Study Period	Post-Discontinuation Short Term Follow-Up	Postdiscontinuation Long Term Follow-Up	
		Visit	801	802-X	
		Approximate Visit Duration (days)	30±5	Variable	
		Relative day	30		
Procedure Category	**Procedure**	**Protocol Reference**			**Comments**
Tumor Assessment continued	X-ray, CT scan with bone windows, or MRI	Section 10.1.1 Attachment 5	X	X	**ONLY For patients who discontinue study treatment without objectively measured progressive disease (PD), focused studies** are performed for patients with bone lesions previously identified by bone scintigraphy. During long term follow up period, repeat scans should performed approximately every 8 weeks for the first 18 months following randomization, and subsequently approximately every 12 weeks until disease progression or study completion.
Survival Information		Section 10.1.4	X	X	Although preferable to collect during a clinic visit, survival information may be collected by contacting the patient or family directly (for example, via telephone) if no procedures required. This should be collected at minimum every 90 days if no other procedures are performed. Additional long-term follow-up data collection will include post-discontinuation anticancer therapies.
Adverse Events Collection/CTCAE Grading		Section 10.3	X	X	After Visit 801, only study protocol or drug-related events are reported. If a patient has ongoing AE or SAE possibly related to study drug (not co-administered drug) (for instance, abnormal electrolytes), the patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Any subsequent follow-up(s) for AEs will be no more than 30 days ± 5 days in duration.
Concomitant Medications Notation		Section 9.6	X		
Lab/ Diagnostic Tests	Central hematology	Attachment 2	X		
	Central chemistry	Attachment 2	X		
	Biomarker plasma sample	Section 10.4.2	X		Draw sample only for patients discontinuing due to PD.
	ECG	Section 10.3.2.1	X		Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
Health Outcomes	EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D 5L	Section 10.2	X		

Abbreviations: AE = adverse event; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-BR23 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast cancer; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D 5L = EuroQol 5-Dimension 5 Level; MRI = magnetic resonance imaging; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events.

Protocol I3Y-MC-JPBM Study Schedule for the Continued Access Period only		Study Period	Patients on Study Treatment	Continued Access Period Follow-Up	
		Cycle	X	Follow-Up[a]	
		Visit	501-5XX	901	
		Approximate Visit Duration (days)	28±3	30±5	
		Relative day within a cycle	1		
Procedure Category	Procedure	Protocol Reference			Comments
Adverse Events Collection/CTCAE Grading		Section 10.3	X	X	Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly safety system
Study Drug	LY2835219	Section 9.1	X		Only patients assigned to LY2835219 at randomization and receiving clinical benefit will continue to receive LY2835219 during the continued access period. LY2835219 is to be administered orally every 12 hours on Days 1 through 28 of each cycle. Patients who were assigned to placebo, will no longer receive placebo during the continued access period and cannot crossover to LY2835219.
Co-Administered Drugs	Anastrozole	Section 9.1	X		Patients receiving clinical benefit will continue to receive anastrozole or letrozole during the continued access period. Anastrozole or letrozole is to be administered orally every 24 hours on Days 1 through 28 of each cycle
	Letrozole	Section 9.1	X		

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; OS = overall survival; SAEs = serious adverse events.

[a] The continued access period begins after study completion (that is, after final OS analysis) and ends at the end of trial (that is, the last patient visit).

Source: MONARCH 3 Protocol, pages 75-83.

Study Endpoints

The primary endpoint of the study was investigator-assessed progression-free survival determined using RECIST 1.1 criteria. The key secondary endpoint was overall survival in the ITT population and overall survival (OS) in the visceral disease population. Additional secondary endpoints included PFS assessed using a blinded independent review committee, OS rate at 1, 2, and 3 years, overall response rate, duration of response, clinical benefit rate (CBR), safety and tolerability, the PK of abemaciclib, its metabolites, and NSAI therapy. Patient-reported outcome measurements include the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), EORTC QLQ-BR23 (breast) questionnaire, and the health status score from the EuroQol 5-Dimension 5-Level (EQ-5D-5L). Of the secondary objectives, only the OS endpoint had a formal alpha spending function associated with it.

Exploratory objectives included change in tumor size, and to explore potential biomarkers related to the mechanism of action of abemaciclib, the cell cycle, and/or the pathogenesis of breast cancer.

Reviewer Comments: *The choice of primary endpoint is appropriate as PFS is an accepted surrogate endpoint for clinical benefit in metastatic breast cancer. There was no formal analysis plan or alpha spending function for secondary endpoints aside from OS, so these analyses are considered descriptive.*

Statistical Analysis Plan

This study planned to enroll 450 patients to demonstrate a hypothesized hazard ratio of 0.67 with 80% statistical power. The final PFS analysis was to occur when 240 progression events had occurred. Based upon feedback from the Agency, a single interim look for PFS was to be conducted when 189 PFS events had occurred, with a stopping rule of HR < 0.56.

The sponsor plans for a 4-look analysis of overall survival with an alpha spending plan shown in Figure 4. There is a 2% alpha allocation for OS in the ITT population and 0.5% allocation for alpha in the visceral disease population. Alpha is to be shared between the two OS endpoints, using a standard alpha gatekeeping plan.

After conducting the interim analysis of PFS, the study was deemed successful since the hazard ratio crossed the preset boundary. Nevertheless, the applicant continued to follow patients, who had not yet progressed, for progression. Note that patients will remain blinded to their randomized treatment until the final OS and patients are not permitted to crossover. Using this updated progression data, the applicant provided an updated analysis of PFS that closely mimics the “final” planned PFS analysis at 240 progression events. Table 8 below summarizes the statistical plan for alpha spending for the overall survival analysis.

Table 8. Alpha Spending Plan for Overall Survival

Test	Node α at Analysis	Nominal Significance Level				
		Interim PFS Analysis	Final PFS Analysis	189 OS events	252 OS events	Final OS analysis
1. Initial Graph						
PFS	0.025	0.00025	.0249993	n/a	n/a	n/a
2. Graph following signficant PFS result						
VIS OS	0.005	1*10^-9	3*10^-7	.0003	.0016	.0045
ITT OS	0.020	2*10^-9	2*10^-5	.0027	.0085	.0171
3. Graph following significant PFS and VIS OS result						
ITT OS	0.025	7*10^-9	4*10^-5	.0038	.0110	.0211
4. Graph following significant PFS and ITT OS result						
VISC OS	0.025	7*10^-9	4*10^-5	.0038	.0110	.0211

Source: Statistical analysis plan, page 22.

Protocol Amendments

This study had two protocol addenda and two major protocol amendments. Both protocol addenda were approved at the time of initial protocol approval on September 3, 2014, and prior to the first patient enrolled which was November 18, 2014. The first protocol addendum was to comply with local laws and regulatory requirements in Taiwan and to enroll only patients ≥20 years of age and specify the genetic testing that would occur. The second was to comply with Japanese regulatory authorities for monitoring for interstitial lung disease (ILD) and to require pharmacokinetic samples from all Japanese patients to characterize the exposure of abemaciclib in Japanese female patients. Amendment (A) (November 13, 2015) updated the dosing guidance for cases of hematological toxicity and diarrhea and to give guidance on the use of blood cell growth factors. Additional modifications were to provide clarity for supportive management of diarrhea and advice regarding co-administered drugs with narrow therapeutic margins. The SAP was modified to change the timing of the PFS (b) (4) analyses based on data from (b) (4) PALOMA 3 demonstrating that the combination of CDK4/6 inhibitor therapy had a larger effect size than originally assumed. Amendment (B) (December 16, 2016) removed one of two planned interim analyses for PFS and set the

stopping boundary to the agency recommended boundary.

Reviewer Comments: *Neither amendment is likely to have major effect of the interpretation of the study results.*

8.1.2. Study Results

Compliance with Good Clinical Practices

According to the applicant, MONARCH 3 (I3Y-MC-JPBM) and MONARCH 2 (I3Y-MC-JPBL) were conducted in full conformance with the ethical principles of the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) as required by the major regulatory authorities and in conformance with the principles set forth in the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines as well as with applicable laws and regulations. Written informed consent was obtained from each study participant or their legal representative. The study protocols and amendments were approved by local Independent Ethics Committees (IEC) or Institutional Review Boards (IRB).

Financial Disclosure

All investigators were assessed for equity interest, other significant payments, and other compensation by the applicant as well as proprietary interest in this agent. Financial disclosure information is provided for the MONARCH 3 (I3Y-MC-JPBM) study and was reviewed previously in NDA 208716 for the MONARCH 2 study (I3Y-MC-JPBL). Of the 1117 investigators listed for the MONARCH 3 study, all provided certification.

Study I3Y-MC-JPBM (MONARCH 3) included 169 principal investigators and 948 subinvestigators. One had financial information to disclose and this information is summarized in the table below (Table 7).

Table 9. Summary of Financial Disclosures for MONARCH 3

Clinical Site Number	Investigator Name (PI or SI)	Patient Enrollment at Site	Disclosure
(b) (6)			$70,349

Reviewer Comments: *There was only* (b) (6) *investigator with a significantly disclosable financial interest reported. There was one study participant enrolled at that site making up 0.2% of the total study population. This is not likely to affect the results of the study.*

Patient Disposition

A total of 579 patients at 158 sites in 22 countries signed informed consent and entered the study. Of these patients, 86 patients were not randomized.

From November 18, 2014 to November 12, 2015, a total of 493 patients were enrolled and randomized. Three hundred twenty-eight were randomized to receive abemaciclib plus NSAI and 165 were randomized to receive placebo plus NSAI. Of the 328 randomized to abemaciclib plus NSAI, 326 were treated and of the 165 randomized to placebo plus NSAI, 162 were treated.

At the time of the primary analysis of PFS with a data cutoff of January 31, 2017, 162 patients continued on study treatment in the abemaciclib plus NSAI arm and 64 patients continued on study treatment in the placebo plus NSAI arm. Reasons for treatment discontinuation are displayed in Table 10 below.

Table 10. MONARCH 3 Study Disposition (data cutoff January 31, 2017)

	Abemaciclib N=328 n (%)	**Placebo N=165 n (%)**
Randomized, never treated	2 (0.6)	3 (1.8)
Off treatment	164 (50.0)	98 (59.4)
Progressive Disease	91 (27.7)	86 (52.1)
Adverse Event	35 (10.7)	2 (1.2)
Withdrawal	18 (5.5)	2 (1.2)
Death	9 (2.7)	3 (1.8)
Physician Decision	7 (2.1)	5 (3.0)
Noncompliance	3 (0.9)	0
Protocol Deviation	1 (0.3)	0
Post treatment discontinuation follow-up	132 (40.2)	87 (52.7)
Off post-treatment discontinuation follow-up	37 (11.3)	17 (10.3)
Death	23 (7.0)	14 (8.5)
Withdrawal	11 (3.4)	1 (0.6)
Lost to follow-up	3 (0.9)	1 (0.6)

Source: Reviewer analysis and modification of Table JPBM 10.1, MONARCH 3 CSR, page 84

Reviewer Comments: *The patient disposition demonstrates that there was an increased rate of study treatment discontinuation in the abemaciclib plus NSAI arm due to adverse events as compared to placebo plus NSAI. However, those who were on the placebo plus NSAI arm were more likely to discontinue study treatment due to progressive disease. While the CSR reported that one patient in the placebo plus NSAI arm was terminated by the study sponsor, this was noted to be an error and that the patient was incorrectly coded. As this patient continued on post-discontinuation follow-up, the reviewer table was modified from that in the CSR to reflect this. At the 90-day safety update, data cutoff August 11, 2017, 135 (41.2%) patients continued on study treatment with abemaciclib plus NSAI while 44 (26.7%) patients continued on study treatment with placebo plus NSAI. These data support that abemaciclib in combination with NSAI provides improved disease control compared to NSAI alone, though with increased risk of adverse events.*

Protocol Violations/Deviations

In the MONARCH 3 study, a total of 276 (84.1%) patients in the abemaciclib plus NSAI arm and 128 patients in the placebo plus NSAI arm had one or more major protocol deviations. Table 11 below demonstrates the incidence of major protocol deviations by type in the intention to treat population.

Table 11. Protocol Deviations in MONARCH 3

Deviation Category	Abemaciclib N=328 n (%)	Placebo N=165 n (%)	Total N=493 n (%)
Patients with ≥1 major protocol deviation	276 (84.1)	128 (77.6)	404 (81.9)
Key measurements not collected properly	226 (68.9)	107 (64.8)	333 (67.5)
Incorrect stratification factors for IWRS	94 (28.7)	45 (27.3)	139 (28.2)
Improper administration of informed consent	50 (15.2)	30 (18.2)	80 (16.2)
Inappropriate handling of the investigational product	43 (13.1)	17 (10.3)	60 (12.2)
Incorrect dose adjustments	36 (11.0)	13 (7.9)	49 (9.9)
Inclusion/exclusion criteria not met	28 (8.5)	17 (10.3)	45 (9.1)
Improper treatment discontinuation	23 (7.0)	18 (10.9)	41 (8.3)
Use of prohibited concomitant medications	3 (0.9)	2 (1.2)	5 (1.0)

Source MONARCH 3 CSR page 85 with additional review of Table JPBM 10.3 on page 86

Reviewer Comments: *There were multiple major protocol deviations. Most of the key measurement deviations were that the post-baseline tumor assessments were not completed properly. Additionally, six patients were continued on study therapy after documented objective disease progression ([redacted] (b) (6)). Four of these patients were in the placebo plus NSAI arm and 2 were in the abemaciclib plus NSAI arm. Overall the incidence of protocol deviations was similar across treatment arms and was not thought to have a significant impact on interpreting the primary endpoint.*

Table of Demographic Characteristics

Demographic data for the intention to treat population for the MONARCH 3 study are included below in Table 12.

Table 12. Demographic characteristics of MONARCH 3

Demographic Parameters	**Abemaciclib plus NSAI N=328 n (%)**	**Placebo plus NSAI N=165 n (%)**	**Total N=493 n (%)**
Sex			
Female	328 (100)	165 (100)	493 (100)
Age			
Mean years	63.13	62.92	63.05
Median (years)	63	63	63
Min, max (years)	38, 87	32, 88	32, 88
Age Group			
< 65 years	180 (54.9)	91 (55.2)	271 (55.0)
≥ 65 and <75 years	106 (32.3)	54 (32.7)	160 (32.5)
≥75 and <85 years	37 (11.3)	18 (10.9)	55 (11.2)
≥85 years	5 (1.5)	2 (1.2)	7 (1.4)
Race			
White	186 (56.7)	102 (61.8)	288 (58.4)
Black or African American	5 (1.5)	3 (1.8)	8 (1.6)
Asian	103 (31.4)	45 (27.3)	148 (30.0)
American Indian or Alaska Native	4 (1.2)	3 (1.8)	7 (1.4)
Native Hawaiian or Other Pacific Islander	0	1 (0.6)	1 (0.2)
Other[1]	30 (9.1)	11 (6.7)	41 (8.3)
Ethnicity			
Hispanic or Latino	32 (9.8)	12 (7.3)	44 (8.9)
Not Hispanic or Latino	230 (70.1)	125 (75.8)	355 (72.0)
Region (optional)			
United States	24 (7.3)	12 (7.3)	36 (7.3)
Rest of the World	304 (92.7)	153 (92.7)	457 (92.7)
Canada	14 (4.3)	11 (6.7)	25 (5.1)
South America	0	0	0
Europe	116 (35.4)	59 (35.8)	175 (35.5)
Asia	102 (31.1)	45 (27.3)	147 (29.8)
Australia/New Zealand	10 (3.0)	6 (3.6)	16 (3.2)

[1] Data on race and/or ethnicity were not collected in France because of local regulations.
Source: Reviewer analysis using adsl.xpt and review of JPBM 11.1, MONARCH 3 CSR, page 88

Reviewer Comments: *The treatment arms were relatively balanced across various demographic groups. Patients over the age of 65 were well-represented in this trial, though numbers decreased when older than 75. This was an international study with most patients from Europe or Asia. The largest racial subgroups were White and Asian. Small numbers of Black or African-American patients were included in this trial and this is consistent with other trials. France does not report race, and most missing data from race are in patients from this country.*

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Disease characteristics for the patients in the ITT population in the MONARCH 3 study are included in Table 13 below.

Table 13. Baseline Disease Characteristics MONARCH 3

Pretreatment Disease Characteristic	Abemaciclib + NSAI N=328	Placebo + NSAI N=165	Total N=493
Duration of disease in months			
Mean (Std Dev)	79.6 (92.3)	74.5 (77.6)	77.9 (87.6)
Median (Q1-Q4)	53.5 (1.4, 132.0)	63.1 (2.2, 120.6)	56.6 (1.6, 127.1)
Min, Max	0.4, 521.6	0.3, 319.8	0.3, 521.6
	Abemaciclib + NSAI N=328 n (%)	**Placebo + NSAI N=165 n (%)**	**Total N=493 n (%)**
Initial Pathological Diagnosis			
Ductal carcinoma, breast	229 (69.8)	128 (77.6)	357 (72.4)
Lobular carcinoma, breast	32 (9.8)	18 (10.9)	50 (10.1)
Other	63 (19.2)	18 (10.9)	81 (16.4)
Initial Diagnosis Disease Stage			
Stage 0-II	121 (36.9)	73 (44.2)	194 (39.3)
Stage III	62 (18.9)	24 (14.5)	86 (17.4)
Stage IV	132 (40.2)	61 (37.0)	193 (39.1)
Stage at Study Entry			
Recurrent locally advanced	9 (2.7)	5 (3.0)	14 (2.8)
Metastatic	316 (96.3)	159 (96.4)	475 (96.3)
Unknown	3 (0.9)	1 (0.6)	4 (0.8)
Nature of disease			
Visceral	172 (52.4)	89 (53.9)	261 (52.9)
Bone only	70 (21.3)	39 (23.6)	109 (22.1)
Other	86 (26.2)	37 (22.4)	123 (24.9)
Measurable Disease			
Yes	267 (81.4)	130 (78.8)	397 (80.5)
No	61 (18.6)	35 (21.2)	96 (19.5)
Prior (neo)adjuvant endocrine therapy			
Aromatase inhibitor	85 (25.9)	50 (30.3)	135 (27.4)
Other prior endocrine therapy	65 (19.8)	30 (18.2)	95 (19.3)
None	178 (54.3)	85 (51.5)	263 (53.3)
Number of organs involved at baseline			
1	96 (29.3)	47 (28.5)	143 (29.0)
2	76 (23.2)	42 (25.5)	118 (23.9)
3 or more	154 (47.0)	75 (45.5)	229 (46.5)

Source MONARCH 3 CSR, adapted from table JPBM 11.2, 11.4, and 11.5, page 90, 92, 93

Reviewer Comments: *The groups were generally well-balanced with respect to baseline disease characteristics. There was a numerically greater number of patients with de novo metastatic disease in the abemaciclib plus NSAI arm. These patients may have a different natural history as well as treatment sensitivity than those who relapse after local therapy and adjuvant chemotherapy/endocrine therapy.*

Hormone receptor status for patients in the MONARCH 3 ITT population is included in Table 14 below.

Table 14. MONARCH 3 ITT Population Hormone Receptor Status

Receptor Status	Abemaciclib + NSAI N=328 n (%)	Placebo + NSAI N=165 n (%)	Total N=493 n (%)
Hormone receptor positive			
ER+/PgR+	253 (77.1)	127 (77.0)	380 (77.1)
ER+/PgR-	70 (21.3)	36 (21.8)	106 (21.5)
ER+/PgR unknown	3 (0.9)	1 (0.6)	4 (0.8)
ER-/PgR+	2 (0.6)	0	2 (0.4)
Missing	0	1 (0.6)	1 (0.2)
HER2 Status			
Negative	328 (100)	164 (99.4)	492 (99.8)
Missing	0	1 (0.6)	1 (0.2)

Source MONARCH 3 CSR, JPBM 11.3, page 91

Reviewer Comments: *The hormone receptor status was well balanced between arms. Most patients were ER and PgR positive and this is thought to possibly be associated with a more favorable natural history as compared to those patients with ER positive, PgR negative tumors.*

Table 15 below is a summary of the preexisting conditions in ≥10% of the patients in the safety population of MONARCH 3.

Table 15. Summary of Preexisting Conditions in 10% or more of the MONARCH 3 Safety Population

	Abemaciclib + NSAI N=327 n (%)	Placebo + NSAI N=161 n (%)	Total N=488 n (%)
Patients with ≥ 1 preexisting condition	287 (87.8)	136 (84.5)	423 (86.7)
Vascular disorders	140 (42.8)	61 (37.9)	201 (41.2)
Hypertension	119 (36.4)	52 (32.3)	171 (35.0)
Musculoskeletal and connective tissue disorders	120 (36.7)	70 (43.5)	190 (38.9)
Osteoporosis	36 (11.0)	17 (10.6)	53 (10.9)
Bone pain	33 (10.1)	23 (14.3)	56 (11.5)
Metabolism and nutrition disorders	112 (34.3)	53 (32.9)	165 (33.8)
Hypercholesterolemia	51 (15.6)	20 (12.4)	71 (14.5)
Hyperglycemia	44 (13.5)	18 (11.2)	62 (12.7)
Psychiatric disorders	69 (21.1)	33 (20.5)	102 (20.9)
Insomnia	35 (10.7)	14 (8.7)	49 (10.0)

Source: Adapted from MONARCH 3 CSR, page 96

Reviewer Comments: *Preexisting conditions as recorded as adverse events in the safety database prior to initiation of therapy were reasonably well-balanced between the groups. There were numerically more patients in the abemaciclib arm with preexisting vascular conditions and more in the placebo arm with musculoskeletal disorders. The rate of preexisting fatigue was approximately 7-8% in patients in both arms and diarrhea was a preexisting condition in 1% of patients.*

Stratification Factors

In the MONARCH 3 study, patients were stratified by disease site (visceral, bone only, other) and prior endocrine therapy. Table 16 below demonstrates that stratification factors were well-balanced between the two treatment arms.

Table 16. MONARCH 3 Stratification Factors by IWRS and CRF for ITT Population

	Abemaciclib + NSAI N=328 n (%)	Placebo + NSAI N=165 n (%)	Total N=493 n (%)
IWRS			
Nature of disease			
Visceral	177 (54.0)	89 (53.9)	266 (54.0)
Bone-only	89 (27.1)	45 (27.3)	134 (27.2)
Other	62 (18.9)	31 (18.8)	93 (18.9)
Prior endocrine therapy ([neo]advjuant)			
Prior AI therapy	85 (25.9)	50 (30.3)	135 (27.4)
Other prior endocrine therapy	65 (19.8)	30 (18.2)	95 (19.3)
None	178 (54.3)	85 (51.5)	263 (53.4)
CRF			
Nature of disease			
Visceral	172 (52.4)	89 (53.9)	261 (52.9)
Bone-only	70 (21.3)	39 (23.6)	109 (22.1)
Other	86 (26.2)	37 (22.4)	123 (24.9)
Prior endocrine therapy ([neo]advjuant)			
Prior AI therapy	85 (25.9)	50 (30.3)	135 (27.4)
Other prior endocrine therapy	65 (19.8)	30 (18.2)	95 (19.3)
None	178 (54.3)	85 (51.5)	263 (53.4)

Source, MONARCH 3 CSR, Table JPBM 11.4 and 11.21, page 92 and 125.

Table 17 below summarizes post study treatment discontinuation therapies and procedures as of data cut-off date of January 31, 2017.

Table 17. Postdiscontinuation Therapies in MONARCH 3 ITT Population

	Abemaciclib + NSAI N=328 n (%)	Placebo + NSAI N=165 n (%)	Total N=493 n (%)
Patients on study treatment	162 (49.4)	64 (38.8)	226 (45.8)
Patients off treatment	164 (50.0)	98 (59.4)	262 (53.1)
Systemic therapy	111 (33.8)	80 (48.5)	191 (38.7)
Chemotherapy	47 (14.3)	35 (21.2)	82 (16.6)
Endocrine therapy	84 (25.6)	60 (36.4)	144 (29.2)
Targeted therapy	22 (6.7)	25 (15.2)	47 (9.5)
Surgical Procedure	1 (0.3)	4 (2.4)	5 (1.0)
Radiotherapy	20 (6.1)	16 (9.7)	36 (7.3)

Reviewer Comments: *This table demonstrates the post-discontinuation therapies received by patients after discontinuing abemaciclib or placebo plus NSAI. More patients in the placebo arm discontinued study treatment than did in the abemaciclib arm. For those that did discontinue therapy, 111/164 (67.7%) of the abemaciclib plus NSAI and 80/98 (81.6%) of the placebo plus NSAI arm went on to receive further systemic therapy. There was a numerically greater proportion of patients in the placebo arm who went on to receive surgery and/or radiotherapy despite there being similar proportions of patients with locally advanced disease in each treatment arm.*

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance with abemaciclib or placebo and NSAI was measured by pill counts and summarized. Table 18 below demonstrates the applicant's analysis of treatment compliance. As was noted in their analysis, there were abnormally high levels of noncompliance that were due to patients discontinuing study therapy and not returning their medications. The last rows of the table include the reviewer's analysis leaving these outliers out to better understand treatment compliance.

Table 18. FDA Reviewer Analysis of Treatment Compliance in MONARCH 3

	Abemaciclib plus NSAI N=327 (%)	**Placebo plus NSAI N=161 (%)**
Compliance[a]		
Median	98.25	98.78
Q1-Q3	94.86-99.78	96.51-99.74
Min, Max	18.24-350.00	54.55-254.55
Mean (Std Dev)	97.48 (18.71)	99.89 (16.96)
Reviewer analysis excluding patients with >150% adherence		
Compliance[a]		
Median	98.23	98.74
Q1-Q3	94.8-99.75	96.50-99.74
Min, Max	18.24-147.37	54.55-149.40
Mean (Std Dev)	96.31 (11.47)	98.5 (10.62)

[a]Dose compliance was calculated as total amount of drug taken/total amount prescribed x 100
Dose adjustments were taken into account to measure compliance
Source MONARCH 3 CSR page 101 and Reviewer Analysis using adex.xpt dataset

Reviewer Comments: *As seen in the table above, there were numerical differences in the compliance rates that became more clear when patients who had a >150% compliance recorded were excluded from the analysis. Measuring treatment compliance is difficult, and pill counts can be problematic. It is notable that a numerically larger difference between groups occurred when the outliers were discarded as higher compliance rates were patients who were*

nonadherent and did not return study drug. The numerical difference persisted if patients who had >110% compliance recorded were excluded from the analysis.

Concomitant Medications and Rescue Medications

Prohibited medications included the use of megestrol acetate as an appetite stimulant. Additionally, as studies indicate that abemaciclib is extensively metabolized via the CYP3A system, grapefruit juice, strong inhibitors and inducers of CYP3A were to be substituted or avoided. These drugs include carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, rifabutin, St. John's Wort, HIV protease inhibitors, clarithromycin, itraconazole, ketoconazole, and nefazodone. Dexamethasone was permitted as a supportive care therapy where indicated, preferably for a treatment course of ≤7 days.

The most common concomitant medications during the study were analgesics, antidiarrheals, antiemetics, bone modifying agents and hematopoietic growth factors. Table 19 below demonstrates concomitant therapies by treatment arm.

Table 19. Concomitant Therapies in MONARCH 3

	Abemaciclib plus NSAI N=327 n (%)	**Placebo plus NSAI N=161 n (%)**
Patients with ≥1 antidiarrheal	224 (68.5)	26 (16.1)
Patients with ≥1 analgesic	213 (65.1)	104 (64.6)
Patients with ≥1 bone modifying agent	151 (46.2)	68 (42.2)
Patients with ≥1 antiemetic or antinauseant	45 (13.8)	8 (5.0)
Patients with ≥1 G-CSF or GM-CSF	14 (4.3)	2 (1.2)
Patients with ≥1 erythropoietic agent	5 (1.5)	0

Source Reviewer Modified from MONARCH 3 CSR page 100

Reviewer Comments: *There was a marked difference in the use of antidiarrheal therapies between treatment arms which is consistent with the high incidence of diarrhea with the use of abemaciclib. Additionally, there was greater use of antiemetics and hematopoietic growth factors including G-CSF and erythropoietin. The increased use of these medications is consistent with adverse event reporting of nausea and hematologic abnormalities including neutropenia and anemia. Numerically more patients in the abemaciclib and NSAI arm as compared to the placebo plus NSAI arm received bone modifying agents which are known to have benefits in patients with bony metastatic disease.*

Efficacy Results – Primary Endpoint

The primary analysis results, based upon the interim analysis, are presented in Table 20. The updated primary analysis results are presented in Table 21. The updated results were conducted at 246 progression events, and closely mimics the pre-planned final PFS analysis. Since the updated results allow for the estimation of the median in the treatment arm, the agency used these results in the package insert.

A Kaplan-Meier plot of the primary PFS results based upon the updated data is shown in Figure 5.

Using the data cutoff for the interim analysis, the applicant sent the radiological scans to a blinded independent review committee to assess PFS. The results of this reanalysis are shown in Table 22. Note that the BIRC PFS endpoint for the updated analysis was not yet available at the time of this review.

Reviewer's Comment: *The primary endpoint of investigator assessed PFS demonstrated a statistically and clinically meaningful improvement in PFS with the addition of abemaciclib to an NSAI. The PFS analysis by blinded review provided support for the investigator PFS analysis.*

Table 20. MONARCH 3 Primary Endpoint Results (PFS by local investigator)

	Abemaciclib plus NSAI N = 328	**Placebo plus NSAI N = 165**
Events, n (%)	108 (32.9)	86 (52.1)
Censored, n (%)	220 (67.0)	79 (47.9)
Median, months (95% CI)	NE (NE, NE)	14.7 (11.1, 17.5)
Hazard ratio, estimate (95% CI)	0.543 (0.409, 0.723)	
p-value	< 0.0001	

Source: CSR table 11.14. NE = not estimable. Cutoff date for this analysis was 1/31/2017.

Table 21. MONARCH 3 Primary Endpoint Updated Results (PFS by local investigator)

	Abemaciclib plus NSAI N = 328	**Placebo plus NSAI N = 165**
Events, n (%)	138 (42.1)	108 (65.5)
Censored, n (%)	190 (57.9)	57 (34.5)
Median, months (95% CI)	28.2 (23.5, NE)	14.8 (11.2, 19.2)
Hazard ratio, estimate (95% CI)	0.540 (0.418, 0.698)	
p-value	< 0.0001	

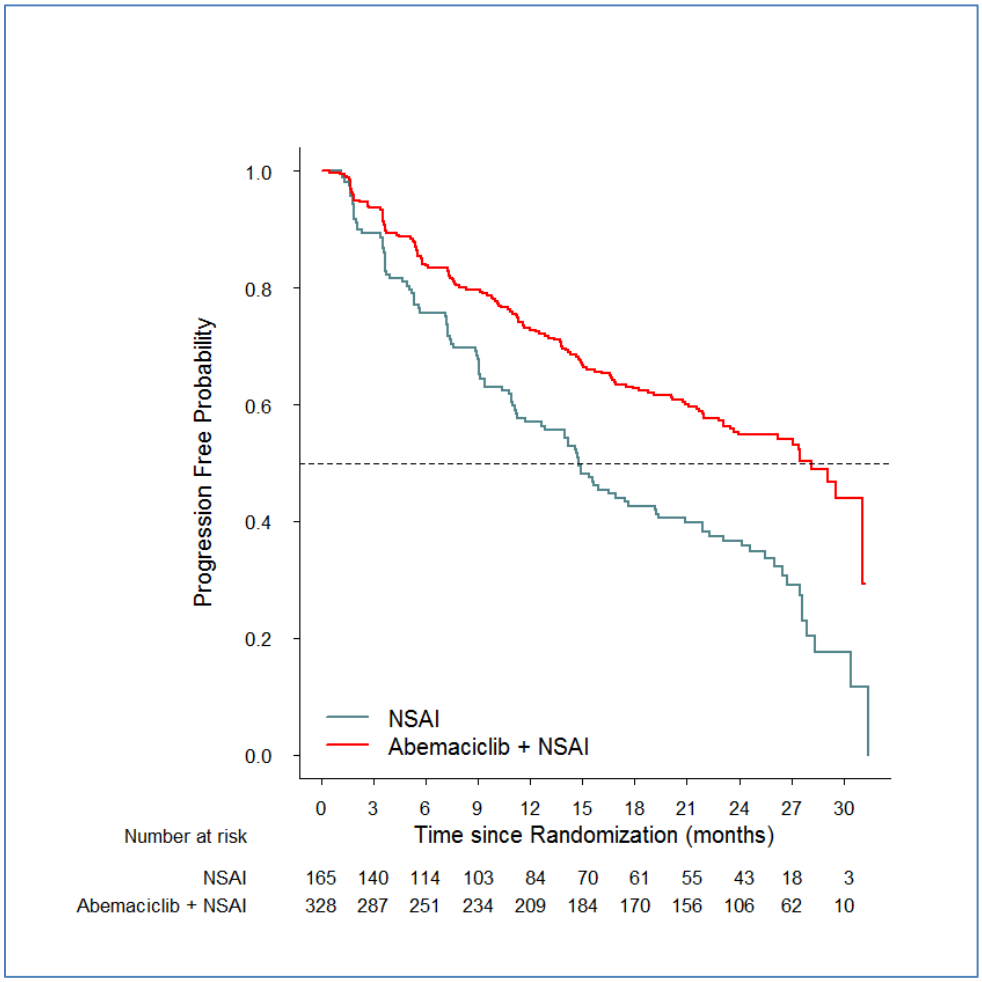
Source: Sponsor provided briefing document. NE = not estimable. Cutoff date for this analysis was 11/3/2017.

Table 22. MONARCH 3 Primary Endpoint Results (PFS by blinded review committee)

	Abemaciclib plus NSAI N = 328	**Placebo plus NSAI N = 165**
Events, n (%)	72 (22.0)	59 (35.8)
Censored, n (%)	256 (78.0)	106 (64.2)
Median, months (95% CI)	NE (NE, NE)	19.2 (16.0, NE)
Hazard ratio, estimate (95% CI)	0.51 (0.359, 0.720)	
p-value	<0.0001	

Source: MONARCH 3 CSR table 14.20. NE = not estimable. Cutoff date for this analysis was 1/31/2017.

Figure 4. Kaplan-Meier plot of Primary PFS Results (Updated Analysis)



Source: Reviewer's analysis, dataset: adtte.xpt (updated).

Data Quality and Integrity

The data were of good quality and consistency. It was generally easy to recreate the results found in the study CSR.

Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoint of overall survival was immature at the time of the interim PFS and updated PFS analysis. The overall survival results at the time of updated PFS analysis are shown in Table 23 and Figure 6.

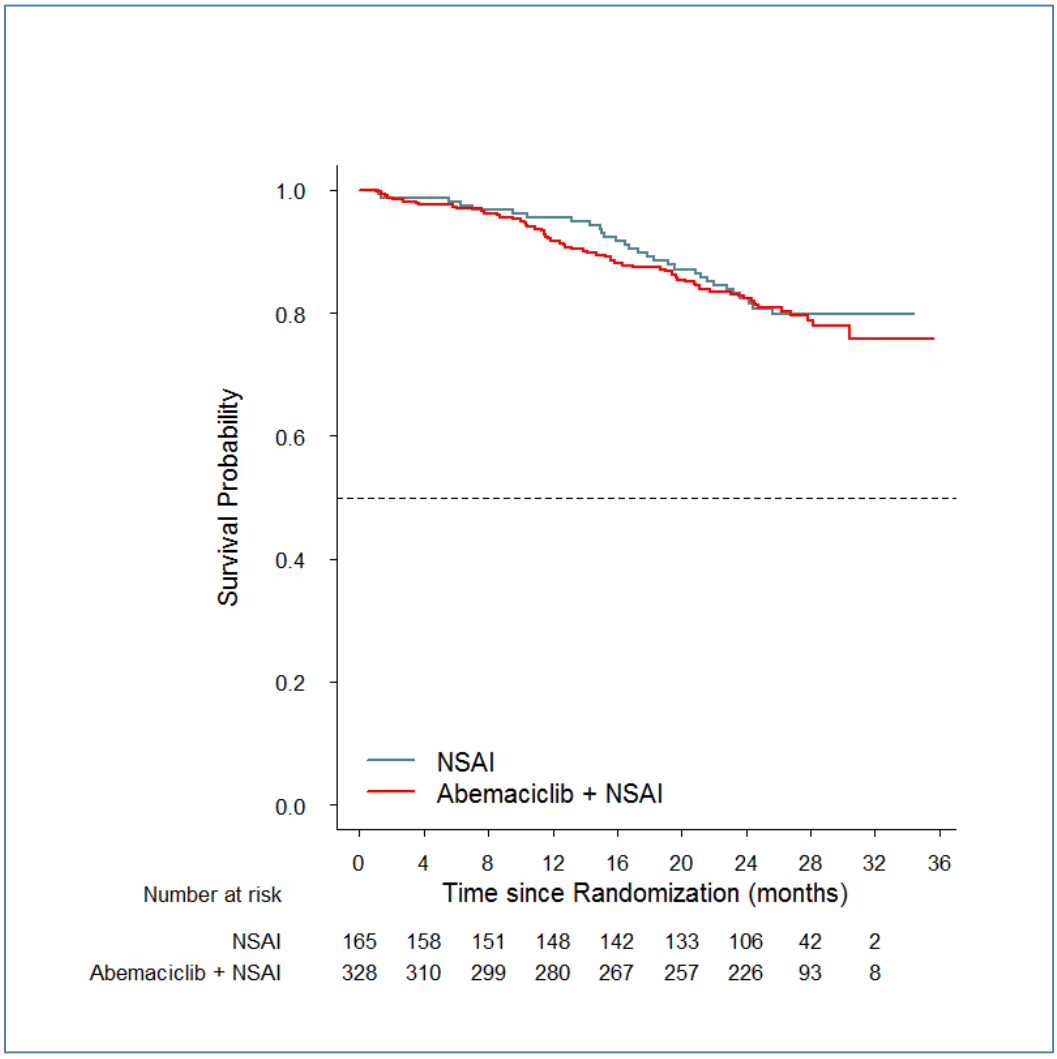
Reviewer's Comment: *The overall survival results are immature and it is difficult to make conclusions on the survival benefit at this point. Nevertheless, there does not appear to be any detriment to survival.*

Table 23. MONARCH 3 Overall Survival Results (Updated results)

	Abemaciclib plus NSAI N = 328	**Placebo plus NSAI N = 165**
Events, n (%)	63 (19.2)	38 (18.2)
Censored, n (%)	265 (80.8)	127 (77.0)
Hazard ratio, estimate (95% CI)	1.06 (0.68, 1.63)	

Source: Sponsor briefing document JPBM Clinical Study Report Addendum for the Final Progression-Free Survival Analysis, data cutoff 11/3/2017.

Figure 5. Overall Survival Results (Updated Results)



Source: Reviewer's analysis, dataset: adtte.xpt (updated).

Additional secondary endpoints of interest include overall response rate and duration of response. According to the protocol, overall response rate was to be unconfirmed but duration of response was to be based upon confirmed response rate (i.e. two consecutive PR or CR measurements). For consistency, overall response and duration of response are provided for both confirmed and unconfirmed responses in Table 24 (in the measurable disease population). These values are based upon the updated data, not the interim analysis data.

Table 24. MONARCH 3 Overall Response and Duration Endpoints (measurable disease)

	Abemaciclib plus NSAI N = 267	Placebo plus NSAI N = 132
Confirmed		
Overall Response Rate	55.4 (49.5, 61.4)	40.2 (31.8, 48.5)
Duration of response, months (95% CI)	NE (25.7, NE)	17.5 (11.6, 22.2)
Unconfirmed		
Overall Response Rate	61.0 (55.2, 66.9)	45.5 (37.0, 53.9)
Duration of response, months (95% CI)	27.4 (25.7, NE)	17.5 (11.2, 22.2)

Source: Sponsor briefing document, reviewer's analysis. NE = not estimable.

Reviewer's Comment: *The response rate data further supports the activity of abemaciclib.*

Dose/Dose Response

Not applicable since only one dose level was used.

Durability of Response

Not applicable to this study as treatment was continued until progression or unacceptable toxicity.

Persistence of Effect

Not applicable to this study.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Patient reported outcome measurements were taken at the same time as the radiological scans were done for the primary endpoint. Completion rates were typically very good, with average response after progression, i.e. 70%. Table 25 displays the completion rates for the three measurement scales across each cycle. There does not appear to be any major difference between the treatment and control arms in terms of completion rates.

Table 25. PRO Completion Rates for MONARCH 3

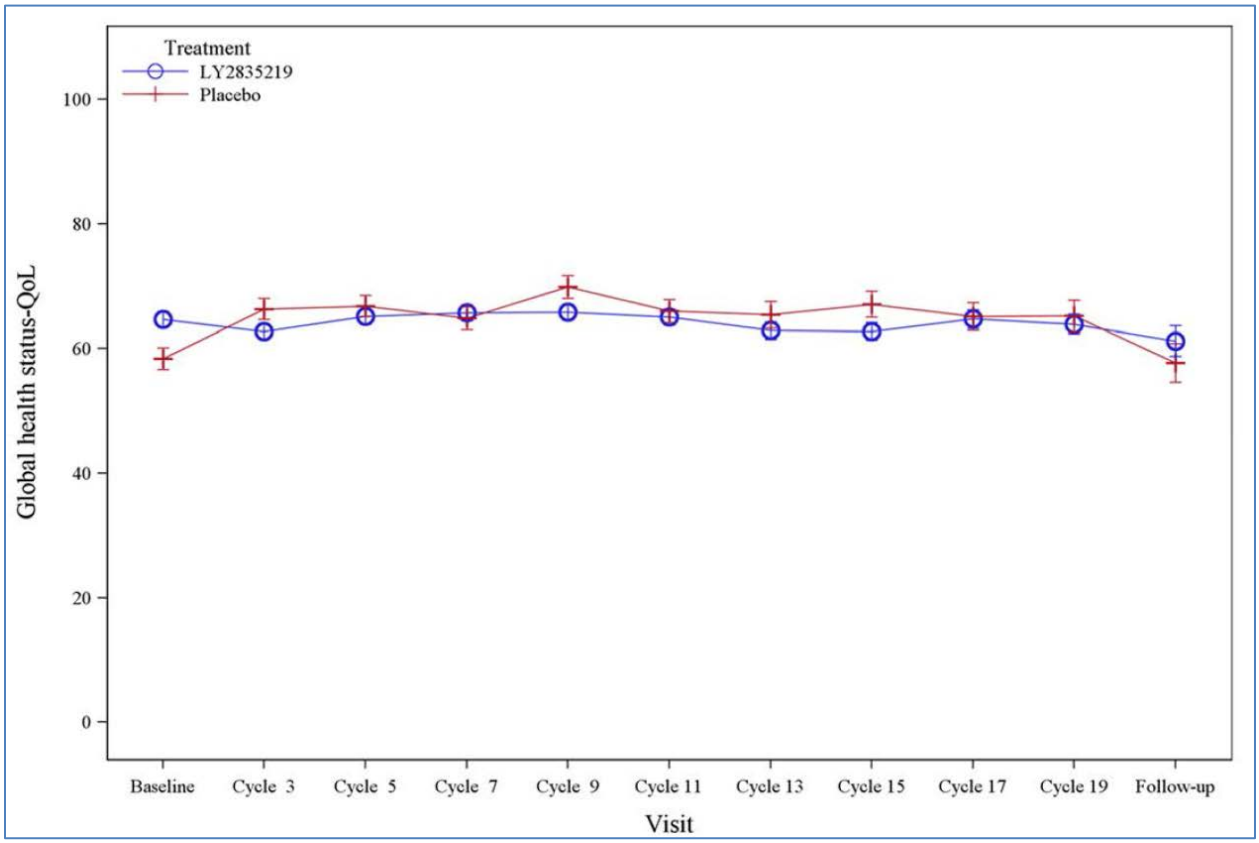
Cycle	QLQ C30 Trt, %	QLQ C30 Cntl, %	QLQ BR23 Trt, %	QLQ BR23 Cntl, %	EQ-5D Trt, %	EQ-5D Cntl, %
Baseline	96.96	98.1	95.7	97.5	97.6	96.9
3	98.3	98.6	97.3	98.6	98	98.6
5	97	97.6	96.6	96.9	97	96.9
7	97.2	95.7	97.2	96.6	96.4	98.3
9	96.9	97.2	96.5	96.3	96.5	96.3
11	94.5	96.9	94.5	95.9	95.9	96.9
13	94.1	95.4	95.1	95.4	94.1	95.4
15	95.4	96.4	95.1	96.4	95.1	96.4
17	96.4	94.6	95.8	93.2	95.2	94.6
19	97.4	91.3	96.5	91.3	96.5	93.5
22	92.3	70.6	92.3	70.6	94.1	64.7
25	100	100	100	100	100	100
28	100	n/a	100	n/a	100	n/a
Flw-Up	77.5	70.2	78.1	67.9	76.6	69

Source: CSR Table 14.26, 14.28, 14.30. n/a = no patient on study at that timepoint.

EORTC QLQ-C30

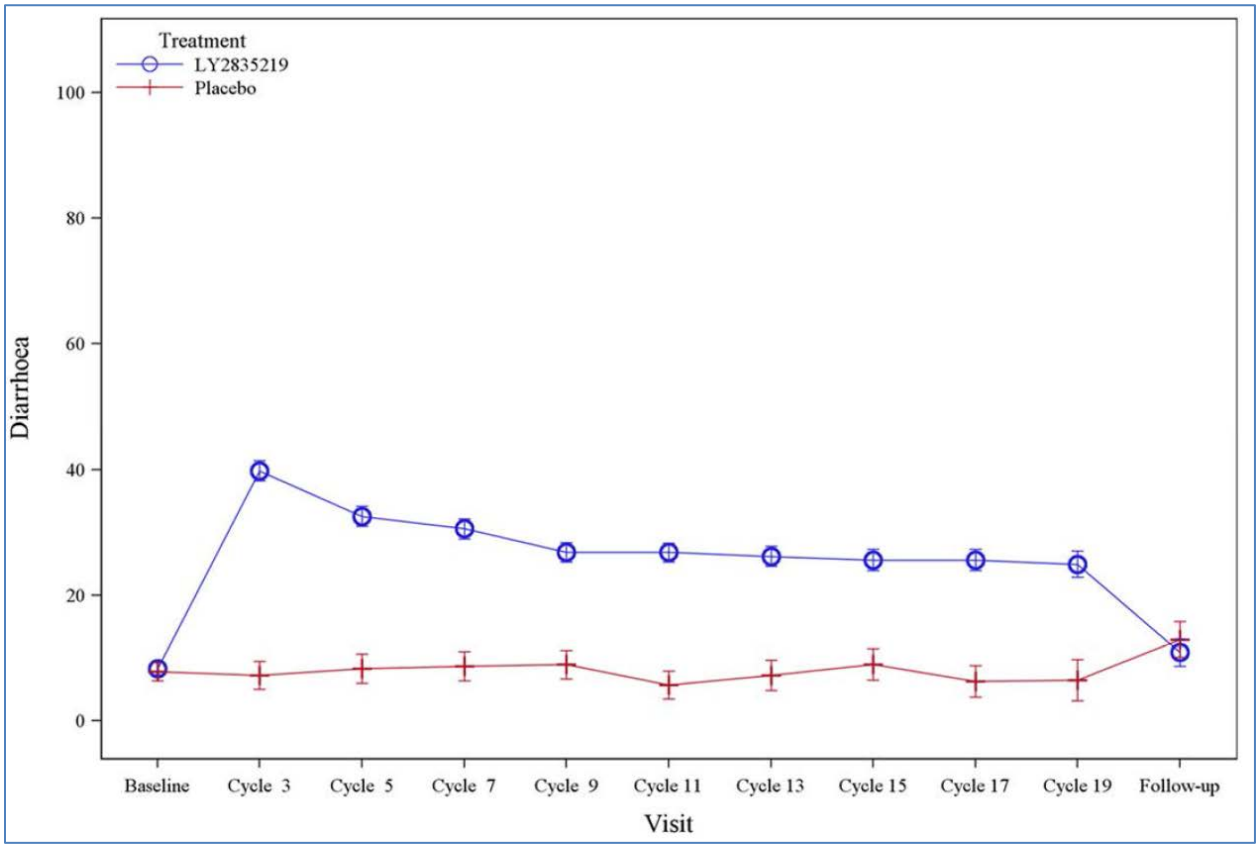
For the overall quality of life, there was no major difference between treatment and placebo. See Figure 6 for a visual display of quality of life measurements. Like Monarch 2, diarrhea reported much higher scores in the treatment arm vs the control (Figure 7). This is consistent with the safety profile.

Figure 6. EORTC QLQ-C30 Global Health Status Over Time



Source: CSR Figure 14.12. Note that higher scores represent better quality of life.

Figure 7. EORTC QLQ-C30 Plot of Diarrhea Symptoms Over Time



Source: CSR Figure 14.25. Note that higher scores represent worse symptoms.

EORTC QLQ-BR23

For the BR23 measurement tool, there were no major differences (similar to the level seen on the diarrhea scale in the C30) on any of the individual measurements. Of note, patients in treatment arm tended to report slightly worse body image scores as well as slightly worse systemic therapy side effect scores. The worse side effect scores are likely due to diarrhea, see Figure 7.

EQ-5D

There were no major differences over time for the overall quality index or the visual analog scale. These results are consistent with the global health status of the EORTC-QLQ-C30.

Additional Analyses Conducted on the Individual Trial

Subgroup Analyses

Subgroup analyses of the primary endpoint are presented in Table 26. The results are consistent with those in the overall population.

Table 26. Subgroup Analysis of Primary Endpoint (updated analysis)

	N	HR	95% CI
Age			
< 65 Years Old	271	0.489	0.35, 0.68
>= 65 Years old	222	0.612	0.41, 0.91
Race			
White	288	0.671	0.49, 0.93
Asian	148	0.332	0.21, 0.54
Other	57	0.747	0.34, 1.65
Region			
USA	36	0.803	0.29, 2.26
Rest of World	457	0.520	0.40, 0.68

Source: Reviewer's analysis, datasets: adtte.xpt, adsl.xpt.

MONARCH 2

The sponsor included 44 endocrine therapy naïve metastatic breast cancer patients from their MONARCH 2 trial to support the claim (b) (4) This cohort included 28 patients randomized to fulvestrant + abemaciclib and 16 patients randomized to fulvestrant + placebo. Each arm had 9 progression events that lead to an estimated hazard ratio of 0.51 (95% CI 0.2, 1.3).

Reviewer's Comment: *The Agency noted that there appears to be* (b) (4) *however, the lack of prespecified PFS analysis and limited sample size, as well as the inclusion of both pre- and postmenopausal patients in this small sampl* (b) (4)

Integrated Review of Effectiveness

Results from the MONARCH 3 study demonstrate a statistically significant and clinically meaningful improvement in progression free survival with the addition of abemaciclib to a NSAI for the initial endocrine based treatment of postmenopausal women with HR positive, HER2 negative locally advanced or metastatic breast cancer. Clinical pharmacology data demonstrate that there is no clinically relevant effect of exemestane on abemaciclib pharmacokinetics and data from I3Y-MC-JPBH demonstrated no alteration in safety signal between letrozole,

anastrozole and exemestane. Overall survival data are immature; however, there is no compelling evidence of harm at this point.

These data further support the efficacy of abemaciclib for patients with advanced or metastatic HR positive, HER2 negative breast cancer as the MONARCH 2 and MONARCH 1 trials also did, though in different lines of therapy. While no pooled analysis can be made across trials due to their different study populations, the totality of evidence thus far demonstrates that abemaciclib, whether as a single agent or in combination with endocrine based therapy, is an effective therapy for the treatment of HR positive, HER2-negative metastatic breast cancer.

8.1.3. Assessment of Efficacy Across Trials

Primary Endpoints

Not applicable.

Secondary and Other Endpoints

Not applicable.

Subpopulations

Not applicable.

Additional Efficacy Considerations

Abemaciclib has been studied in MONARCH 3 as initial endocrine based therapy with NSAI, in MONARCH 2 with fulvestrant for patients who progressed on initial endocrine therapy, and in MONARCH 1 as a single agent for patients after 1-2 lines of chemotherapy. Each indication has been in patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer. For the indications with endocrine based therapies, this has been limited to female patients based on differences between males and females regarding the role of circulating estrogens which differ. It is unclear what the efficacy of the indications of abemaciclib combined with endocrine therapy might be in this indication.

It is also not clear what the efficacy of an AI in combination with ovarian function suppression might be in premenopausal patients, though this combination may be used in the postmarket setting.

(b) (4)

(b) (4)

Abemaciclib has not yet been fully evaluated in combination with tamoxifen. Given the overlapping increased risk of VTE and hepatotoxicity, it is not clear whether this combination might be associated with increased toxicity.

No CDK4/6 inhibitor has been studied as treatment after a previous CDK4/6 inhibitor and thus it is not clear whether there is any benefit of therapy with these agents after progression with another agent or combination.

8.1.4. Integrated Assessment of Effectiveness

MONARCH 3 demonstrates the activity and efficacy of abemaciclib in combination with an NSAI in the initial endocrine based therapy setting for postmenopausal women. Additionally, MONARCH 1 has demonstrated the activity of abemaciclib as a single agent and the MONARCH 2 trial has demonstrated the efficacy of abemaciclib in combination with fulvestrant in women who have progressed on initial endocrine based therapy.

The improvement in PFS demonstrated in the MONARCH 3 trial with the use of abemaciclib in combination with an NSAI as compared to placebo combined with NSAI is both statistically significant and clinically meaningful. Overall survival data are immature, however demonstrate no compelling evidence of harm to overall survival at this time.

8.2. Review of Safety

8.2.1. Safety Review Approach

For this sNDA, the applicant submitted safety data from MONARCH 3, a phase 3 trial of abemaciclib plus NSAI versus placebo plus NSAI. Abemaciclib is currently approved based on data from the MONARCH 2 and MONARCH 1 studies where 573 patients had received at least one dose of abemaciclib. In the MONARCH 3 study, 326 patients received at least one dose of abemaciclib in combination with an NSAI. Adverse events were assessed at baseline and during the study treatment period and for at least 39 days after study completion. The incidence and severity of adverse events were compared to prior and ongoing trials with abemaciclib and were placed in the context of other drugs in the same class. Laboratory studies were obtained at baseline and day 1 of each cycle. Hematology labs included a complete blood cell count with differential. Serum chemistries included a liver function evaluation, renal function evaluation, and electrolytes. There were no clinical holds for safety during the development of abemaciclib.

At the time of data cutoff of February 14, 2017, the Lilly Safety System contained 1613 patients who had been treated with at least one dose of abemaciclib. Of these, 328 were healthy subjects. The safety data supporting this application include MONARCH 2, 1 and 3, the three

registration studies that provide the primary safety data supporting the use of abemaciclib in combination with endocrine therapies and as a single agent.

8.2.2. Review of the Safety Database

Overall Exposure

As of August 11, 2017, 135 patients in the abemaciclib plus NSAI arm and 44 patients in the placebo plus NSAI arm continued to receive protocol directed therapy. The median daily dose of abemaciclib was 253.34 mg per day (range 51.52-350.00) and of placebo was 294.34 (280.67-298.78). The median duration of abemaciclib exposure was 66.57 weeks (range 20.00-104.43).

Table 27. Summary of Drug Exposure and Dose Intensity for Abemaciclib or Placebo in MONARCH 3

	Abemaciclib plus NSAI N=326	**Placebo plus NSAI N=161**
Cycles received per patient		
Median	16	15
Q1-Q3	5-26	6-24
Min, max	1, 33	1, 31
Mean (Std Dev)	15.7 (10.4)	14.9 (9.6)
Duration of therapy (weeks)		
Median	66.6	60.3
Q1-Q3	20.0-104.4	23.6-100.0
Min, max	0.71, 135.43	1.6-127.0
Mean (Std Dev)	65.0 (42.9)	60.6 (39.5)
Cumulative dose (mg)		
Median	101675	109200
Q1-Q3	33450-272850	47100-198250
Min, max	900, 272850	47100-261700
Mean (Std Dev)	107380.4 (78281.0)	120330.8 (79801.0)
Dose intensity (mg/day)		
Median	254.3	294.3
Q1-Q3	190.9-293.2	280.7-298.8
Min, max	51.5, 350.0	145.6-763.6
Mean (Std Dev)	237.3 (61.8)	288.6 (52.8)
Relative dose intensity	84.5%	98.1%

Source: From 90-day safety update for MONARCH 3 provided on November 8, 2017

Reviewer Comments: *As demonstrated here, there were dose reductions and dose interruptions in the abemaciclib plus NSAI arm that reduced dose intensity. Patients were on abemaciclib and*

NSAI for a numerically greater time period which may be related to the improvement in progression seen with the addition of this agent to NSAI therapy.

Relevant characteristics of the safety population:

Demographic information for the patients included in the safety database from the MONARCH 3 study is included in section 8.1.2 above. Baseline characteristics of the patients in the two treatment arms of the MONARCH 3 study were well-balanced. All patients in this study were postmenopausal females and the majority of patients were white. Approximately 30% of patients in the MONARCH 3 study were of Asian descent. The median age of patients in the MONARCH 3 study was 63 (32-88). No patients had received prior systemic therapy in the metastatic setting. Over 50% of patients had visceral disease at baseline and 53.3% of patients had received no prior endocrine therapy. Most patients in this study had one or more comorbid conditions. Over half of the patients in MONARCH 3 had an ECOG PS of 0 at study entry.

Based on these data, the patients included in the safety database from MONARCH 3 is generally representative of the population of women with metastatic HR positive, HER2 negative breast cancer in the overall population, though Black or African-American patients are underrepresented in this study population.

Adequacy of the safety database:

The safety database from 488 patients treated in the MONARCH 3 study is adequate. Additionally, as noted previously, over 1600 cancer patients have received this drug in studies across the abemaciclib clinical development program. The age and sex of the patients is expected for those patients with breast cancer. No male patients and no premenopausal women were included in this study. While the MONARCH 3 study included a sizeable number of Asian patients, Black or African-American patients were underrepresented in both trials. Patients included in these studies had a performance status that was better than patients with metastatic breast cancer as a whole. Based on these data, the patients included in the safety database are of similar age, but are likely healthier than the population of women in the US with metastatic HR positive, HER2 negative breast cancer.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall the data quality for the MONARCH 3 study was acceptable. Case report forms (CRFs) were reviewed and compared to the datasets and narratives. The data in the CRFs and AE databases was generally consistent with any exceptions noted within the course of the review.

Categorization of Adverse Events

The investigator used adverse event terms and severity grading using version 4.0 of CTCAE. AE text was mapped by the sponsor to corresponding terminology within MedDRA.

Preexisting conditions were defined as AEs that began prior to the first dose of study drug.

Treatment emergent AEs TEAEs were defined as any AE beginning between the day of the first dose and 30 days after the last dose of any study drug (or any time if serious and related to study treatment) or any preexisting condition that increased in CTCAE grade between the day of the first dose and 30 days after the last dose of study drug. A serious AE was any AE during the study that resulted in death, initial or prolonged hospitalization, a life-threatening experience, persistent or significant disability, congenital anomaly or birth defect, or was considered significant for any other reason.

Important medical events that may not have resulted in death, were life threatening, or required hospitalization may have been considered SAEs when thought to have jeopardized the patient and may have required medical or surgical intervention to prevent an outcome listed above.

The relationship of the AE was to study treatment was also assessed and per standard procedures, all “related” and “possibly related” AEs and SAEs were defined as related to study treatment.

All relevant hematology and chemistry laboratory values were graded according to CTCAE v. 4.0. Grading was summarized by cycle and maximum postbaseline grade over the course of the study.

Reviewer Comment: *The applicant used standard definitions of SAE. The safety review was performed to describe TEAEs regardless of investigator assessment of attribution.*

Routine Clinical Tests

Routine laboratory testing including a CBC with differential (WBC, absolute neutrophil count, absolute lymphocyte count, hemoglobin, hematocrit, and platelets), serum chemistries (creatinine, BUN, sodium, potassium, calcium, ALT, AST, alkaline phosphatase, total bilirubin, albumin) were collected at baseline and on day 1 of each cycle. Vital signs including blood pressure (systolic and diastolic), pulse and respiration rate, weight and height were collected at baseline and all except for height were reassessed at each study visit and physical examination was performed. Collection of concomitant medications and adverse event collection and grading were performed at each study visit as well. Local ECG was performed at baseline and at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 1 and at short term follow-up.

Reviewer Comment: *The frequency of laboratory assessments was less than is currently recommended in the USPI based on in the incidence and timing of the adverse events so as to better assess neutrophils given the risk of neutropenia and hepatic transaminases given the risk*

of hepatotoxicity.

8.2.4. Safety Results

Deaths

In the MONARCH 3 study, at the time of the 90-day safety update (August 11, 2017), there were 13 deaths on therapy or within 30 days of treatment discontinuation in the abemaciclib plus NSAI arm and 3 deaths in the placebo plus NSAI arm. Of these deaths 3 on the abemaciclib plus NSAI arm were attributed to progressive disease while 1 on the placebo plus NSAI arm were attributed to this. Ten (10) deaths on the abemaciclib plus NSAI arm and 2 on the placebo plus NSAI arm were attributed to adverse events. A review of the narratives of the patients who died during this period was performed. Table 28 below is the applicant's summary of deaths on treatment or within 30 days of treatment discontinuation.

Table 28. MONARCH 3 Summary of Deaths for the Entire Study Period

	Abemaciclib plus NSAI N=327 n (%)	**Placebo plus NSAI N=161 n (%)**
All deaths	52 (15.9)	24 (14.9)
Death on therapy or within 30 days of treatment discontinuation	13 (4.0)	3 (1.9)
Reason for death		
Adverse events	10 (3.1)	2 (1.2)
Cerebral Ischemia	1 (0.3)	0
Cerebrovascular accident	1 (0.3)	0
Embolism	2 (0.6)	0
General Physical Health Deterioration	0	1 (0.6)
Lung Infection	3 (0.9)	0
Pneumonitis	2 (0.6)	0
Respiratory Failure	1 (0.3)	0
Sudden death	0	1 (0.6)
Adverse events related to study treatment	5 (1.5)	0
Cerebral Ischemia	1 (0.3)	0
Cerebrovascular accident	1 (0.3)	0
Lung Infection	1 (0.3)	0
Pneumonitis	1 (0.3)	0
Respiratory Failure	1 (0.3)	0
Study disease	3 (0.9)	1 (0.6)
Deaths after 30 days of treatment discontinuation	39 (11.9)	21 (13.0)

Source MONARCH 3 90-day Safety Update, page 28

Narratives of Patients who Died on the Abemaciclib Plus NSAI Arm within 30 Days of Treatment Discontinuation

I3Y-MC-JPBM-(b) (6) This was an approximately 62-year-old Caucasian female with a past medical history significant for arthritis, thoracic back pain, and dyspnea with no past medical history of smoking, COPD or asthma. She had stage IV breast cancer and was previously treated with 30 Gy radiation to the thoracic spine in (b) (6) 2015. She initiated treatment with abemaciclib and NSAI on (b) (6). At the time of study initiation, she had metastatic disease to the lungs, pleural effusions, and pleural involvement by metastatic disease.

On (b) (6), the patient's ANC was 1800. Her last dose of study drug was (b) (6). The patient developed chills, night sweats, and nasal congestion and had worsening shortness of breath. The patient was hospitalized on (b) (6) and was noted to be hypoxic with oxygen saturation of 86% on room air. CT scan on (b) (6) demonstrated interstitial pneumonia and the patient was treated with antibiotics and steroids. Blood cultures were negative. ANC was normal and BNP was within normal limits. Target lesions on CT scan were improved. The patient died on (b) (6) due to an acute RUL pneumonia. No autopsy was performed. The investigator assessed the death as related to study drug. The applicant determined there was insufficient evidence to attribute this death to study drug due to the timing of the event occurring after discontinuation of study drug, the history of prior radiation therapy, the known metastatic disease to the lung, and the underlying dyspnea.

Reviewer Comments: *It is unclear whether this event is directly related to study drug. While there was no evidence of neutropenia, there is increased risk for infections with CDK4/6 inhibitors more generally. Given the patient's history of radiation, this may have been a radiation associated pneumonitis as it was focal, however, she did not clinically improve on steroids. Given the clinical history of chills, night sweats and nasal congestion preceding this event, an infectious etiology sounds probable. This reviewer concurs that there is insufficient evidence to link the study drug to this death.*

I3Y-MC-JPBM-(b) (6) This is a 66-year-old African-American female with a past medical history of type 2 diabetes, obesity, hypertension, hyperlipidemia, former smoker, chronic L arm edema and history of cellulitis, and peripheral neuropathy who reportedly died from study disease. She had visceral metastases at the time of study entry. She was initiated on study therapy on (b) (6) and discontinued study therapy on (b) (6) due to worsening cellulitis. She was admitted to the hospital on (b) (6) with worsening left arm cellulitis and was found to have blood cultures positive for group A beta hemolytic strep. Her absolute neutrophil count was within normal range during this. She was noted to have had her cellulitis resolve on (b) (6) She died on (b) (6). No autopsy was performed.

Reviewer Comments: *Given that she had the recent adverse event of upper extremity cellulitis*

with accompanying bacteremia, it is likely that this played a role in her death. She did have multiple comorbidities including diabetes, obesity, and lymphedema that put her at increased risk for cellulitis. There is no objective evidence documenting disease progression. While this reviewer differs in the opinion for cause of death, it is agreed with the applicant that there is insufficient evidence to directly link this death to study drug given the patient's comorbidities and lack of neutropenia during the event.

I3Y-MC-JPBM-(b) (6) This is a 58-year-old Latina female with a past medical history significant for diabetes mellitus, hypertension, pulmonary embolism, and stage IV breast cancer who initiated study therapy on (b) (6). At the end of (b) (6), she experienced dyspnea and study drug was eventually withdrawn on (b) (6). She went to the Emergency Room with respiratory failure on (b) (6). No CT scan was performed. The investigator noted the cause of death as pulmonary embolism. No autopsy was performed. The applicant noted there was no study performed to document this and given this did not think this event could be considered reasonably related to study drug given the broad differential for respiratory failure.

Reviewer Comments: *There is inadequate clinical information given the lack of imaging or autopsy to determine the cause of death and relatedness to study drug, however increased risk for VTE and PE are known AEs associated with abemaciclib. Agree with the applicant that there is insufficient evidence to link the study drug to this death.*

I3Y-MC-JPBM-(b) (6) This was a 51-year-old Caucasian female with a past medical history significant for metastatic breast cancer with pulmonary fibrosis and pleural effusion who initiated study therapy on (b) (6) and developed dyspnea on (b) (6). She was admitted for further management on (b) (6) and on (b) (6) was diagnosed with aspiration pneumonia though there was no evidence of aspiration prior to the event. She had a cardiopulmonary arrest on (b) (6) and died on that day. There was no autopsy and no death certificate was available. There was no ANC available. The investigator thought this death not likely related to study therapy.

Reviewer Comments: *This reviewer agrees with the applicant that there is insufficient evidence to attribute this death to study therapy. While attributing the event to aspiration pneumonia is questionable, the patient has a recorded pretreatment AE of cough as well as comorbid conditions of pleural effusion and pulmonary fibrosis which may have contributed to the event. It is unclear whether an infectious etiology was the cause as well. The patient was noted to be on multiple inhaled medications for underlying pulmonary disease and she had visceral disease at study entry. Thus, the differential for the causes of her cardiopulmonary arrest are broad, but this is likely due to study disease, and there is insufficient evidence to link this to study therapy.*

I3Y-MC-JPBM(b) (6) This was a 79-year-old Caucasian female with a history of glaucoma, arthritis, history of tobacco abuse who died from cerebrovascular ischemia on (b) (6) after last receiving study therapy on (b) (6). She was hospitalized on (b) (6) and was found to have occlusion of the L carotid artery and was outside of the window for thrombectomy or

thrombolysis. No autopsy was performed. In the opinion of the investigator, the event was related to study drug treatment. In the opinion of the applicant, this event was not considered reasonably possibly related to study drug.

Reviewer Comments: *This reviewer agrees that this event is not likely related to study drug. Though the patient had no atherosclerosis, given the patient's age she was at increased risk for a CVA. Additionally, review of the abemaciclib safety database has been performed to assess for increased risk of arterial events and there does not appear to be an association.*

I3Y-MC-JPBM-(b) (6) This was a 63-year-old female with a past medical history significant for hypertension, dyslipidemia, and tobacco abuse who was also taking megestrol acetate in addition to study treatment. Study treatment began on (b) (6) and ended on (b) (6). She previously experienced the adverse events of vomiting. On (b) (6) she presented in the ED with complaints of a seizure and CT of the head demonstrated a hypodense area that was thought due to chronic ischemic injury. MRI of the brain performed on (b) (6) confirmed this. On (b) (6), the patient was admitted with dyspnea and low venous saturation and CT PE protocol was negative for PE but demonstrated bilateral pneumonia. She died from infectious pneumonia. Autopsy demonstrated massive tumor infiltration by lobular carcinoma of the chest wall, diffuse alveolar damage, and bilateral emphysema. Additionally, there was left pleuropulmonary lymphangitic carcinomatosis. Per the investigator, this was not related to blinded study drug. Per the applicant, there is insufficient evidence to link this to study drug.

Reviewer Comments: *This reviewer agrees with the applicant's assessment. In addition to evidence of lymphangitic spread, the patient had known ongoing tobacco use that likely led to the non-cancer associated pulmonary changes. It is not clear that there was any evidence of infectious pneumonia as the cultures grew candida and coagulase negative staph which are not likely to be pathogens. The cause of death is likely disease progression rather than infectious pneumonia based on the autopsy findings.*

I3Y-MC-JPBM-(b) (6) This was a 72-year-old Caucasian female with a past medical history of diabetes mellitus, hypertension, osteoporosis, cataracts, and amygdalectomy who initiated study therapy on (b) (6). She had known lung metastases. On (b) (6) she was diagnosed with pneumonitis and treated with steroids. Serologies were positive for mycoplasma pneumoniae and cytomegalovirus. She was treated with ganciclovir and levofloxacin. Bronchoscopy was not performed. The patient died on (b) (6). Autopsy was not performed. The investigator attributed pneumonitis as possibly related to study drug. The applicant did not think this was reasonably possibly related to study drug in the absence of additional diagnostic information such as bronchoscopy, and the known positive serologies for infectious causes.

Reviewer Comments: *Reviewer agrees with applicant that it is not clear that study drug is directly related given the probable infection and underlying pulmonary metastatic disease. In the absence of definitive biopsy, imaging findings could also be consistent with lymphangitic carcinomatosis. Concern for increased risk of pneumonitis continues to remain a safety signal of*

interest.

I3Y-MC-JPBM-(b) (6) This was a 60-year-old female with a past medical history significant for hypertension, coronary artery disease, chronic pancreatitis, current tobacco use, who began study therapy on (b) (6). On (b) (6), she presented with dyspnea and died within an hour of developing symptoms. The investigator initially noted the cause of death as disease progression, but then noted it to be due to thromboembolism. The investigator did not relate this to study drug, nor did the applicant.

Reviewer Comments: *While there was no radiological study documented embolic event, given the acuity of the patient's symptoms and subsequent rapid decline and death, this is a reasonable cause of death. While she did have a history significant for tobacco abuse which could contribute to her risk, data from both MONARCH 2 and MONARCH 3 demonstrate an increased risk of VTE with abemaciclib. Given this, and the short period that the patient had been on study drug, it is reasonable to consider this death as possibly related to study therapy.*

(b) (6) This was a 67-year-old Asian female with a past medical history significant for prior tobacco abuse, and elevation of AST who initiated study treatment on (b) (6) and discontinued therapy on (b) (6). She had metastatic breast cancer to the lungs, axillary nodes, and bone. On (b) (6) she was admitted to an outside hospital with dyspnea and CT scan demonstrated a new pleural effusion and increase in size of her pulmonary metastases. Labs performed on (b) (6) demonstrated a CRP of 10 mg/dL. CT on (b) (6) demonstrated bilateral ground glass opacities and what was thought to be stable if not slightly improved disease. She was reinitiated on letrozole; however, this was discontinued after she had worsening. She subsequently died on (b) (6). It was thought she may have had an aspiration event on (b) (6), though possible ILD was also considered with an elevated KL-6 level of 1410. The investigator assessed the event as related to study drug, though the cause of death was noted to be study disease. The applicant did not feel there was sufficient information to link this to study drug, given that there was no further evaluation with bronchoscopy, blood gas, or pulmonary function tests, and that the patient had a significant smoking history and known pulmonary metastases.

Reviewer Comments: *This reviewer agrees with the applicant's analysis. While there remains concern for possible drug induced pneumonitis from abemaciclib, the reports of these events are inadequate to fully attribute these cases to study drug. There may be increased risk in patients with a previous smoking history, however each of these cases has also had pulmonary metastases as well. In the absence of definitive biopsy, imaging findings could also be consistent with lymphangitic carcinomatosis. This continues to remain a safety signal of interest.*

I3Y-MC-JPBM(b) (6) This was a 72-year-old female with a past medical history significant for type 2 diabetes, hyperlipidemia, and anemia who died from pneumonitis. She initiated study therapy on (b) (6) and discontinued therapy on (b) (6) when she was admitted to the hospital for pneumonia and diagnosed with Influenza A. Her WBC at that time was 4,200 with

88.5% neutrophils. She developed a progressive pneumonia and died on (b) (6) with severe septic shock after being found to have Acinetobacter in her sputum. No autopsy was performed. The investigator did not consider this event related to study drug. The applicant did not consider this event related to study drug.

Reviewer Comments: *This reviewer considers the cause of death infectious pneumonia rather than pneumonitis given her documented infection with Influenza A and Acinetobacter. Agree with not attributing this event to study drug as the patient was not neutropenic at the time.*

I3Y-MC-JPBM (b) (6) This was an 86-year-old Caucasian female with a past medical history significant for hyperlipidemia, history of arterial thrombosis, gout, history of venous thrombosis, and hypertension who started treatment on (b) (6) and stopped treatment on (b) (6). She developed a pulmonary embolism on (b) (6). She was admitted to the hospital on (b) (6) for left leg erysipelas. CT chest, abdomen, and pelvis on (b) (6) demonstrated liver metastases, ascites, and left pleural effusion consistent with progressive disease. The patient died on (b) (6) from study disease and no autopsy was performed. The investigator assessed the death as not related to study treatment and the applicant agreed.

Reviewer Comments: *While there is an increased risk of infections seen in abemaciclib both with and without neutropenia, it is likely that this patient's death was due to progressive disease. There were no cultures performed nor other indications of possible sepsis. Given the CT findings, this was most likely due to study disease.*

I3Y-MC-JPBM- (b) (6) This was an 80-year-old female with a past medical history of hypertension, anxiety, hyperlipidemia, and obesity who died due to a hemorrhagic stroke. She initiated study therapy on (b) (6) and discontinued study therapy on (b) (6) the same day she was taken to the emergency room unconscious with tachycardia. EKG demonstrated atrial fibrillation. CT demonstrated massive hemorrhage with probable vertebral aneurysm rupture. There was no evidence of CNS metastases. No autopsy was performed. In the opinion of the investigator, the event was possibly related to anastrozole but not blinded study drug. In the opinion of the applicant, this event was not related to blinded study drug.

Reviewer Comments: *This reviewer concurs with the assessment that this event was not related to study drug. Given the patient's age and comorbidities, it is not likely related to anastrozole therapy either, as the patient had multiple risk factors for CVA.*

I3Y-MC-JPBM- (b) (6) This was a 70-year-old female with a past medical history significant for tuberculosis, arthritis, and no family or personal history of VTE who initiated study therapy on (b) (6) On (b) (6) the patient was hospitalized for a pulmonary embolism, and was found to have a right popliteal DVT. The patient died on (b) (6) with the cause of death listed as pulmonary embolism. The investigator did not consider this related to blinded study drug. The applicant did not think that this event was related to study drug.

Reviewer Comments: *Increased risk for venous thromboembolic events was noted in the abemaciclib development program across two randomized controlled trials. Based on this information, these data are included in the USPI as a Warning and Precaution. This reviewer considers this event to be related to abemaciclib therapy.*

Table 29. Reviewer Assessment of Deaths within 30 days of Study Therapy for MONARCH 3

	Abemaciclib plus NSAI N=327 n (%)	**Placebo plus NSAI N=161 n (%)**
All deaths	52 (15.9)	24 (14.9)
Death on therapy or within 30 days of treatment discontinuation	13 (4.0)	3 (1.9)
Reason for death		
Adverse events	10 (3.1)	2 (1.2)
CVA	2 (0.6)	0
Embolism	3 (0.9)	0
General Physical Health Deterioration	0	1 (0.6)
Pneumonia/Lung Infection	3 (0.9)	0
Pneumonitis	1 (0.3)	0
Infection/Sepsis	1 (0.3)	
Sudden death	0	1 (0.6)
Adverse events related to study treatment	3 (0.9)	0
Embolism	3 (0.9)	0
Study disease	3 (0.9)	1 (0.6)
Deaths after 30 days of treatment discontinuation	39 (11.9)	21 (13.0)

Source Reviewer Analysis

Serious Adverse Events

In addition to review of the safety reports including the 90-day safety update, the Integrated Summary of Safety, applicant narratives and patient case report forms were reviewed where appropriate. Table 30 below contains SAEs observed in MONARCH 3 by descending frequency.

Table 30. Monarch 3 SAEs Occurring in >1 Patient

	Abemaciclib plus NSAI N=327 n (%)	Placebo plus NSAI N=161 n (%)
Patients with ≥1 SAE	90 (27.5)	24 (14.9)
Infection	18 (5.5)	5 (3.1)
Lung Infection	9 (2.8)	0
VTE Event	8 (2.4)	1 (0.6)
Diarrhea	5 (1.5)	0
Anemia	5 (1.5)	0
Acute Kidney Injury	4 (1.2)	0
Dehydration	4 (1.2)	2 (1.2)
Dyspnea	3 (0.9)	1 (0.6)
Vomiting	2 (0.6)	2 (1.2)

Source: Reviewer adaptation of Table JPBM.12.8 MONARCH 3 CSR, page 167 using adae.xpt

Reviewer Comments: *The SAE table in the MONARCH 3 CSR was reviewed and adapted by based on the reviewer's analysis from the using the adae.xpt dataset. There was a numerically increased frequency of infections and VTE events in the abemaciclib arm. As noted in previous studies, SAEs of diarrhea and acute kidney injury were also noted. Based on the SAEs noted in the MONARCH 3 trial, there were no modifications of the Warnings and Precautions in the USPI.*

Hospitalizations

The number of patients with one or more hospitalizations in the MONARCH 3 study was 59 (18.0) in the abemaciclib plus NSAI arm and 18 (11.2) in the placebo plus NSAI arm. The most common AE leading to hospitalization was infection with 12 (3.7) in the abemaciclib plus NSAI arm and 5 (3.1) in the placebo plus NSAI arm. This was followed by vascular disorders with 10 (3.1) in the abemaciclib plus NSAI arm and 1 (0.6) in the placebo plus NSAI arm.

Dropouts and/or Discontinuations Due to Adverse Effects

In the MONARCH 3 study, 42 patients (12.8%) discontinued study treatment in the abemaciclib plus NSAI arm due to TEAEs and 4 patients (2.5%) discontinued study treatment due to AEs in the placebo plus NSAI arm. The most common reasons to discontinue study treatment in the abemaciclib plus NSAI arm were ALT increased (5 patients, 1.5%), diarrhea (5 patients, 1.5%), embolism (4 patients, 1.2%), and lung infection (4 patients, 1.2%).

AEs leading to discontinuation of any study drug were reported for 64 patients (19.6%) in the abemaciclib plus NSAI arm and 5 (3.1%) in the placebo plus NSAI arm. The most common reasons for study drug discontinuation were ALT increased, diarrhea, and neutropenia with 6 patients each (1.8%). Reasons for study treatment discontinuation are in Table 31 below and

for any study drug discontinuation are in Table 32 below.

Table 31. Adverse Events Reported as Reason for Study Treatment Discontinuation

	Abemaciclib plus NSAI N=327 n (%)	**Placebo plus NSAI N=161 n (%)**
Patients discontinued study therapy due to AE	42 (12.8)	4 (2.5)
ALT increased	5 (1.5)	0
Diarrhea	5 (1.5)	0
Embolism	4 (1.2)	0
Lung infection	4 (1.2)	0
Neutropenia	3 (0.9)	0
AST increased	2 (0.6)	0
Dyspnea	2 (0.6)	0
Pulmonary fibrosis	2 (0.6)	0
Urinary tract obstruction	0	1 (0.6)
General health deterioration	0	1 (0.6)
Non-cardiac chest pain	0	1 (0.6)
Sudden death	0	1 (0.6)

Table 32. Adverse Events Reported as Reason for Any Study Drug Discontinuation

	Abemaciclib plus NSAI N=327 n (%)	Placebo plus NSAI N=161 n (%)
Patients discontinued any study drug due to AE	64 (19.6)	5 (3.1)
ALT increased	6 (1.8)	0
Diarrhea	6 (1.8)	0
Neutropenia	6 (1.8)	0
Blood creatinine increased, CKD	6 (1.8)	0
Lung infection	5 (1.5)	0
Nausea	5 (1.5)	0
Embolism	4 (1.2)	0
Pulmonary fibrosis/Pneumonitis	4 (1.2)	0
Dyspnea	3 (0.9)	0
AST increased	2 (0.6)	0
Anemia	2 (0.6)	0
Rash	2 (0.6)	0
Urinary tract obstruction	0	1 (0.6)
General health deterioration	0	1 (0.6)
Non-cardiac chest pain	0	1 (0.6)
Muscle spasms	0	1 (0.6)
Sudden death	0	1 (0.6)

Dose reductions due to adverse events were made in the treatment for 142 patients (43.4%) on the abemaciclib plus NSAI arm and 10 patients (6.2%) on the placebo plus NSAI arm. The most common events leading to dose reduction were diarrhea 42 (12.8%) and neutropenia 37 (11.3%). Dose omissions occurred at least once for 203 patients (62.1%) in the abemaciclib plus NSAI arm with 184 patients (56.3%) having dose omissions due to AEs. The most frequent AEs leading to dose omission were diarrhea 50 (15.3%) and neutropenia 51 (15.6%).

Significant Adverse Events

The incidence of Grade 3 and 4 adverse events in the abemaciclib plus NSAI arm was higher with 188 (57.7%) patients experiencing a Grade ≥3 event and 37 patients (23.0%) experiencing this in the placebo plus NSAI arm. The most common (≥10%) Grade 3 or 4 TEAEs associated with abemaciclib plus NSAI was neutropenia 64 (21.1%).

Treatment Emergent Adverse Events and Adverse Reactions

Table 33. Adverse Events in ≥10% of Patients in MONARCH 3

	VERZENIO plus Anastrozole or Letrozole N=327			Placebo plus Anastrozole or Letrozole N=161		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	266 (81.3)	31 (9.5)	0	48 (29.8)	2 (1.2)	0
Nausea	126 (38.5)	3 (0.9)	0	32 (19.9)	2 (1.2)	0
Abdominal pain	94 (28.7)	4 (1.2)	0	19 (11.8)	1 (0.6)	0
Vomiting	93 (28.4)	4 (1.2)	0	19 (11.8)	3 (1.9)	0
Constipation	52 (15.9)	2 (0.6)	0	20 (12.4)	0	0
Infections and Infestations						
Infections[a]	126 (38.5)	4	<1	29	2	1 (0.6)
Blood and Lymphatic System Disorders						
Neutropenia	135 (41.3)	64 (19.6)	5 (1.5)	3 (1.9)	1 (0.6)	1 (0.6)
Anemia	93 (28.4)	19 (5.8)	0	8 (5.0)	2 (1.2)	0
Leukopenia	60 (20.8)	24 (7.3)	1 (0.3)	3 (1.9)	0	1 (0.6)
Thrombocytopenia	34 (10.4)	8 (2.4)	1 (0.3)	3 (1.9)	1 (0.6)	0
General Disorders and Administration Site Conditions						
Fatigue	131 (40.1)	6 (1.8)	0	51 (31.7)	0	0
Influenza like illness	34 (10.4)	0	0	13 (8.1)	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	87 (26.6)	0	0	17 (10.6)	0	0
Rash	47 (14.4)	3 (0.9)	0	8 (5.0)	0	0
Pruritus	43 (13.1)	0	0	14 (8.7)	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	80 (24.5)	4 (1.2)	0	15 (9.3)	1 (0.6)	0
Investigations						
Blood creatinine increased	62 (19.0)	7 (2.1)	0	6 (3.7)	0	0
Alanine aminotransferase increased	51 (15.6)	19 (5.8)	1 (0.3)	11 (6.8)	3 (1.9)	0
Aspartate aminotransferase increased	48 (14.7)	11 (3.4)	0	12 (7.5)	2 (1.2)	0

Weight decreased	33 (10.1)	2 (0.6)	0	5 (3.1)	1 (0.6)	0
Respiratory, Thoracic, and Mediastinal Disorders						
Cough	43 (13.1)	0	0	15 (9.3)	0	0
Dyspnea	39 (11.9)	2 (0.6)	1 (0.3)	9 (5.6)	1 (0.6)	0
Nervous System Disorders						
Dizziness	37 (11.3)	1 (0.3)	0	15 (9.3)	0	0

[a] Includes all reported preferred terms that are part of the Infections and Infestations system organ class. Most common infections (>1%) include upper respiratory tract infection, lung infection, and pharyngitis.

Source: Reviewer analysis using adae.xpt datasets and modification of Table JPBM.12.6 MONARCH 3 CSR, page 153

Laboratory Findings

Table 34. Treatment Emergent Laboratory Abnormalities Reported in MONARCH 3

	Abemaciclib + NSAI N=327						Placebo + NSAI N=161					
	CTCAE Grade											
	Nl	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	Nl	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Patients with ≥1 CTCAE term	316	27 (8.5)	146 (46.2)	121 (38.3)	21 (6.6)	315 (99.7)	158	97 (61.4)	38 (24.1)	14 (8.9)	1 (0.6)	150 (94.9)
Creatinine increased[a,b]	314	135 (43.0)	166 (52.9)	7 (2.2)	0	308 (98.1)	156	124 (79.5)	7 (4.5)	0	0	131 (84.0)
WBC decreased	313	84 (26.8)	134 (42.8)	40 (12.8)	0	258 (82.4)	156	30 (19.2)	11 (7.1)	1 (0.6)	0	42 (26.9)
Neutrophil count decreased	313	62 (19.8)	120 (38.3)	60 (19.2)	9 (2.9)	251 (80.2)	156	24 (15.4)	4 (2.6)	4 (2.6)	0	32 (20.5)
Anemia	313	129 (41.2)	122 (39.0)	5 (1.6)	0	256 (81.8)	156	29 (18.6)	14 (9.0)	0	0	43 (27.6)
Lymphocyte count decreased	313	77 (24.6)	63 (20.1)	23 (7.3)	2 (0.6)	165 (52.7)	156	22 (14.1)	15 (9.6)	3 (1.9)	0	40 (25.6)
Platelet count decreased	312	97 (31.1)	10 (3.2)	4 (1.3)	2 (0.6)	113 (36.2)	155	17 (11.0)	0	1 (0.6)	0	18 (11.6)
ALT increased	313	98 (31.3)	29 (9.3)	20 (6.4)	2 (0.6)	149 (47.6)	155	33 (21.3)	3 (1.9)	3 (1.9)	0	39 (25.2)
AST increased	313	91 (29.1)	12 (3.8)	12 (3.8)	0	115 (36.7)	155	29 (18.7)	6 (3.9)	1 (0.6)	0	36 (23.2)

Hyponatremia	314	74 (23.6)	0	15 (4.8)	1 (0.3)	90 (28.7)	156	37 (23.7)	0	0	0	37 (23.7)
Hypokalemia	314	69 (22.0)	0	22 (7.0)	1 (0.3)	92 (29.3)	155	18 (11.6)	0	0	0	18 (11.6)
Hypercalcemia	314	94 (29.9)	0	0	2 (0.6)	96 (30.6)	156	49 (31.4)	1 (0.6)	0	0	50 (32.1)
Hypocalcemia	314	60 (19.1)	10 (3.2)	1 (0.3)	1 (0.3)	72 (22.9)	156	24 (15.4)	3 (1.9)	0	1 (0.6)	28 (17.9)
Alkaline phosphatase increased	314	45 (14.3)	8 (2.5)	1 (0.3)	0	54 (17.2)	156	17 (10.9)	3 (1.9)	1 (0.6)	0	21 (13.5)
Hypoalbuminemia	314	6 (1.9)	5 (1.6)	0	0	11 (3.5)	156	2 (1.3)	1 (0.6)	0	0	3 (1.9)
Hyperkalemia	314	14 (4.5)	10 (3.2)	0	3 (1.0)	27 (8.6)	155	4 (2.6)	2 (1.3)	2 (1.3)	0	8 (5.2)
Hypernatremia	314	14 (4.5)	0	0	0	14 (4.5)	156	5 (3.2)	0	0	0	5 (3.2)
Blood bilirubin increased	313	11 (3.5)	4 (1.3)	1 (0.3)	0	16 (5.1)	155	7 (4.5)	2 (1.3)	0	0	9 (5.8)
Lymphocyte count increased	313	0	4 (1.3)	0	0	4 (1.3)	156	0	0	0	0	0
Hemoglobin increased	313	3 (1.0)	0	0	0	3 (1.0)	156	6 (3.8)	0	0	0	6 (3.8)

Source, MONARCH 3 CSR pages 226-227.

Reviewer Comments: *As was noted in the MONARCH 2 and MONARCH 1 studies, there were multiple lab abnormalities, including creatinine, ALT, AST, decreased white blood cells, anemia, and thrombocytopenia that were proportionally greater in the abemaciclib arm. Additionally, the incidence and severity of electrolyte abnormalities, including hypokalemia and hyponatremia was greater in the abemaciclib arm as well. This is likely due to diarrhea related side effects and the USPI has information regarding close patient follow-up for the appropriate medical management of these patients. Additionally, the USPI has labelling recommendations to evaluate CBC and liver enzymes more frequently than was performed as part of the MONARCH 3 study.*

Vital Signs

In the MONARCH 3 study, there were numerically more patients who developed a high pulse rate as defined by ≥100 bpm and increase by ≥15 bpm. There were no clinically meaningful differences in blood pressure, temperature, or respirations as demonstrated in Table 33 below.

Table 35. Treatment Emergent Abnormal Vital Signs in the MONARCH 3 Safety Population

	Abemaciclib plus NSAI N=327		Placebo plus NSAI N=161	
	N	n (%)	N	n (%)
Systolic blood pressure (mmHg)				
Low: ≤90 and decrease ≥20	320	15 (4.7)	159	8 (5.0)
High: ≥140 and increase ≥20	320	83 (25.9)	159	50 (31.5)
Diastolic blood pressure (mmHg)				
Low: ≤50 and decrease ≥10	320	24 (7.5)	159	7 (4.4)
High: ≥90 and increase ≥10	320	66 (20.6)	159	42 (26.4)
Pulse (beats/min)				
Low: ≤50 and decrease ≥15	320	2 (0.6)	159	0
High: ≥100 and increase ≥15	320	61 (19.1)	159	16 (10.1)
Temperature (°C)				
Low: ≤35	318	11 (3.5)	159	4 (2.5)
High: >39	318	0	159	0
Respiratory Rate (breaths/min)				
Low: <10	312	2 (0.6)	155	1 (0.7)
High: >25	312	6 (1.9)	155	3 (1.9)

Source MONARCH 3 CSR page 234

Electrocardiograms (ECGs)

In the MONARCH 3 study, ECGs were obtained at baseline, 2-4 hours after abemaciclib dosing on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 4 Day 1 and at the short term follow up visit. Clinically relevant ECG findings observed in MONARCH 3 were reported as TEAEs are in below.

Table 36. Clinically Relevant ECG Findings in MONARCH 3

	Abemaciclib plus NSAI N=327			Placebo plus NSAI N=161		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
ECG QT prolonged	1 (0.3)	0	0	0	0	0
Sinus tachycardia/tachycardia/atrial tachycardia/supraventricular tachycardia	8 (2.4)	2 (0.6)	0	4 (2.5)	0	0

Atrial fibrillation/flutter	5 (1.5)	3 (0.9)	0	0	0	0
Arrhythmia	2 (0.6)	0	1 (0.3)	0	0	0

Source: *Reviewer analysis using adae.xpt*

Reviewer Comment: *There were more patients in the abemaciclib plus NSAI arm with atrial fibrillation/flutter than in the placebo plus NSAI arm. However, the numbers are small and this may be due to chance. This reviewer concurs with the applicant's assessment that there were no clinically meaningful differences in ECG results between the two arms of the study.*

QT

A QTc analysis was performed based on data submitted in both the healthy and cancer populations as part of the initial abemaciclib NDA submission (208716). The effect of abemaciclib on the QTcF interval was evaluated in 144 patients with advanced cancer. No change >20 ms in the QTcF interval was detected at the mean observed maximal steady state abemaciclib concentration following a regular dosing schedule. Exposure-response analysis in healthy subjects at up to 1.2 times the exposures observed in 200 mg twice daily dosing did not prolong the QTcF interval to a clinically relevant extent.

In the MONARCH 3 study, there was one patient who developed QT prolongation while on abemaciclib therapy. There were no grade 3 or 4 findings. This is consistent with findings in the MONARCH 2 and MONARCH 1 studies.

Reviewer Comments: *Based on the current safety database, abemaciclib does not appear to prolong the QT interval.*

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

Based on data from the MONARCH 2 and MONARCH 1 studies, the increase in AEs of diarrhea, neutropenia, blood creatinine increased, hepatotoxicity, infections, VTE events, and pneumonitis were known safety issues. Data from the MONARCH 3 study do not identify new safety issues.

Diarrhea

Similar to the MONARCH 2 and 1 studies, the incidence of diarrhea in MONARCH 3 on the abemaciclib plus NSAI arm was greater than 80%. Based on this finding, the USPI language in the Warnings and Precautions section about diarrhea was maintained. There remain few Grade 3 events and given the adverse events associated with diarrheal prophylaxis, there is no indication at this time for primary prophylaxis. A safety study is ongoing to evaluate this.

Diarrhea should be able to be managed with appropriate supportive care and dose omissions and/or reductions as necessary.

Neutropenia

The addition of abemaciclib to NSAI therapy results in an increased risk of neutropenia and has been associated with febrile neutropenia in patients within the abemaciclib development studies. There is a Warning and Precaution in the existing label and this maintained for subsequent labeling.

Blood Creatinine Increased

Based on studies as part of the abemaciclib development program, abemaciclib increases serum creatinine by what is thought to be inhibition of renal tubular secretion of serum creatinine without effect on glomerular function. This information is reported in the USPI along with alternative methods of assessing renal function in these patients.

Hepatotoxicity

As with the previous studies, the AEs of ALT and AST increased were more frequent in the abemaciclib plus NSAI arm than in the placebo plus NSAI arm. There was not evidence of increased bilirubin. The Warnings and Precautions section of the USPI contains information regarding this risk and liver enzyme monitoring.

Thromboembolic events

As with the MONARCH 2 study, the MONARCH 3 study demonstrated a numerically greater incidence of VTE events in the abemaciclib plus endocrine therapy arm as compared to the placebo plus endocrine therapy arm. Based on this, signs and symptoms of VTE events are included in the Warnings and Precautions and in patient labeling.

Pneumonitis

Given the frequency of events considered atypical pneumonia and pneumonitis, an information request was submitted to the applicant to query the safety database about the frequency of these events, deaths associated with these events, and the frequency of disease progression related to these events. Response was received on August 25, 2017. The incidence across the abemaciclib program was 19/2766 or 0.007 in patients treated with abemaciclib and 2/490 or 0.002 in non-abemaciclib treated patients. The events had multiple confounding factors including parenchymal lung metastases, evidence of lymphangitic spread, history of radiation pneumonitis, and concomitant or previous therapy associated with pulmonary changes. In patients with pneumonitis, independent review of chest CT scans was completed and the findings were not typical of drug induced pneumonitis as there were bilateral and focal changes

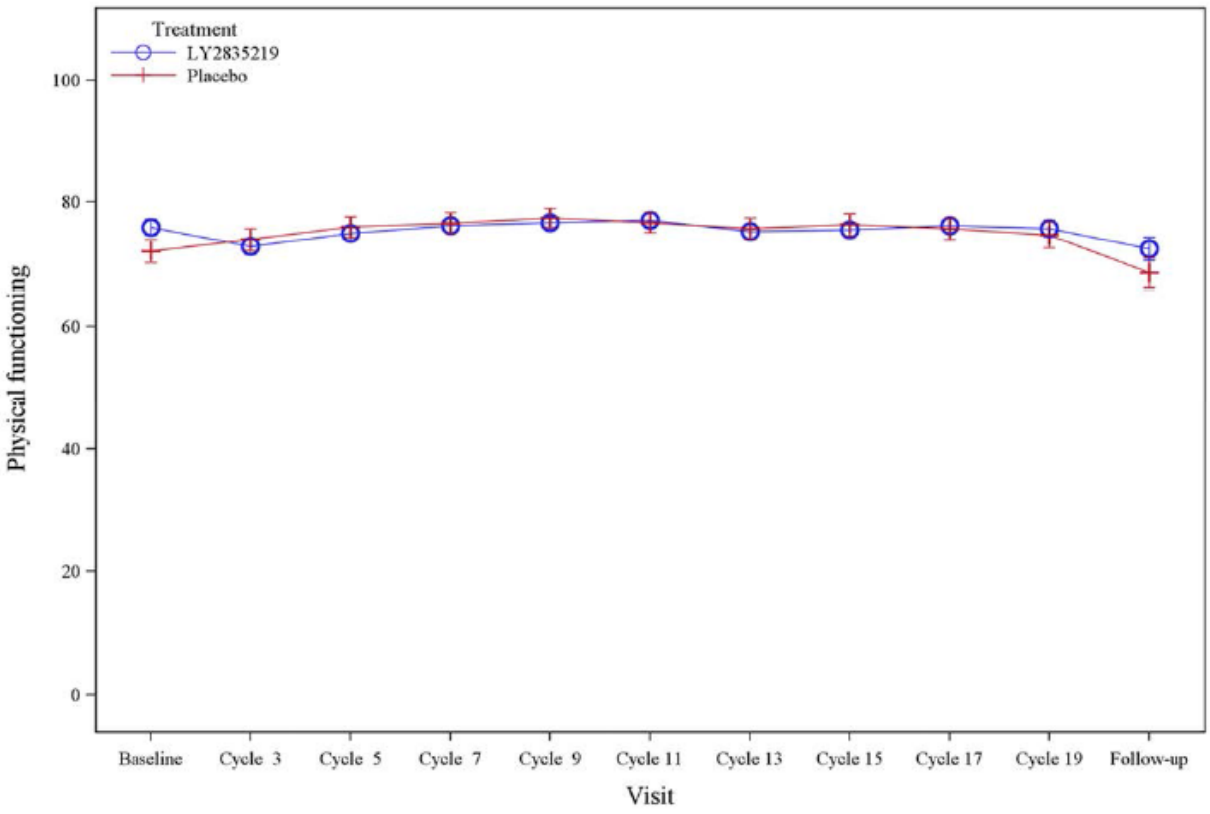
which are not typical of iatrogenic pneumonitis. Based on these data, it is unclear at this time that there is an increased risk of pneumonitis associated with abemaciclib and there is no additional labelling recommendation at this time. This is a safety signal that will be monitored carefully in additional abemaciclib clinical trials as well as in postmarketing adverse event reporting.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

As noted in the efficacy review, there was a numerically higher rate of patients reporting diarrhea symptoms over time. The proportion reporting this at the initial visit was greatest and there was a modest improvement over time, however the difference between the arms was noted to be persistent.

There were no notable differences in physical function or role function using the scales from the EORTC QLQ-C30.

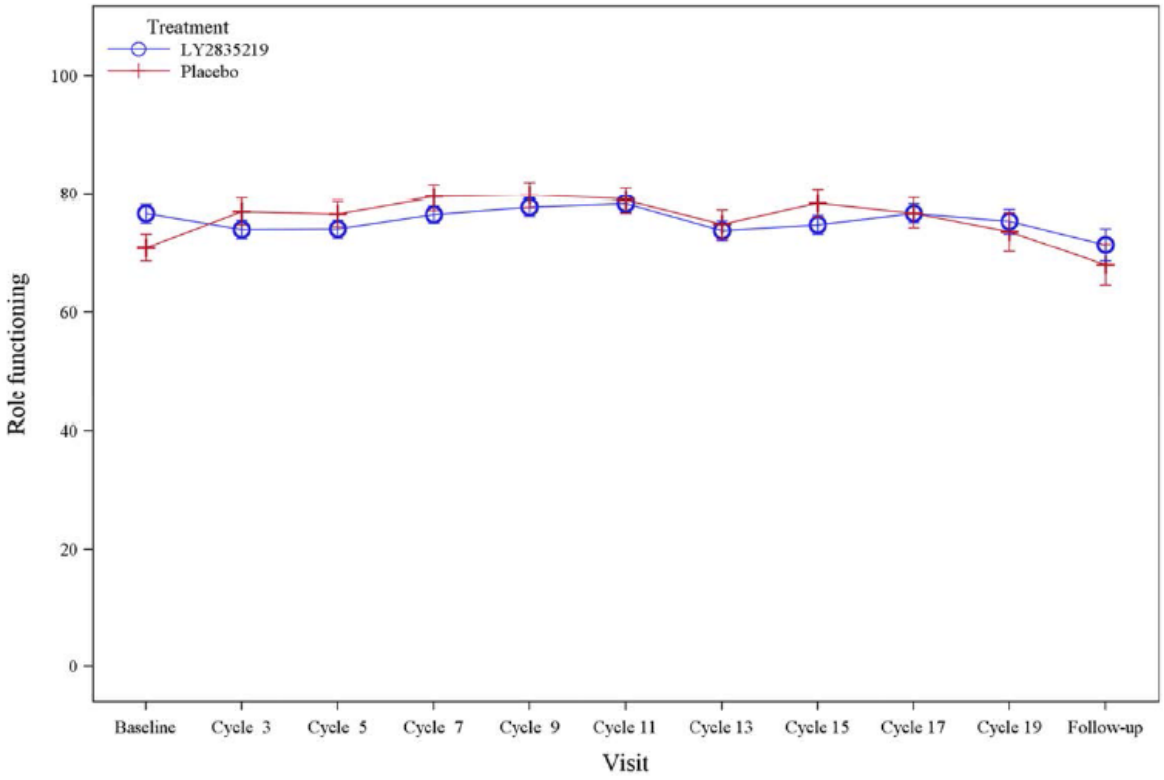
Figure 8. Plot of EORTC QLQ-C30 Physical Function Domain by Cycle



Abbreviation: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.
Source: f_lsm_c30.rtf.

Source MONARCH 3 CSR Page 440

Figure 9. Plot of EORTC QLQ-C30 Role Function Domain by Cycle



Abbreviation: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.
Source: f_lsm_c30.rtf.

Source MONARCH 3 CSR Page 441

Reviewer Comments: *Patient reported data regarding diarrhea demonstrate persistent differences with the addition of abemaciclib to NSAI as compared to placebo. These data help to capture the longitudinal nature of this adverse event. Despite these differences, there appears to be little difference in physical or role function between the treatment arms.*

8.2.7. Safety Analyses by Demographic Subgroups

Age

In the MONARCH 3 study, 45.1% of patients (148/328) in the abemaciclib and NSAI were age 65 or greater and 44.8% of patients (72/161) in the placebo plus NSAI group were age 65 or greater.

The overall incidence of SAEs was numerically greater in patients ≥65 years of age (39.9%, 59/148) than in patients <65 years of age (24.4%) 44/180 in the abemaciclib plus NSAI arm. The most frequently reported (≥10%) TEAEs in patients ≥65 years are in Table 37 below.

Table 37. TEAEs in ≥10% of Patients ≥65 in MONARCH 3

	Abemaciclib plus NSAI, n=148			Placebo plus NSAI, n=72		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Diarrhea	120 (81.1)	18 (12.2)	0	13 (18.1)	1 (1.4)	0
Fatigue	68 (45.9)	3 (2.0)	0	31 (34.8)	0	0
Nausea	67 (45.3)	3 (2.0)	0	12 (16.7)	1 (1.4)	0
Neutropenia, neutrophil count decreased	62 (41.9)	33 (22.3)	2 (1.4)	2 (2.8)	1 (1.4)	0
Infections and infestations	62 (41.9)	10 (6.8)	2 (1.4)	25 (34.7)	3 (4.2)	0
Anemia	53 (35.8)	12 (8.1)	0	5 (6.9)	1 (1.4)	0
Vomiting	50 (33.8)	4 (2.7)	0	8 (11.1)	2 (2.8)	0
Decreased appetite	45 (30.4)	3 (2.0)	0	5 (6.9)	0	0
Creatinine increased	42 (28.4)	2 (1.4)	0	4 (5.6)	0	0
Leukopenia, WBC decreased	33 (22.3)	13 (8.8)	1 (0.7)	0	0	0
Rash	21 (14.2)	2 (2.8)	0	2 (2.8)	0	0
Constipation	31 (20.9)	2 (1.4)	0	10 (13.9)	0	0
Cough	27 (18.2)	0	0	5 (6.9)	0	0
Weight decreased	19 (12.8)	2 (1.4)	0	3 (4.2)	1 (1.4)	0
Thrombocytopenia, platelet count decreased	19 (12.8)	6 (4.1)	0	1 (1.4)	0	0
Dizziness	18 (12.2)	1 (0.7)	0	5 (6.9)	0	0
Edema Peripheral	18 (12.2)	0	0	4 (5.6)	0	0
Pruritus	17 (11.0)	0	0	8 (8.9)	0	0
Headache	17	1 (0.6)	0	3 (3.3)	0	0

	(11.0)					
Stomatitis	16 (10.8)	0	0	4 (5.6)	0	0

Source: MONARCH 3 CSR and reviewer analysis from pages 155-156 and Table JPBM.14.49

Reviewer Comments: *The incidence of adverse events in older patients was greater than that of younger patients. There was additional data added to the USPI to reflect these findings so that providers are aware of increased toxicities in older patients.*

8.2.8. Specific Safety Studies/Clinical Trials

There are two ongoing studies in the abemaciclib clinical development program: I3Y-MC-JPCB(d) and I3Y-MC-JPCG (a).

The first study, I3Y-MC-JPCB, is a pharmacokinetic study evaluating the effects of abemaciclib on the pharmacokinetics of cytochrome P450 1A2, CYP2C9, CYP2D6, and CYP3A substrates including caffeine, warfarin, dextromethorphan, and midazolam in cancer patients. A secondary objective of this study is to evaluate the effect of abemaciclib on the pulse rate and blood pressure of multiple doses of abemaciclib in cancer patients. Exploratory objectives are to assess the effect of abemaciclib on markers of renal function including creatinine, cystatin-C, kidney injury molecule-1, and neutrophil gelatinase-associated lipocalin as well as to characterize bowel habits through a diary and a stool assessment tool as well as through patient reported outcome data using FACIT-D and custom-generated PRO items. This protocol has been previously reviewed.

The second study, I3Y-MC-JPCG, is a randomized, open label, phase 2 study of abemaciclib plus tamoxifen plus abemaciclib or abemaciclib alone. As part of this, abemaciclib 200 mg Q12H is administered with primary prophylactic loperamide in Arm C. Arm A is evaluating abemaciclib with tamoxifen, Arm B is evaluating abemaciclib monotherapy at 150 mg twice daily, and Arm C is evaluating abemaciclib at 200 mg twice daily with primary prophylaxis with loperamide for the first 28 days of therapy. This protocol has been reviewed previously and is an arm in the larger Phase 2 study that is evaluating the use of abemaciclib alone vs. abemaciclib and tamoxifen for women with previously treated hormone receptor positive, HER2-negative MBC. This design appears appropriate and will help to further characterize the safety and efficacy of abemaciclib as single agent in multiple doses (150 mg vs. 200 mg with loperamide).

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

See Pharmacology/Toxicology Review from NDA 208716.

Human Reproduction and Pregnancy

See Pharmacology/Toxicology Review from NDA 208716.

Pediatrics and Assessment of Effects on Growth

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose
No accidental overdoses were reported in MONARCH 3.

Drug Abuse Potential
There are no data available on the potential for abuse or dependence with abemaciclib.

Withdrawal and Rebound
There has been no formal study of withdrawal and/or rebound after treatment discontinuation of abemaciclib.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The applicant submitted their first postmarket safety assessment on January 22, 2018 which identified 14 non-alert cases. Events included diarrhea, nausea, vomiting, abdominal pain, pancytopenia, dehydration, blood creatinine increased, dyspnea and deep venous thrombosis. These are known adverse effects that are identified in patient labelling and there have been no new safety signals identified in the postmarket setting.

Expectations on Safety in the Postmarket Setting

Abemaciclib has been on the market for approximately four months. In that time, the applicant issued a postmarketing safety update that identified no new safety signals, but include reports of adverse events consistent with those seen in clinical trials. Current labeling characterizes adverse events well, as diarrhea and risk of VTE events are included in the Warnings and Precautions section. There have not been signals that risk of diarrhea or VTE merits recommendations for primary prophylaxis; however, this will continue to be monitored in the postmarket and ongoing development setting.

8.2.11. Integrated Assessment of Safety

The safety profile of abemaciclib and NSAI as the initial therapy for postmenopausal women with HR-positive, HER2 negative locally advanced or metastatic breast cancer is acceptable with adverse reactions typically manageable though use of abemaciclib dose reduction, temporary treatment discontinuation, and/or standard medical care.

Unlike other agents in this class, there is an increased risk of diarrhea. Like other agents in this class, there is an increased risk of neutropenia and infection. Additionally, an increased risk of VTE was seen in both the MONARCH 3 and MONARCH 2 studies. These risks were identified in the initial approval of abemaciclib and are captured in provider and patient labelling so that they are aware of the signs and symptoms of these events and can promptly address them.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

There are no major statistical issues with this application.

8.4. Conclusions and Recommendations

Based on the favorable risk-benefit profile, the clinical and statistical reviewers recommend approval for abemaciclib in combination with AI for postmenopausal women with HR-positive, HER2-negative MBC as initial endocrine based therapy. The risks identified are addressed in product labeling and are manageable by medical oncologists.

X	X
Erik Bloomquist, PhD Primary Statistical Reviewer	Shenghui Tang, PhD Statistical Team Leader
X	X
Lynn Howie, MD Primary Clinical Reviewer	Laleh Amiri-Kordestani, MD Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held for this NDA.

10 Pediatrics

Abemaciclib was not studied in pediatric patients. The applicant has submitted a PREA waiver and the Pediatric Review Committee agreed with the plan for a full waiver.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

VERZENIO tablets received initial regulatory approval under NDA 208716 on September 28, 2017, for use in HR positive, HER2 negative advanced or metastatic breast cancer as a monotherapy for patients (b) (4) prior chemotherapy (b) (4) endocrine therapy. This NDA proposes a new indication for the use of Verzenio in combination with an aromatase inhibitor as initial endocrine-based therapy (b) (4)

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling** *(As of 2/9/18)*
Highlights		
Indications and Usage	*See Full Prescribing Information, 1 Indications and Usage.*	*See Full Prescribing Information, 1 Indications and Usage.*
Dosage and Administration	…	FDA revised the recommended starting dose from " (b) (4) to "in combination with fulvestrant or an aromatase inhibitor".
Warnings and Precautions	…	FDA added Warnings and Precautions for Diarrhea, Venous Thromboembolism, and Embryo-Fetal Toxicity. FDA revised the Warning and Precaution for " (b) (4) " to "Hepatotoxicity" and added additional information. *See Full Prescribing Information, 5 Warnings and Precautions.*
Adverse Reactions	…	FDA revised the most common adverse reactions statement from an incidence of (b) (4) to ≥ 20%, removed (b) (4) and added headache as a new adverse

		reaction.
Full Prescribing Information		
1. Indications and Usage	(b) (4)	FDA removed the proposed indications statement for use in combination with fulvestrant (b) (4) and revised back to the currently approved indication for use after disease progression following endocrine therapy. *See 8.1.2, Additional Analyses Conducted on the Individual Trial MONARCH 2 for more information.*
2. Dosage and Administration	2.1 Recommended Dose and Schedule …	FDA revised the recommended starting dose from "(b) (4) to "in combination with fulvestrant or an aromatase inhibitor" to ensure this information was accurate and consistent with the recommended concomitant products. FDA revised this subsection to: • Add bullets to clearly separate the different doses used for monotherapy and combination regimens

		• Add the dose and regimen for fulvestrant when used in combination with VERZENIO • Add cross references to aromatase inhibitor prescribing information for the recommended dose • Remove passive voice
	2.2 Dose Modification …	FDA revised the dose modifications for use with CYP3A inhibitors subsection to add instructions to avoid use of VERZENIO with ketoconazole.
5. Warnings and Precautions	5.1 Diarrhea …	FDA added a new Warning and Precaution for Diarrhea due to the high incidence of diarrhea, management requirements to prevent severe ARs, and the significant number of patients who experienced Grade 3 diarrhea, dehydration, and infections. *See 1.3 Benefit-Risk Assessment for more information.*
	5.2 Neutropenia …	FDA added the following statement: "Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia [*see Dosage and Administration (2.2)*]." FDA added the following information related to febrile neutropenia: "Febrile neutropenia has been reported in <1% of patients exposed to VERZENIO in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider [*see Patient Counseling Information (17)*]."
	5.3 Hepatotoxicity	FDA revised the title of this Warning

	…	and Precaution from "(b) (4)" to "Hepatotoxicity" to better characterize the toxicities associated with VERZENIO. FDA added: "Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation [*see Dosage and Administration (2.2)*]."
	5.4 Venous Thromboembolism	FDA added a new Warning and Precaution for Venous Thromboembolism. *See 1.3 Benefit-Risk Assessment for more information.*
	5.5 Embryo-Fetal Toxicity	FDA added a new Warning and Precaution for Embryo-Fetal toxicity to alert healthcare providers that VERZENIO may cause fetal harm when administered to pregnant women. The revisions and additions to this section are consistent with the current best labeling practices for pregnancy (PLLR).
6. Adverse Reactions	6.1 Clinical Studies Experience <u>MONARCH 3: VERZENIO in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole) as Initial Endocrine-Based Therapy</u> *Postmenopausal Women with HR-positive, HER2-negative locoregionally recurrent or metastatic breast cancer with no*	FDA added the following statement: "Dose reductions due to an adverse reaction occurred in 43% of patients receiving VERZENIO plus anastrozole or letrozole". FDA added the following statements: "Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 11 cases (3%) of VERZENIO plus an aromatase inhibitor treated patients versus 3 cases (2%) of placebo plus an aromatase inhibitor treated patients. Causes of death for patients receiving

	prior systemic therapy in this disease setting …	VERZENIO plus an aromatase inhibitor included: 3 (1%) patient deaths due to underlying disease, 3 (0.9%) due to lung infection, 3 (0.9%) due to VTE event, 1 (0.3%) due to pneumonitis, and 1 (0.3%) due to cerebral infarction.". Based on the FDA safety review, FDA modified the Adverse Reaction (AR) table (Table 6) and most common AR statement as follows: • FDA added ARs for abdominal pain, pruritus, blood creatinine increased, weight decreased, cough, dyspnea, and dizziness. • FDA removed "(b) (4) ". To clarify the increase in the incidence rate for patients treated with VERZENIO and aromatase inhibitors (5%), FDA revised the additional AR subsection to add the incidence of thromboembolic events (0.6%) observed in patients treated with only anastrozole or letrozole. FDA also removed (b) (4) . FDA added a subsection to describe the creatinine increased laboratory abnormalities without effects on glomerular function that have been observed in patients treated with VERZENIO.
	6.1 Clinical Studies Experience <u>MONARCH 2: VERZENIO in Combination with</u>	FDA revised the incidence of permanent study discontinuation from adverse events from (b) (4) to 9% of patients receiving VERZENIO plus fulvestrant, and from (b) (4) to 3% for

	Fulvestrant *Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy* …	fulvestrant with placebo. FDA added the following: "Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 18 cases (4%) of VERZENIO plus fulvestrant treated patients versus 10 cases (5%) of placebo plus fulvestrant treated patients. Causes of death for patients receiving VERZENIO plus fulvestrant included: 7 (2%) patient deaths due to underlying disease, 4 (0.9%) due to sepsis, 2 (0.5%) due to pneumonitis, 2 (0.5%) due to hepatotoxicity, and one (0.2%) due to cerebral infarction." FDA moved the information related to diarrhea from section 6.1 to the new Warning and Precaution for Diarrhea (5.1). FDA removed (b) (4) [redacted] FDA revised the additional AR subsection for use with fulvestrant as done for the use in combination with an aromatase inhibitor study (i.e., added venous thromboembolism and creatinine increased information).
	6.1 Clinical Studies Experience VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)	FDA revised the information related to patients who permanently discontinued study treatment because of ARs to increase the incidence from (b) (4) % to 8% and added events for abdominal pain, arterial thrombosis, AST increased, blood

	Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting …	creatinine increased, chronic kidney disease, ECG QT prolonged, hip fracture, and lymphopenia. Based on the FDA safety review, FDA modified the AR table (Table 10) and most common AR statement (when applicable) to add ARs for abdominal pain, constipation, infections, pyrexia, dehydration, cough, headache, dizziness, and weight decreased. FDA revised the additional AR subsection for use with fulvestrant as done for the use in combination with an aromatase inhibitor (i.e., added creatinine increased information).
7. Drug Interactions	7.1 Effect of Other Drugs on VERZENIO …	FDA revised this section to reformat with subsections describing the effect of other drugs on VERZENIO, remove the data and drug interactions without clinical implications, add advice to avoid use with ketoconazole (16-fold increase in AUC), and clarify dose reductions required when used with other Strong CYP3A inhibitors.
8. Use in Specific Populations	8.5 Geriatric Use …	FDA revised this subsection to provide information on the most common Grade 3 and 4 adverse reactions and incidence in patients ≥ 65 years of age treated with VERZENIO.
12. Clinical Pharmacology	12.2 Pharmacodynamics …	FDA removed information related to mechanism of action not required in section 12.2 and revised the Cardiac Electrophysiology information to be more concise and avoid descriptions of patient populations in which VERZENIO is not indicated.
	12.3 Pharmacokinetics …	Based on FDA Clinical Pharmacology review, FDA revised the geometric mean accumulation, mean plasma elimination half-life ((b) (4) hours to 18.3 hours), added the composition of

		the meals used in the food effect study, and removed undefined descriptors of PK results. FDA removed the (b) (4) and replaced with summary text. FDA removed the (b) (4), and replaced with summary text. FDA added data related to drug-drug interactions related to Strong CYP3A inhibitors and specifically for ketoconazole.
14. Clinical Studies	<u>VERZENIO in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole) (MONARCH 3)</u> *Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer with no prior systemic therapy in this disease setting* …	FDA made the following revisions: • Removed (b) (4) • From the efficacy results table (Table 12), FDA removed the (b) (4)
	<u>VERZENIO in Combination with Fulvestrant (MONARCH 2)</u> *Patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease*	FDA made the following revisions: • FDA added the definition of "Primary endocrine therapy resistance" • FDA replaced th (b) (4) with brief text statements and added menopausal status.

	progression on or after prior adjuvant or metastatic endocrine therapy …	• FDA removed (b) (4) also reported in the efficacy results table (Table 13). • FDA removed (b) (4) . • FDA removed (b) (4) • From the efficacy results table (Table 13), FDA removed the (b) (4) • FDA removed the (b) (4)
	<u>VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)</u> *Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting* …	FDA made the following revisions: • FDA replaced the (b) (4) with brief text statements. • FDA removed (b) (4) (Table 14). • FDA removed (b) (4) (b) (4)

16. How Supplied/ Storage and Handling	…	FDA removed the (b) (4) [redacted].
17. Patient Counseling Information	…	FDA revised this section to add information for the new and revised Warnings and Precautions (i.e., diarrhea, hepatotoxicity, and venous thromboembolism).

11.2. Patient Labeling

VERZENIO includes an FDA-approved Patient Package Insert (Patient Information). The FDA DMPP team reviewed the VERZENIO Patient Information and revisions were made to be consistent with the FDA-mandated labeling revisions to the VERZENIO Prescribing Information. These revisions included additional signs and symptoms for hepatotoxicity (liver problems), revisions to the VERZENIO use descriptions to be consistent with the approved indications, and removal of some medications with potential drug interactions that were not consistent with information in the prescribing information. *See the FDA DMPP Review filed under this NDA for more information.*

12 Risk Evaluation and Mitigation Strategies (REMS)

None.

13 Postmarketing Requirements and Commitment

The following Postmarketing Commitments (PMC) were recommended and agreed upon with the applicant:

- Submit the overall survival (OS) data and analysis with final report from clinical trial MONARCH 3 entitled; "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Nonsteroidal Aromatase Inhibitors (Anastrozole or Letrozole) plus LY2835219, a CDK 4/6 Inhibitor, or Placebo in Postmenopausal Women with Hormone Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer with No Prior Systemic Therapy in this Disease Setting."

PMC Schedule Milestones

Draft Protocol Submission:	09/2014
Final Protocol Submission:	01/2017
Interim (OS) Report Submission:	12/2022
Trial Completion:	06/2026

14 Division Director (OB)

X

Jason Schroeder, PhD
Associate Director, Division of Biometrics 5, OB

15 Division Director (Clinical)

X

Julia A. Beaver, MD
Director, Division of Oncology Products 1

16 Appendices

16.1. References

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16.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): MONARCH3 I3Y-MC-JPBM

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1117		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
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: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

16.2. Nonclinical Pharmacology/Toxicology

None.

16.3. OCP Appendices (Technical documents supporting OCP recommendations)

16.3.1. Summary of Bioanalytical Method Validation and Performance

Bioanalytical methods for abemaciclib, associated metabolites, and fulvestrant have been reviewed in NDA 208716 and were deemed acceptable. Summary of bioanalytical methods for letrozole and anastrozole is provided below.

Table 38. Bioanalytical method validation reports for letrozole and anastrozole in Study JPBH and MONARCH 3.

Report Number: Analytes (Date)	Validation Range (ng/mL)	Dilution Factor	Inter-assay Accuracy / Precision	Intra-assay Accuracy / Precision	Stability
8293044: anastrozole (02/14/2014)	0.500 – 100.000	20	%RE: -8.4% to -2.2 %RSD: 3.0% to 10.4%	%RE: -18.6% to 1.4% %RSD: 1.5% to 8.4%	491 days at -10 ~ -30°C and at -60 ~ -80°C
8264525: letrozole (01/29/2013)	1.00 – 1000.00	50	%RE: -5.3% to 2.0% %RSD: 2.2% to 5.1%	%RE: -9.1% to 3.4% %RSD: 0.4% to 4.5%	525 days at -10 ~ -30°C and at -60 ~ -80°C

Method type is HPLC-MS/MS and analysis matrix is plasma sample for both reports. Standard curves have R-square values >0.99 for both methods.
Source: Summarized from bioanalytical-report-anastrozole-i3y-mc-jpbm and bioanalytical-report-letrozole-i3y-mc-jpbm.

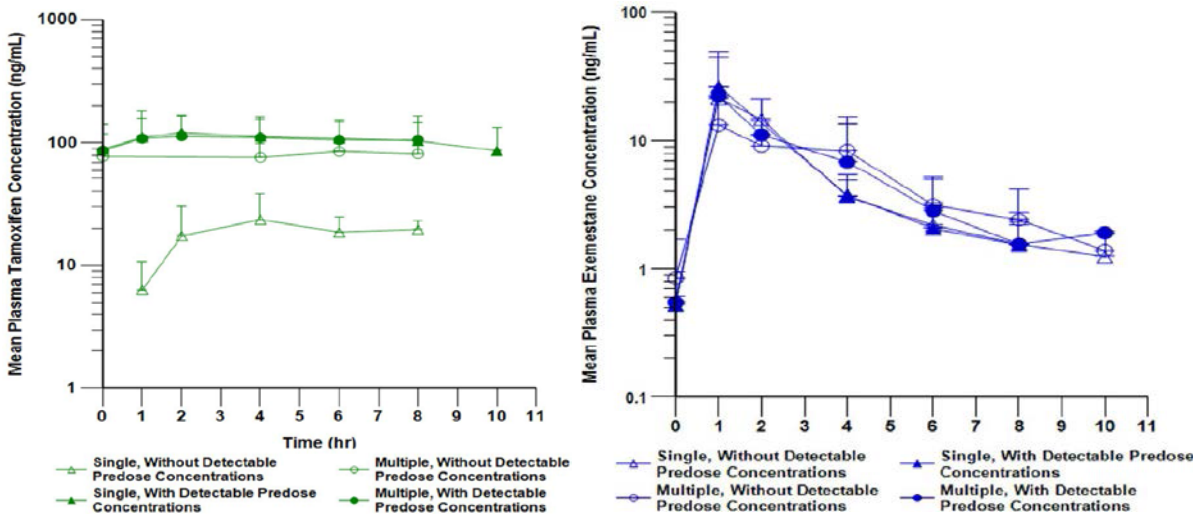
16.3.2. Summary of Clinical Pharmacology Findings in Study JPBH and JPBM

Study JPBH

Study JPBH is a Phase 1b, multicenter, nonrandomized, open-label study of abemaciclib in combination with letrozole, anastrozole, tamoxifen, exemestane, exemestane plus everolimus, or fulvestrant in HR+, HER2- patients with metastatic breast cancer. The objects are to evaluate the safety/tolerability and antitumor activity of abemaciclib in these combinations, and to evaluate PK of study drugs after a single dose and at steady state on Day 28 of Cycle 1. Abemaciclib was initiated at 200 mg BID in four study arms with letrozole (2.5 mg DQ), anastrozole (1 mg QD), tamoxifen (20 mg QD), and exemestane (25 mg QD). C_{max}, T_{max}, C_{last} (last quantifiable concentration), T_{last} (time of the last quantifiable concentration), and $AUC_{0\text{-}tlast}$ (AUC from time 0 to the last time point with a measurable concentration) were reported from the non-compartmental analysis for patients who received at least 1 dose of study drug and had sufficient samples collected to allow the estimation of PK parameters.

There was no apparent effect from abemaciclib on the exposures of anastrozole, letrozole, tamoxifen, or exemestane (Figure 1, Figure 10).

Figure 10. Mean (Std Dev) plasma concentrations versus time profiles of tamoxifen (Left) or exemestane (Right) following administration of abemaciclib in combination with 20 mg of tamoxifen or 25 mg of exemestane every 24 hours.



Source: JPBH clinical study report, Figure 7.14 and 7.15.

The exposures of abemaciclib and major metabolites were generally comparable among the four combinations evaluated in Study JPBH considering the observed PK variability (Figure 11, Table 39). Even though the observed steady state exposure at 200 mg BID dose level appeared lower than expected based on observations in Study JPBA or popPK prediction, given the wide exposure range and variability across the 150 mg BID and 200 mg BID levels, the apparent difference is likely an artifact introduced by small sample size. Considering that the mechanisms of absorption, distribution, metabolism and excretion for the study drugs do not suggest a high potential for drug-drug interaction at the PK level, it appeared reasonable to conclude a lack of clinically significant effect from letrozole, anastrozole, tamoxifen, and exemestane on abemaciclib PK, based on data from Study JPBH.

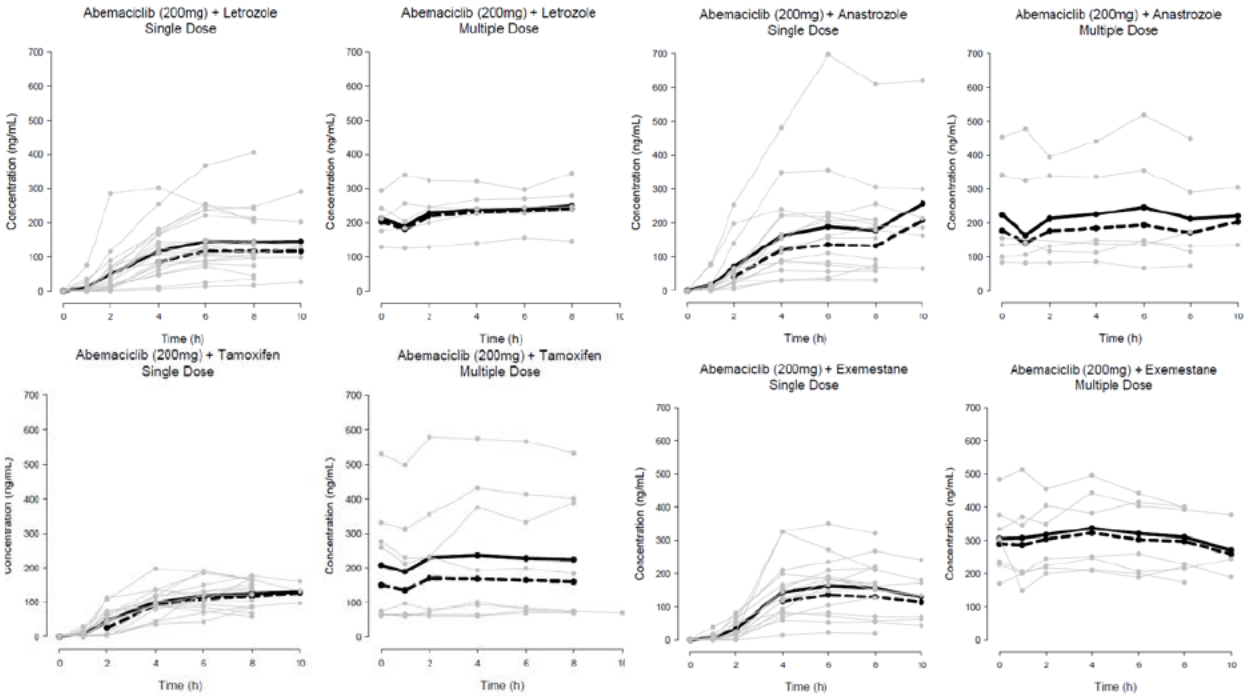
Table 39. Summary of abemaciclib and metabolites exposures following administration of 200 mg single dose, 200 mg BID doses, or 150 mg BID doses of abemaciclib in combination with therapies in patients with metastatic breast cancer.

Geometric Mean (%CV)		Abemaciclib		M2		M20	
		Cmax.ss	AUC	Cmax.ss	AUC	Cmax.ss	AUC
Letrozole (2.5 mg QD)	200 mg SD (n=9)	129 (80)	608 (101)	34.9 (62)	179 (68)	51.2 (62)	249 (77)
	200 mg BID (n=5)	246 (30)	1800 (34)	137 (29)	947 (29)	219 (29)	1600 (30)
	150 mg BID (n=4)	312 (55)	2280 (53)	138 (55)	935 (49)	198 (65)	1440 (73)
Anastrozole (1 mg QD)	200 mg SD (n=16)	141 (99)	752 (120)	39.7 (90)	216 (107)	57.1 (87)	304 (98)
	200 mg BID (n=5)	205 (83)	1530 (87)	106 (24)	772 (38)	179 (37)	1350 (51)

	150 mg BID (n=6)	221 (84)	1580 (89)	119 (59)	828 (59)	180 (53)	1320 (56)
Tamoxifen (20 mg QD)	200 mg SD (n=15)	130 (32)	628 (43)	37.7 (41)	198 (39)	53 (40)	259 (42)
	200 mg BID (n=8)	185 (104)	1280 (104)	107 (50)	755 (50)	149 (61)	1110 (59)
	150 mg BID (n=4)	277 (29)	1910 (30)	122 (34)	852 (36)	171 (24)	1240 (28)
Exemestane (25 mg QD)	200 mg SD (n=15)	147 (84)	770 (91)	29.1 (85)	156 (94)	46.7 (77)	247 (92)
	200 mg BID (n=7)	332 (32)	2520 (33)	125 (24)	953 (26)	212 (31)	1670 (36)
	150 mg BID (n=3)	289 (50)	2210 (45)	97.1 (37)	694 (26)	168 (13)	1340 (2)

Cmax.ss (ng/mL) and AUC(0-last) (hr*ng/mL) values reported in the 200 mg BID group represents steady state exposure in the study patients while values in the 150 mg BID group may not present steady state at the specific dose level.
Source: Adapted from JPBH clinical study report, Table JPBH 7.3 and 7.4

Figure 11. Individual and summary abemaciclib concentration-time profiles for patients taking abemaciclib in combination with letrozole or anastrozole after single and multiple dosing in Study JPBH.



Multiple dose data were presented on Day 28 of Cycle 1 in patients without dose reduction. Black solid line: arithmetic mean. Black dashed line: geometric mean. Gray lines: individual observations.
Source: Response to Information Request, Figures 3.1, 3.2, 3.3, and 3.4.

Study JPBM (MONARCH 3)

Study JPBM is a randomized, double blind, placebo-controlled, Phase 3 study for postmenopausal women with HR+, HER2- locoregionally recurrent or metastatic breast cancer randomized to receive abemaciclib or placebo plus a nonsteroidal aromatase inhibitor

(anastrozole or letrozole). PK of abemaciclib, its metabolites, and NSAI therapy is one the secondary objectives of this study.

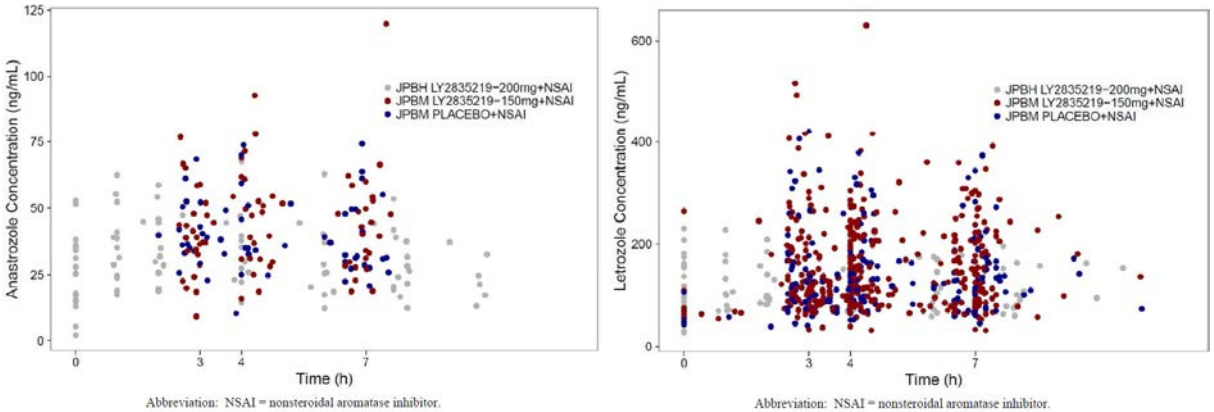
Table 40. Pharmacokinetic Sampling Schedule in Study JPBM.

Cycle (C) and Day (D)	PK Sample Number	Study Drug Dose	Dosing of Anastrozole/ Letrozole	Sampling Time for PK from Blood[a]
Baseline (Day -14 to Day -1)				Day of visit
C1D1	1	X[b]	X[b]	2 to 4 hrs after NSAI and blinded study drug dosed in clinic
C2D1	2	X[c]	X[c]	Upon arrival at site (that is, at least 4 hrs after taking NSAI and blinded study drug doses at home)
C2D1	3			3±0.5 hrs after arrival at site (that is, at least 7±0.5 hrs after taking NSAI and blinded study drug doses at home)
C3D1	4	X[b]	X[b]	Prior to NSAI and blinded study drug doses. Patient was dosed in clinic after sample collection.
C3D1	5			3±0.5 hrs after NSAI and blinded study drug dosing in clinic
C4D1		X[b]	X[b]	2 to 4 hrs after NSAI and blinded study drug dosing in clinic.
30 Day Follow-Up				Day of visit

Source: JPBM clinical study report, Table JPBM.9.6

In the 327 patients who received abemaciclib + NSAI treatment, 196 patients provided a total of 810 abemaciclib, 810 M2, and 811 M20 concentration-time data points during the first 2 treatment cycles. PopPK and E-R analyses of abemaciclib are summarized in Section 4.3. A total of 236 anastrozole and 998 letrozole concentration-time data points from 59 and 241 patients were obtained during the first 2 treatment cycles. Observed concentration-time data for anastrozole and for letrozole are comparable in the abemaciclib arm and the placebo arm, suggesting that a single dose 150 mg abemaciclib does not have an apparent effect on anastrozole or letrozole PK (Figure 12).

Figure 12. Observed anastrozole (left) and letrozole (right) concentrations versus time from first abemaciclib dose in patients with cancer in MONARCH 3 and Study JPBH.



Source: I3Y-MC-JPBM Population PK/PD Report Amendment (a), Figure 8.4 and 8.5

16.3.3. Population PK and Exposure-Response Analyses

Overall Strategy of popPK and ER Analyses in MONARCH 3 Study

Plasma concentration data for abemaciclib and its active metabolites (M2 and M20) were combined with dosing information, demographic data, efficacy and safety data, and clinical laboratory results using SAS® and R to produce the dataset used in popPK and E-R analyses. The popPK model based on a meta-analysis of 12 other studies (including MONARCH 1 and MONARCH 2, reviewed in NDA 208716) was fitted to the MONARCH 3 data. Individual post hoc PK parameters were estimated using NONMEM version 7.3. The popPK model was used to predict the time-course of abemaciclib, M2, and M20 concentrations over a 12-hour period after a single dose and at steady state. PK/PD models were developed in NONMEM version 7.3 to characterize the time course for the effect of abemaciclib exposure on efficacy (e.g., change in tumor size and PFS) and safety (neutropenia and diarrhea).

Population PK Analyses

In the 327 patients who received abemaciclib + NSAI treatment, 195 individuals provided PK data for abemaciclib, M2, and M20, for the popPK analysis. The existing mechanistic model described the observed data well, as evaluated by goodness-of-fit plots and the prediction- and variability-corrected VPCs. In 4 patients (ID (b) (6)), the estimate of oral bioavailability was unusually low (25.0%) compared with other patients (mean 45.3%, interquartile range: 44.2% to 46.2%). In these patients the population predictions were compatible with the observations, whereas the individual predictions exceeded even the highest observed concentrations in MONARCH 2 or 3. The individual predictions from these 4 patients were excluded E-R analyses and PK/PD modeling.

130 patients provided abemaciclib dosing and covariate information and therefore were included in the estimation of post hoc PK parameters by the population estimates given their body weight at study entry, dosing, and diarrhea histories.

Based on the current popPK analyses, the mean terminal half-life is predicted to be approximately 20 hours (43% CV) in MONARCH 3 patients who took abemaciclib in combination with NSAI. The model estimated mean abemaciclib $C_{max,ss}$, $C_{min,ss}$, and $AUC_{tau,ss}$ were 249 ng/mL (42% CV), 181 ng/mL (47% CV), and 2540 ng*h/mL (42% CV), respectively, based on the average dose on study of 132 mg.

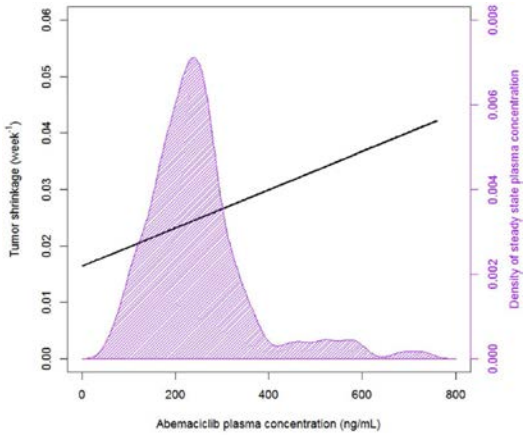
Reviewer's Comment: Applicant's approach for popPK analysis is acceptable. In addition to goodness-of-fit plot and VPCs, post hoc analysis suggested that the distributions of individual PK parameters are comparable in the proportion of patients who provided evaluable PK samples in MONARCH 3 and in MONARCH 1 and 2 studies (Figure 1). Additional covariate-parameter relationships were explored by visual inspection and no apparent covariate-parameter relationships were identified. Therefore, the existing model is adequate to describe PK data in MONARCH 3.

Because the individual estimates of PK parameters were similar in the MONARCH 3 study and in previous clinical trials, an update to the PK parameters in product label does not appear necessary.

E-R Analyses for Efficacy

A tumor shrinkage model with the same model structure as that reviewed in NDA 208716 was used to fit the observed tumor size data in 393 patients with measurable disease. The post hoc PK parameters from the mechanistic model were used to predict abemaciclib plasma concentrations according to the actual dosing history. The tumor growth rate in the model was fixed to the MONARCH 2 value because it could not be estimated in MONARCH 3 due to relatively few patients having increases in tumor size. The model described the data well, as evidenced by the low residual error, goodness-of-fit plots, and individual plots. A positive relationship was observed between the abemaciclib plasma concentration and the tumor shrinkage (Figure 13).

Figure 13. Typical concentration-effect relationship of abemaciclib.



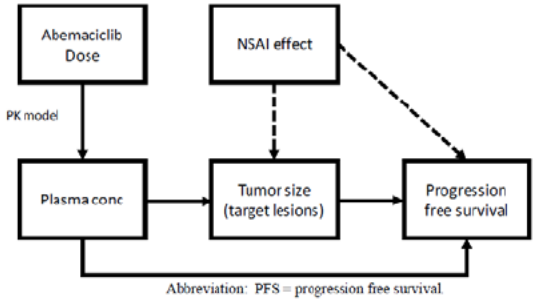
The black line is the E-R relationship from the linear drug effect model. Overlaid is a density plot showing the range of average steady-state concentration (predicted using average dose for each patient) for patients in MONARCH 3.
Source: I3Y-MC-JPBM Population PK/PD Report Amendment (a), Figure 8.17

The sponsor also conducted exploratory E-R analysis with dynamic PFS modeling, evaluating the effect of individual post hoc prediction of abemaciclib concentration or tumor size change on the risks of disease progression (Figure 14). The hazard model that best described PFS was described by an Emax drug effect model presenting drug effect on PFS at non-target lesions and a linear model presenting the effect of change from baseline tumor size on the target lesions (for patients with measurable diseases only): $\frac{dHaz}{dt} = HBASE \times e^{CFB \times THAZ - \frac{E_{max} \times CONC}{EC50 + CONC}}$, where *Haz* is the hazard at time t, *HBASE* is the baseline hazard, *CFB* is the change in tumor size from the baseline, *THAZ* is the effect of *CFB* on the hazard, *Emax* is the maximum drug effect on non-target lesion, *EC50* is the abemaciclib concentration that results in half the maximal effect, and *CONC* is the abemaciclib plasma concentration at time t. For patients with measurable disease, the interval censoring approach was used to calculate the likelihood of disease progression as the difference in the survival probability at the last known time when no progression was

observed from the survival probability at the recorded time of the progression. For patients with non-measurable disease, the likelihood of disease progression was calculated by the event density function as the negative derivative of the survival function with respect to time at the time of assessment.

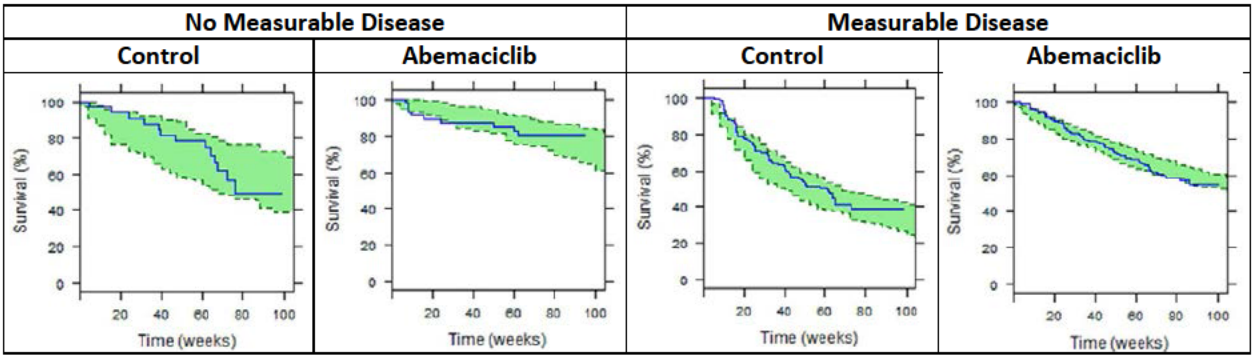
Parameter estimates for the final model were generally estimated with good precision. VPC suggested reasonable model fitting (Figure 15). Results suggested that patients with no measurable disease had higher predicted survival than those with measurable disease. In addition, higher abemaciclib concentration was associated with a lower hazard for disease progression outside the target lesion and change from baseline tumor size (which is positively correlated with concentration) was associated with lower hazard at the target lesions (Figure 16). The presence of hepatic metastases was the only significant covariate on the baseline hazard of progression.

Figure 14. PK-Change-in-Tumor-Size-PFS Model diagram.



Source: I3Y-MC-JPBM Population PK/PD Report Amendment (a), Figure 8.20

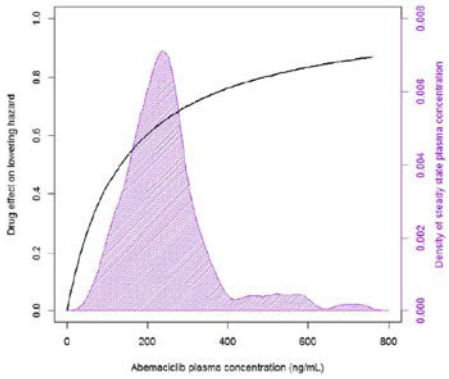
Figure 15. Visual predictive check of final PFS model.



The solid blue line is a Kaplan-Meier curve of the observed data, while the green shaded area is the 95% confidence interval from the model simulation.

Source: I3Y-MC-JPBM Population PK/PD Report Amendment (a), Figure 8.21

Figure 16. Abemaciclib exposure-response relationship for hazard of progression.



Source: I3Y-MC-JPBM Population PK/PD Report Amendment (a), Figure 8.23

Reviewer's Comment:

- *Reviewer agreed with applicant's conclusion that higher abemaciclib concentration is associated with higher tumor shrinkage and higher chances of best objective response in patients with measurable disease.*
- *Reviewer agreed with application's conclusion that higher abemaciclib exposure was associated with longer PFS in the MONARCH 3 population. In the dynamic PFS model, the applicant used the interval censoring approach in patients with measurable disease and used the event density function to calculate the likelihood of disease progression at specific times in patients without measurable diseases. The reviewer does not agree that this differential treatment based on measurable disease status was fully justified. Nevertheless, in sensitivity analysis when the model and dataset were revised to consistently apply the event density function or interval censoring approach on all patients, the reviewer arrives at the same conclusions of positive E-R relationship between abemaciclib exposure and longer PFS.*

E-R Analyses for Safety

Data from 474 patients were used in a time-to-first diarrhea event analysis. While abemaciclib use was associated with shorter time to first diarrhea event, there was no statistically significant relationship between abemaciclib concentration and the time to first diarrhea. In addition, the risk of diarrhea in the abemaciclib arm was 34% higher for patients taking anastrozole than for with patients taking letrozole. The hazard of diarrhea was 30% higher in patients taking opioids and 37% higher in Japanese patients.

The MONARCH 2 neutropenia model (based on the model by Friberg et al. 2002 and reviewed in NDA 208716) was used to analyze the effect of abemaciclib and NSAI on neutrophil counts in MONARCH 3. Abemaciclib effect on neutrophil production rate was revised to include a relationship between the predicted first day Cmax (total active species) in the first 2 cycles and the effect of steady state Cmax on later cycles. A total of 6570 post dose neutrophil counts from 477 patients from MONARCH 3 were used in the analysis. Higher abemaciclib exposure

was predicted to be associated with lower neutrophil product rate and hence higher risks of neutropenia.

Table 41. Parameters in the final population neutropenia model.

Parameter	Estimate (%SSE)		%CV BSV[a] (%SEE)	
		Both treatment arms		
NSAI neutrophil count (10^9 cells/L)	θ_1	3.43 (3.8)	$\omega_{1,1}$	37.4 (4.3)
Abemaciclib neutrophil count (10^9 cells/L)	θ_8	2.32 (0.2)	$\omega_{1,1}$	37.4 (4.3)
MTT (h)	θ_2	189 *fix*[b]	$\omega_{2,2}$	21.7 *fix*[b]
Gamma	θ_3	0.37 *fix*[b]	$\omega_{3,3}$	41.4 *fix*[b]
Early effect of abemaciclib on progenitor pool during Cycles 1 and 2	θ_4	0.118 (5.7)	$\omega_{4,4}$	67.7 (16.8)
Later effect of abemaciclib on progenitor pool (%) after Cycle 2	θ_5	0.0599 (0.5)	$\omega_{5,5}$	582 (7.3)
$C_{max,d1,total}$ relationship for abemaciclib effect during Cycles 1 and 2[c]	θ_7	0.417 (5.7)		
$C_{max,ss,total}$ relationship for abemaciclib effect after Cycle 2[d]	θ_6	0.16 (0.5)		
Proportional residual variability (%)	$\delta_{1,1}$	28.9 (3.6)		
Additive residual variability (10^9 cells/L)	$\delta_{2,2}$	0.000003 *fix*		

Abbreviations: BSV = between subject variability; $C_{max,d1}$ = maximum plasma concentration after a single dose ; $C_{max,ss}$ = maximum plasma concentration at steady state; CV = coefficient of variation; MTT = mean transit time; NSAI = nonsteroidal aromatase inhibitor; SEE = standard error of the estimate.

a Reported as %CV, calculated using equation $100 \cdot \sqrt{e^{\omega^2} - 1}$, where ω^2 is the NONMEM output for the intersubject variability of the parameter.

b Values for fixed parameters were obtained from the MONARCH 2 neutropenia model (MONARCH 2 Population PK/PD Report).

c Relationship = $\theta_6 \cdot log(1 + C_{max,d1,total})$.

d Relationship = $\theta_7 \cdot log(1 + C_{max,ss,total})$.

Source: I3Y-MC-JPBM Population PK/PD Report Amendment (a), Table 8.12

Reviewer's Comment: Based on prior experience with neutrophil count in abemaciclib treatment, neutrophil count is lowest around 3 weeks after the first abemaciclib dose. The PK/PD model for neutrophil count is limited by the fact that the sample collection schedule of MONARCH 3 does not allow an estimate of neutropenia rate around the expected nadir. While the model over-predicts the probability of Grade 3/4 neutropenia after 2 cycles, there was a reasonable agreement between the observed and simulated neutrophil counts after 2 cycles. Overall, reviewer agreed with applicant's conclusion on a positive relationship between abemaciclib exposure and the risks of neutropenia.

16.4. Additional Clinical Outcome Assessment Analyses

Not applicable.

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/s/

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