CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208716Orig1s000

MULTI-DISCIPLINE REVIEW

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

Division Director review is complete and has been added to the NDA Multidisciplinary Review and Evaluation. My recommendation for this application is approval.

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/s/

JULIA A BEAVER
09/28/2017

CDTL review is complete and has been added to the NDA 208716 abemaciclib Multidisciplinary Review and Evaluation. My recommendation for this application is regular approval.

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/s/

LALEH AMIRI KORDESTANI
09/28/2017

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	208,716
Priority or Standard	Priority
Submit Date(s)	5 May 2017
Received Date(s)	5 May 2017
PDUFA Goal Date	5 January 2018
Division/Office	DOP1/OHOP/OND
Review Completion Date	26 September 2017
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 fulvestrant 200 mg orally twice daily as a single agent
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	VERZENIO™ is a kinase inhibitor indicated: 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 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

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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
DMPP=Division of Medical Policy Programs

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BICR	blinded independent central review
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 a new molecular entity and inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in signaling pathways which lead to cell cycle progression and cellular proliferation.
This is a 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:

(b) (4)

The proposed dose is 200 mg orally Q12H daily when used as a single agent and 150 mg orally Q12H when used in combination with 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 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*

- *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 basis for the recommendation for indication as combination with fulvestrant is a favorable benefit-risk profile for abemaciclib when added to fulvestrant in women with HR-positive, HER2-negative advanced or metastatic breast cancer that has progressed on prior endocrine therapy. In a randomized, double-blind, placebo-controlled phase 3 study, MONARCH 2 (I3Y-MC-JPBL), there was a clinically meaningful and statistically significant improvement that favored the abemaciclib plus fulvestrant treatment arm. The estimated median progression-free survival (PFS) in the abemaciclib plus fulvestrant arm was 16.4 months compared to 9.3 months in the placebo plus fulvestrant arm HR=0.55 (95% CI :0.449, 0.681, p<0. 0001). Results of blinded independent central review (BICR), subgroup analyses, and sensitivity analyses all support the results of the primary efficacy endpoint.

The basis for the recommendation for indication as monotherapy is the efficacy and safety data from a single arm phase 2 MONARCH 1 trial in 132 patients who have received 1-2 prior chemotherapies in the metastatic setting. The confirmed ORR observed was 19.7% (95% CI 13.3, 27.5) which is comparable or better than other agents available in the similar setting. While the lower bound of the confidence interval did not exclude 15%, a value based on historical data for ORR in approved chemotherapies, abemaciclib as monotherapy in this setting offers an additional orally administered treatment option, with acceptable safety profile, for patients in a treatment setting where the goal is disease control and improvement of symptoms, rather than cure.

Overall, abemaciclib was generally tolerable with adverse reactions managed through the use of 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 86% of patients in the MONARCH 2 trial and 90% of patients in the MONARCH 1 trial. There were few cases of Grade 3 diarrhea, and this was generally treated by temporary treatment discontinuations and dose reductions when persistent or severe. Like other cyclin dependent kinase 4/6 inhibitors, neutropenia was also a common adverse reaction that occurred in 46% patients across MONARCH 2 and 37% of patients in MONARCH 1. The rate

of neutropenic fever and neutropenic sepsis was low; however, there were deaths due to neutropenic sepsis. Additional common adverse reactions were fatigue, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache.

There was a numerical increase in the number of venous thromboembolic events reported in patients receiving abemaciclib plus fulvestrant compared with those receiving placebo plus fulvestrant. This imbalance was apparent in other trials in the abemaciclib program as well. 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 modest. The safety profile of this agent is acceptable for this patient population who has a serious and life-threatening disease.

In summary, abemaciclib in combination with fulvestrant for the treatment of women with HR-positive, 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 demonstrates a favorable benefit-risk profile with adequate evidence to recommend approval. All disciplines were in agreement with approval of abemaciclib for both indications, or 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. Males with breast cancer tend to present at a higher stage than female patients given differences in screening.

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; however, not all patients respond to first-line therapy due to primary or *de novo* resistance and those patients who do respond will go on to progress developing acquired or secondary endocrine resistance. Treatment options at the time of disease progression include additional endocrine therapies, cyclin dependent kinase 4/6 inhibitors, mTOR inhibitors, or chemotherapy. Male patients with HR-positive, HER2-negative MBC have few approved treatment options due to sex based differences in estrogen production and thus their endocrine based therapy options are limited. Metastatic breast cancer is incurable and has a 5-year survival rate of approximately 25% (American Cancer Society 2017). Therefore, 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 fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or MBC who have received prior endocrine therapy as well as a (b) (4) for (b) (4) with HR-positive, HER2-negative advanced or MBC who have progressed following endocrine therapy and chemotherapy in the metastatic setting. 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

Reference ID: 4159689

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 2 of abemaciclib in combination with fulvestrant and also on the phase 2 trial MONARCH 1 of abemaciclib as a single agent. MONARCH 2 was a randomized, double-blind, placebo-controlled trial in women with HR-positive, HER2-negative advanced or MBC whose disease had progressed on prior endocrine therapy. 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 fulvestrant arm was 16.4 months compared with 9.3 months in the placebo plus fulvestrant arm (HR=0.55, 95% CI: 0.449, 0.681, p<0. 0001). Abemaciclib plus fulvestrant demonstrated a 7.1 month improvement in the estimated median PFS when compared with placebo plus fulvestrant. Results from a BICR audit, subgroup analyses, and sensitivity analyses all supported the primary efficacy endpoint results. Overall survival (OS) data are immature at this time.

MONARCH 1 was a multicenter, single-arm, open-label trial in patients with HR-positive, HER2-negative MBC whose disease had progressed after endocrine therapy and who had received 1-2 prior chemotherapy regimens in the metastatic setting. This was a well-designed trial with no comparator arm, given that there is no single standard of care in this setting. The primary endpoint was investigator assessed objective response rate (ORR). The ORR for patients who received abemaciclib as a single agent was 19.7% (95% CI 13.3, 27.5). The median duration of response was 8.6 months (95% CI 5.8, 10.2). Results were similar in the BICR analysis with an ORR of 17.4% (95% CI 11.4, 25.0) and a median duration of response of 7.2 months (95% CI 5.6, NR). This demonstrates activity of abemaciclib for patients who have limited treatment options and provides an additional orally administered therapy for patients. Taken with the PFS results of abemaciclib in combination with fulvestrant there is enough evidence to recommend regular approval for this indication. As there was no requirement that women who participated in this trial be postmenopausal and male patients have received and responded to abemaciclib in other clinical programs, the clinical benefit for male patients with HR-positive, HER2-negative MBC would be expected to be similar supporting expanding this indication to include male patients.

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 86% of patients experiencing this in MONARCH 2 and 90% of patients experiencing this in MONARCH 1. Neutropenia was additionally common as seen in other agents in this class with 46% of patients having an AE of neutropenia in MONARCH 2 and 37% of patients having an AE of neutropenia in MONARCH 1.

Additional adverse effects seen at increased incidence with the use of this agent include venous thromboembolic events. At the time of review,

additional safety data were available from other trials within the abemaciclib clinical development program and a similar higher incidence of VTE events was seen in the study therapy arm and deaths due to VTE were seen in other studies. Given this, an additional Warnings and Precautions was added to labeling.

In conclusion, based on a favorable risk-benefit profile for abemaciclib in combination with fulvestrant as well as a single agent in patients with MBC after chemotherapy in the metastatic setting, the reviewers recommend regular approval for the following indications:

"VERZENIO™ is a kinase inhibitor indicated:

- 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.
- 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."

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 20%. While male breast cancer is far more rare, making up <1% of all breast cancer cases, male patients are more likely to present with advanced disease and have fewer approved treatment options for HR positive, HER2-negative metastatic disease.	Locally advanced and metastatic breast cancer are serious and life-threatening conditions
Current Treatment Options	• As it is not curable, the goals of treating MBC 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 MBC include aromatase inhibitors (AIs) such as anastrazole, exemestane, and letrozole and the estrogen receptor downregulator fulvestrant. Endocrine therapy options for premenopausal women and men include tamoxifen. There are data to support the use of AIs and fulvestrant in premenopausal women who have ovarian function suppression. Endocrine therapies in combination with CDK 4/6 inhibitors and mTOR inhibitors are also available agents. There are few data to regarding the use of AIs and fulvestrant in male patients. • For patients with HR-positive, HER2-negative MBC whose disease has progressed on endocrine therapy, chemotherapy is an additional treatment option. These therapy options include paclitaxel, capecitabine, vinorelbine, eribulin, and gemcitabine.	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 2) in women with HR positive, HER2-negative advanced or metastatic breast cancer whose disease has progressed on prior endocrine therapy presented in this NDA demonstrates an improvement in PFS for abemaciclib plus fulvestrant	Evidence of effectiveness was supported by a statistically significant and clinically meaningful PFS improvement. MONARCH 2 was a large, double-blind, placebo controlled, and randomized trial, which decreases uncertainty.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	as compared to placebo plus fulvestrant. The estimated median PFS in the abemaciclib plus fulvestrant arm was 16.4 months compared to 9.3 months in the placebo plus fulvestrant arm (HR=0.55, 95% CI: 0.449, 0.681 , p<0.00001). OS results were immature at the time of analysis with 36% of the planned 441 events occurring as of May 5, 2017. Overall response rate (ORR) was 48.1% for the abemaciclib plus fulvestrant arm and 21.3% for the placebo plus fulvestrant arm in patients with measurable disease at baseline. Estimated median duration of response (DOR) was not yet reached in the abemaciclib plus fulvestrant arm and 25.6 months in the placebo plus fulvestrant arm. • The clinical data from the single arm, open label, phase 2 trial (MONARCH 1) in women with HR positive, HER2-negative, advanced or metastatic breast cancer who have been treated with 1-2 previous chemotherapy treatments in the metastatic setting presented in this NDA demonstrates a comparable ORR to existing therapies of 19.7% (95% CI 13.3, 27.5). Investigator-assessed estimated median DOR from the Kaplan-Meier curve was 8.6 months (95% CI 5.8, 10.2).	Supportive ORR, blinded independent committee review (BICR), 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 delay of progression and postponement of subsequent toxic therapies. A PMC was agreed upon to submit the final OS analysis. The ORR benefit derived from abemaciclib as a single agent (MONARCH 1) is comparable to other available therapies and offers an additional orally administered treatment for patients who have progressive MBC after chemotherapy in the metastatic setting.
Risk	• Diarrhea was reported in >80% of patients in the MONARCH 2 and MONARCH 1 studies. This 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 46% of patients on the MONARCH 2 study and 37% of patients on the MONARCH 1 study. The incidence of febrile neutropenia was low, however deaths due to neutropenic sepsis occurred. • Venous thromboembolic events were increased in the abemaciclib arm in the MONARCH 2 study and in other randomized studies in the	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 Precausions in labeling detail the serious risks of the drug.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	clinical development program. Based on this, a Warning and Precaution was added. • Hepatotoxicity: The incidence of increased ALT and AST was greater in the abemaciclib arm than the placebo arm. While the incidence of increased bilirubin was low, there were treatment discontinuations attributed to drug induced liver injury and one possible Hy's Law Case in the MONARCH 2 study. The Applicant proposed a Warning and Precaution with recommendations regarding LFT monitoring.	
Risk Management	• There is no proposal for a risk management plan.	The safe use of abemaciclib can be managed through accurate labeling and routine oncology care. No REMS is indicated.

Laleh Amiri-Kordestani, MD

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Breast cancer is the most common cancer affecting women in the US and Europe, and is the second leading cause of cancer death in women (National Cancer Institute, 2017). 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 metastatic breast cancer 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 currently incurable and treatments that extend progression free and overall survival are routinely used until evidence of disease progression or lack of tolerability. The median overall survival with MBC is approximately 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 breast cancer subtype (hormone receptor positive, HER-2 positive, and triple negative breast cancer) as well as sites of metastatic disease (visceral metasteses vs. bone only metasteses vs. other)(Kobayashi, Ito et al. 2016, Wedam, Beaver et al. 2016). The symptoms associated with MBCare 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 challenges associated with employment, income, and household duties (Cardoso, Harbeck et al. 2016).

Treatment of patients with metastatic hormone receptor positive, human epidermal growth factor 2 (HER2) negative metastatic breast cancer who do not respond to first line therapy include other endocrine based therapies such as aromatase inhibitors (anastrozole, letrozole, and exemestane), tamoxifen, fulvestrant, fulvestrant in combination with palbociclib, exemestane in combination with everolimus, and cytotoxic chemotherapy. Endocrine therapy options for pre and postmenopausal women are similar, however for premenopausal patients, aromatase inhibitors and fulvestrant should be administered with gonadotropin-releasing hormone agonists to disrupt the ovarian production of estrogen.

Approximately 90% of male breast cancer cases are hormone receptor positive(Anderson, Jatoi et al. 2010). For male patients, endocrine based therapies have demonstrated the superiority of tamoxifen for treatment in the adjuvant setting (Losurdo, Rota et al. 2017). Circulating estrogens in male patients derive from direct production from the testes (approximately 20%) with approximately 80% derived from the aromatization of testicular and adrenal androgens. While there are data regarding the use of AIs as single agents in the metastatic setting, both

ESMO and NCCN guidelines recommend downregulation of testicular function with GnRH agonists or orchiectomy (Sousa, Moser et al. 2013, Network 2017)

Analysis of Current Treatment Options

To date, there are two approved CDK 4/6 inhibitors for the treatment of women with locally advance or metastatic breast cancer: palbociclib and ribociclib. Palbociclib is a CDK 4/6 inhibitor that is currently FDA-approved for the initial treatment of postmenopausal women with HR-positive, HER2-negative metastatic breast cancer based on results from the PALOMA-2 trial demonstrating an improvement HR = 0.576 (95% CI: 0.463, 0.718) and in the estimated median PFS of 24.8 months in the palbociclib plus letrozole arm vs. 14.5 months in the placebo plus letrozole arm. For women who have progressed on previous endocrine based therapies, palbociclib in combination with fulvestrant has been approved for women following disease progression on endocrine therapy based on the results of the PALOMA-3 study demonstrating a HR = 0.461 (95% CI 0.360, 0.591) and an improvement in the estimated median PFS in the palbociclib plus fulvestrant arm of 9.5 months vs. 4.6 months in the placebo plus fulvestrant arm. Ribociclib is a CDK 4/6 inhibitor that has been approved for use as initial endocrine based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer.

For women who have progressed after initial endocrine therapy, everolimus with exemestane has been approved given the increased progression free survival estimated median of 7.8 months with everolimus plus exemestane as compared to 3.2 months for placebo plus exemestane.

For male patients, there are limited data for the use of endocrine therapies aside from tamoxifen.

Once patients are considered to have hormone refractory MBC, treatment includes standard cytotoxic chemotherapy agents including capecitabine, paclitaxel, gemcitabine, vinorelbine, and eribulin. Ixabepilone is another agent that can be used, though it is not often used outside of the setting of patients who progress on taxane based chemotherapy regimens Table 2.

Table 1. Summary of Treatment Armamentarium Relevant to Proposed Indication for Patients with HR-Positive, HER2-Negative Locally Advanced or MBC who have Progressed on Initial Endocrine Therapy

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
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 fulvestrant in women with disease progression following endocrine therapy	2015, 2016	125 mg by mouth daily with food for 21 days followed by 7 days off treatment	Estimated median PFS of palbociclib and fulvestrant 9.5 months (9.2-11.0) vs. placebo and fulvestrant 4.6 months (3.5-5.6), HR 0.461 (0.360, 0.591), p<0.0001, ORR palbociclib and fulvestrant 24.6% (19.6-30.2) vs. placebo and fulvestrant 10.9% (6.2-17.3)	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
Ribociclib (Kisqali)	In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenop	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.	QT prolongation, neutropenia, hepatotoxicity, embryo fetal toxicity	

	ausal women with HR-positive, HER2-negative advanced or metastatic breast cancer			placebo and letrozole 37.1% (31.1, 43.2)		
Other Treatments – [Combine by Pharmacologic Class, if relevant]						
Aromatase Inhibitors (letrozole, anastrazole, exemestane)	For the treatment of postmenopausal women with hormone receptor positive advanced breast cancer	Anastrazole 1995 Letrozole 1997 Exemestane 1999	One tablet taken daily	Anastrazole HR of 1.42, 95% CI 1.11, 1.82 with an estimated median TTP of 11.1 months in the anastrazole 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 megestrol acetate arm	Reduction in bone mineral density, increase in risk of ischemic cardiovascular events, increases in cholesterol, fatigue, dizziness, somnolence	
Fulvestrant	For the treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenop	2002	500 mg IM injection monthly after an initial loading dose of 500 mg IM on days 1 and 15 of month one	HR 0.80, 95% CI 0.68, 0.94 with an estimated overall survival of 26.4 months in the fulvestrant 500 mg arm and 22.3 months in the fulvestrant 250 mg arm	Injection site pain, nausea, bone pain, hot flashes	

	ausal women with disease progression following antiestrogen therapy					
Everolimus	For the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrazole	2012	One tablet taken daily with exemestane	HR 0.45, 95% CI: 0.38, 0.54 with an estimated PFS of 7.8 months in the everolimus plus exemestane arm and 3.2 months in the placebo plus exemestane arm	Stomatitis, infections, rash, fatigue, diarrhea, decreased appetite, hyperglycemia, dyspnea, pneumonitis	

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

Table 2. Summary of Treatment Armamentarium Relevant to Proposed Indication for Patients with HR-positive, HER-2 negative MBC who have Progressed after Chemotherapy

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Paclitaxel	For the treatment of breast cancer after failure of combination therapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy	1994	IV 175 mg/m^2 every 3 weeks or 80-90 mg/m^2 weekly		Febrile neutropenia, peripheral neuropathy	
Capecitabine	As monotherapy in patients resistant to both paclitaxel and an anthracycline containing regimen	2001	1250 mg/m^2 orally twice daily for 14 days then 7 day rest period	RR 25.6%, estimated median duration of response 154 days	Coagulopathy, diarrhea, cardiotoxicity, dehydration, renal failure, mucocutaneous and dermatological toxicity, hyperbilirubinemia, neutropenia, thrombocytopenia	
Vinorelbine(Zelek, Barthier et al. 2001)	N/A	N/A	25 mg/m^2 IV weekly	ORR 25%	Neutropenia, abdominal pain, ileus, fatigue	
Eribulin	For the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease	2010	1.4 mg/m^2 IV on days 1 and 8 of a 21 day cycle	ORR 11% Estimated Median duration of response: 4.2 months, Estimated Median overall survival 13.2 months vs. 10.6 months (HR 0.81, p=0.041)	Neutropenia, peripheral neuropathy, QT prolongation, fatigue, alopecia, nausea, constipation	

Gemcitabine(Rha , Moon et al. 2005)	22-30% (insert citation)	N/A	1000 mg/m^2 IV on days 1, 8 and 15 of a 28 day cycle	ORR 22-30% as a single agent based on various studies	Neutropenia, anemia, LFT abnormalities, thrombocytopenia , diarrhea, nausea, vomiting, alopecia, myalgia	

Source: *Reviewer analysis using Drugs @ FDA, NCCN guidelines, and citations as above*

Reviewer Comment: *Treatment for patients with metastatic HR-positive, HER2 negative breast cancer is palliative. For these patients, there are multiple endocrine therapy options; however, once there is evidence of disease progression on endocrine therapy, there is concern for endocrine resistance. Choice of agent(s) for treatment depends on tumor burden, disease related symptoms, adverse effects from previous therapies, concomitant illness, patient performance status, and patient preference. For male patients with metastatic HR-positive, HER2 negative breast cancer, there is no FDA approved endocrine therapy, though there are data to support the use of tamoxifen in this patient population. The use of agents other than tamoxifen has been less well studied.*

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Abemaciclib is a new molecular entity (NME) and not currently marketed in the United States.

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.

April 1, 2014: MONARCH 2 original protocol submitted.

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)

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.

March 1, 2016: A Type B Pre-NDA meeting was conducted. At this meeting, FDA did not agree that results from MONARCH 1 would provide meaningful therapeutic benefit over existing treatment based on efficacy and safety.

January 30, 2017: Type B guidance teleconference held to discuss Eli Lilly's data package to support a request for a BE study waiver.

March 28, 2017: Teleconference to advise Eli Lilly on the filing strategy for MONARCH 1 and

MONARCH 2. At this time it was agreed that the initial submission would contain the full MONARCH 1 submission and topline data for the MONARCH 2 submission with the full submission to follow.

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

June 30, 2017: MONARCH 2 components were submitted.

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

4.1. Office of Scientific Investigations (OSI)

Office of Scientific Investigations (OSI) audits were requested for this NDA. The OSI inspected eight sites based on enrollment, prior inspection history, and contribution of the site to efficacy endpoints given that the primary efficacy assessment was investigator assessed. A summary of the site inspections is provided in Table 3 and Table 4.

Table 3. OSI Findings in MONARCH 1, I3Y-MC-JPBL

Inspection	Site Number and Number of Subjects	Inspection Date	Interim Classification
Maura Dickler Memorial Sloan Kettering Cancer Center New York, NY, USA	Site: 100 Subjects: 17	July 18-27, 2017	VAI for failure to report adverse events, failing to maintain accurate records, and failing to provide copies of a few records requested
Sara Tolaney Dana Farber Cancer Institute Boston, MA, USA	Site: 400 Subjects: 17	August 2-24, 2017	NAI

Table 4. OSI Findings in MONARCH 2, I3Y-MC-JPBN

Inspection	Site Number and Number of Subjects	Inspection Date	Interim Classification
Claudia Arce Salinas México, Federal District 14080	Site: 280 Subjects: 11	August 21-25, 2017	Preliminary VAI. The inspection identified discrepancies and an FDA Form 483 was issued for failure to prepare or maintain adequate and accurate case histories with respect

			to observations and data pertinent to the investigation. Based on review, there were three subjects who appeared to have changes to their RECIST assessment: 1539, PR to CR 1581, SD to PR 2066, PR to SD, then CR to SD Based on these assessments, two investigator assessments were worse than review and one was better than the review
Maura Dickler Memorial Sloan Kettering Cancer Center New York, NY, USA	Site: 114 Subjects: 6	July 18-27, 2017	VAI for failure to report adverse events, failing to maintain accurate records, and failing to provide copies of a few records requested
Hiroji Iwata Nagoya, Aichi 464-8681	Site: 708 Subjects: 11	August 14-17, 2017	NAI
Peter Kaufman Norris Cotton Cancer Center Lebanon, NH	Site: 104 Subjects: 13	July 17-21, 2017	NAI
Sung-Bae Kim Seoul, Korea 5505	Site: 805 Subjects: 11	August 21-25, 2017	NAI
Sara Tolaney Dana Farber Cancer Institute	Site: 132 Subjects: 6	August 2-24, 2017	NAI

Boston, MA, USA			

Reviewer Comments: *The discrepancies seen at site 280 resulted in an assessment that may have affected the RECIST criteria investigator assessment for 3 patients. For two of these patients the assessment by the inspector was improved as compared to that of the investigator and for one it was worsened. A sensitivity analysis was performed excluding these patients and the results were consistent with the primary analysis. Additionally, IRC was performed and demonstrated consistent results with Investigator Assessed PFS further supporting the results of the primary endpoint.*

The issues at site 114 included underreporting of adverse events and concomitant medications, though it was noted that the nature of the AEs (headache, dysguesia, and fatigue) were noted to be unlikely to have a significant impact on patient safety. The concomitant medications that were underreported were also felt to have little significance as they affected no more than 1-2 subjects each (examples include proton pump inhibitors, vitamin supplements, anticoagulants for VTE prophylaxis, topical treatment for skin rash, pain medications, laxatives, and antidiarrheals).

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

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No

The CMC review team requested an impurity assessment for genotoxic impurity (b) (4) and (b) (4). The proposed specification limits for all impurities were no more than (b) (4)% and acceptable for the proposed patient population. As stated in ICH S9 and draft ICH S9 Q&A, for anticancer pharmaceuticals intended to treat patients with advanced disease, control of impurities below qualification levels specified in ICH Q3A and Q3B are not warranted, even if the impurity is genotoxic. (b) (4) is listed in the Inactive Ingredients Database and used as an excipient in multiple oral products at levels higher than (b) (4) mg, which is the amount that would be administered at (b) (4)% at the maximum recommended dose of 400 mg/day. The specification limit of (b) (4) is acceptable from the pharmacology/toxicology perspective.

4.3. Clinical Microbiology

Not applicable

4.4. Devices and Companion Diagnostic Issues

No device or companion diagnostic is included in this application.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Abemaciclib is a kinase inhibitor with activity against cyclin-dependent kinase 4 (CDK4) and CDK6. CDKs regulate cell cycle entry and commitment to cell division. CDK4 and CDK6 in complex with D-type cyclins (CycD) control progression from G1 to S phase of the cell cycle. CDK4 and CDK6 phosphorylate tumor suppressor retinoblastoma (Rb) protein, resulting in release of Rb-bound E2F transcription factors, upregulation of cell cycle-related genes, and cell cycle progression from G1 to S phase. In estrogen receptor-positive (ER+) breast cancer, ER activation promotes cyclin D1 transcription and activation of CDK4/6-Rb pathway, leading to uncontrolled cell proliferation.

The Applicant conducted several in vitro and in vivo pharmacology studies to assess the inhibitory activity and mechanism of action of abemaciclib. In vitro, abemaciclib inhibited enzymatic activity of purified human CDK4/CycD1, CDK6/CycD1, and CDK6/CycD3 with K_i values in the low nanomolar range. The Applicant tested abemaciclib in a panel of 560 cancer cell lines derived from diverse tumor types. Abemaciclib was active in cancer cells with wildtype Rb expression, copy number amplification of cyclin D1 or Myc family genes, or mutations reported to activate the CDK4/6 pathway. In vitro, abemaciclib treatment for up to four days inhibited Rb phosphorylation, DNA synthesis, and cell metabolism and caused G1 cell cycle arrest, resulting in senescence and apoptosis following treatment for four or more days. As observed with other cancer cell lines, abemaciclib treatment of ER+ breast cancer cells for up to eight days resulted in loss of Rb phosphorylation and downregulation of S-phase cell cycle marker topoisomerase IIα (Topo IIα). Continuous exposure to abemaciclib prevented rebound of Rb phosphorylation, and these results were the basis for the Applicant pursuing a continuous dosing schedule for abemaciclib.

In mouse xenograft models of ER+ breast cancer, daily doses of 50 or 75 mg/kg abemaciclib reduced tumor volume by 65-100% relative to controls and in a few models, caused tumor regression, up to 50% of initial tumor volume. Abemaciclib in combination with hormonal therapies 4-hydroxytamoxifen or fulvestrant further reduced tumor growth by 15 to 50% and prolonged the anti-tumor response relative to abemaciclib alone. Single-agent abemaciclib and combination therapy downregulated tumor mRNA expression of cell cycle-related genes and decreased protein expression of cell cycle markers Topo IIα and phosphorylated histone H3 (pHH3). The submitted nonclinical pharmacology data demonstrated that abemaciclib inhibits CDK4 and CDK6, prevents phosphorylation of Rb protein, and blocks cell cycle progression from G1 to S phase, leading to senescence and apoptosis. The approved Established Pharmacologic Class (EPC) of “kinase inhibitor” is applicable to abemaciclib based on its pharmacologic activity.

Human metabolites M2 and M20 are structurally similar to abemaciclib and present in human plasma at >10% of abemaciclib-related molecules. Following administration of a single dose of 150 mg [^{14}C]abemaciclib to healthy subjects, M2 and M20 plasma exposures were 13% and 26%, respectively, of total drug-related exposure. In single-dose PK studies, M2 was present at 5-9% in rat plasma and 15-18% in dog plasma relative to total parent and metabolites. M20 was not detected in rat and dog plasma in single-dose studies, but was present at <1% and <7% in rat and dog plasma, respectively, relative to abemaciclib exposure in repeat-dose toxicity studies. M2, M20, and abemaciclib had comparable inhibitory activity in the presence of purified CDKs, including CDK4 and CDK6. As observed with abemaciclib, both metabolites caused G1 cell cycle arrest and inhibited Rb phosphorylation and expression of cell cycle markers Topo IIα and pHH3. M2 and M20 arrested cell growth after four to six days of treatment and upregulated expression of senescence biomarkers after eight days of treatment. In general, M20 activity was comparable to abemaciclib. M2 activity was 2 to 5-fold lower than that observed in abemaciclib-treated cells.

Abemaciclib exposure (C_{max} and AUC) in rats and dogs increased with increasing dose and was generally dose proportional across the dose range tested. Pharmacokinetic analysis did not demonstrate gender differences in either species. Oral bioavailability was 30 to 60% following a single oral dose in rats, and the elimination half-life was 3 to 10 h. Abemaciclib equally partitioned in blood and plasma and was primarily excreted through the biliary/fecal route in rats and dogs with approximately 90% in feces.

In GLP-compliant, safety pharmacology studies, abemaciclib and its active metabolites inhibited hERG channel currents with IC_{50} values >1.65 µM and >10 µM, respectively, which are higher than concentrations achieved in patients at the maximum recommended clinical dose. Dogs receiving a single dose of 10 mg/kg abemaciclib demonstrated a slight decrease in blood pressure of 7-8% relative to vehicle controls. Abemaciclib had no effect on heart rate or ECG parameters in dogs receiving single doses up to 10 mg/kg and demonstrated no effect on respiratory and CNS function in rats receiving single doses up to 50 mg/kg.

The Applicant evaluated abemaciclib in GLP-compliant, repeat-dose, toxicology studies in rats and dogs with daily oral administration for up to 13 weeks. In both species, abemaciclib caused lung inflammation and affected organs with rapidly dividing cells, including bone marrow (hypocellularity), lymphoid organs (lymphoid depletion, atrophy), and gastrointestinal (GI) tract (atrophy, lymphoid depletion, necrosis, hemorrhage, hyperplasia), consistent with its mechanism of action. In dogs, a dose of 10 mg/kg caused early mortalities on Day 12 and 15 due to severe GI and hematologic toxicity. Clinical signs included decreased activity, tremors, cold to touch, dehydration, reduced food consumption, body weight loss, fecal changes, vomiting, weakness, and partially closed eyes. Abemaciclib also caused renal toxicity (tubular degeneration/ regeneration, vacuolation, dilatation) in rats at doses ≥10 mg/kg and mild to severe effects on male reproductive organs (intratubular cellular debris, hypospermia, tubular

dilatation, and degeneration/necrosis) at doses ≥10 mg/kg in rats and ≥0.3 mg/kg in dogs. These doses in rats and dogs resulted in exposures that were 2 and 0.02 times, respectively, the exposure (AUC) in humans at the maximum recommended dose of 200 mg twice daily (BID).

In general, toxicological findings were consistent with clinical adverse events of pneumonitis and hematologic and GI toxicities. Animal toxicology studies did not show evidence of thromboembolic events or elevated ALT and AST levels, which were observed in clinical trials. The majority of patients had increased serum creatinine in the first 28-day cycle until treatment discontinuation. Elevated serum creatinine was due to reversible inhibition of renal tubular transporters rather than acute renal injury or reduced glomerular function. Abemaciclib did not increase serum creatinine in rats or dogs. In rats and dogs, the major route of elimination was hepatic, with only a small fraction (~3-7%) eliminated by the kidneys.

Abemaciclib and metabolites M2 and M20 (mesylate salts) were not mutagenic in an in vitro bacterial reverse mutation (Ames) assay at concentrations up to 5000 µg/plate or clastogenic in an in vitro chromosomal aberration assay in Chinese hamster ovary cells or human peripheral blood lymphocytes. Abemaciclib was not clastogenic in an in vivo rat bone marrow micronucleus assay. Metabolites M2 and M20 did cause an increase in endoreduplication in an in vitro chromosomal aberrations test in CHO cells, but this was likely due to the mechanism of action of cell cycle disruption and not due to genotoxicity. Metabolite M2 was present in rat plasma, so it was evaluated in the negative in vivo rat bone marrow micronucleus assay. The weight of evidence suggests that abemaciclib and its metabolites are not genotoxic.

The Applicant did not conduct fertility studies with abemaciclib, and these studies are not warranted to support a marketing application in the proposed patient population, per ICH S9. In repeat-dose toxicology studies, abemaciclib caused adverse effects in the testis, epididymis, prostate, and seminal vesicles, suggesting a potential risk of impaired fertility in male patients. Toxicological findings in male reproductive organs, including decreased organ weights, intratubular cellular debris, hypospermia, tubular dilatation, atrophy, and degeneration/necrosis, occurred at doses ≥10 mg/kg/day in rats and ≥0.3 mg/kg/day in dogs.

Based on its mechanism of action and findings in animal toxicology studies, abemaciclib may cause fetal harm if administered to a pregnant woman. In an embryo-fetal development study, pregnant rats received oral doses up to 15 mg/kg abemaciclib during the period of organogenesis. Doses ≥4 mg/kg caused decreased fetal body weights and increased the incidence of cardiovascular and skeletal malformations and variations, including absent innominate artery and aortic arch, malpositioned subclavian artery, unossified sternebra, bipartite ossification of thoracic centrum, and rudimentary or nodulated ribs in the absence of maternal toxicity. At 4 mg/kg, maternal systemic exposures were similar to the human exposure (AUC) at the maximum recommended clinical dose. Females of reproductive potential should use effective contraception during treatment and for three weeks following the last dose of Verzenio. Due to potential adverse reactions in breast-fed children from abemaciclib,

lactating women should not breastfeed during treatment with Verzenio and for at least three weeks after the last dose.

According to the clinical pharmacology review of clinical trial JPBA, the geometric mean steady-state AUC_{0-12h} was 3000 ng·h/mL at the maximum recommended clinical dose of 200 mg BID. AUC_{0-12h} was doubled to estimate the AUC_{0-24h} of 6000 ng·h/mL and to calculate the animal-to-human exposure ratios in the prescribing information for Verzenio.

The submitted nonclinical pharmacology and toxicology data support approval of Verzenio for the proposed indications.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

The Applicant conducted in vitro and in vivo pharmacology studies, primarily using the (b) (4) abemaciclib. In vitro studies of abemaciclib activity included enzymatic assays using purified protein and cell-based assays using cancer cell lines. Abemaciclib inhibited activity of purified hCDK4/CycD1, hCDK6/CycD1, and hCDK6/CycD3 protein complexes with K_i values of 0.6, 2.4, and 8.2 nM, respectively (Study #QSB40). In a panel of 98 protein kinases, abemaciclib demonstrated similar nanomolar activity against CDK4 and CDK6 complexes and inhibited several other kinases with IC_{50} values less than or equal to the steady state C_{max} of 0.5 µM achieved in patients at a dose of 200 mg BID (Study #CCGS16).

Table 5. Inhibition of Kinases by Abemaciclib

Kinases	IC_{50} (µM)
hCDK4/CycD1	0.00196
hPIM1	0.006
hCDK6/CycD1	0.0099
hHIPK2	0.031
hCDK9/CycT1	0.033
hDYRK2	0.0615
hPIM2	0.114
hCK2	0.117
hGSK3b	0.192
hCDK5/P35	0.287
hCDK5/P25	0.355
hFLT3 (D835Y)	0.403
hCDK2/CycE	0.53

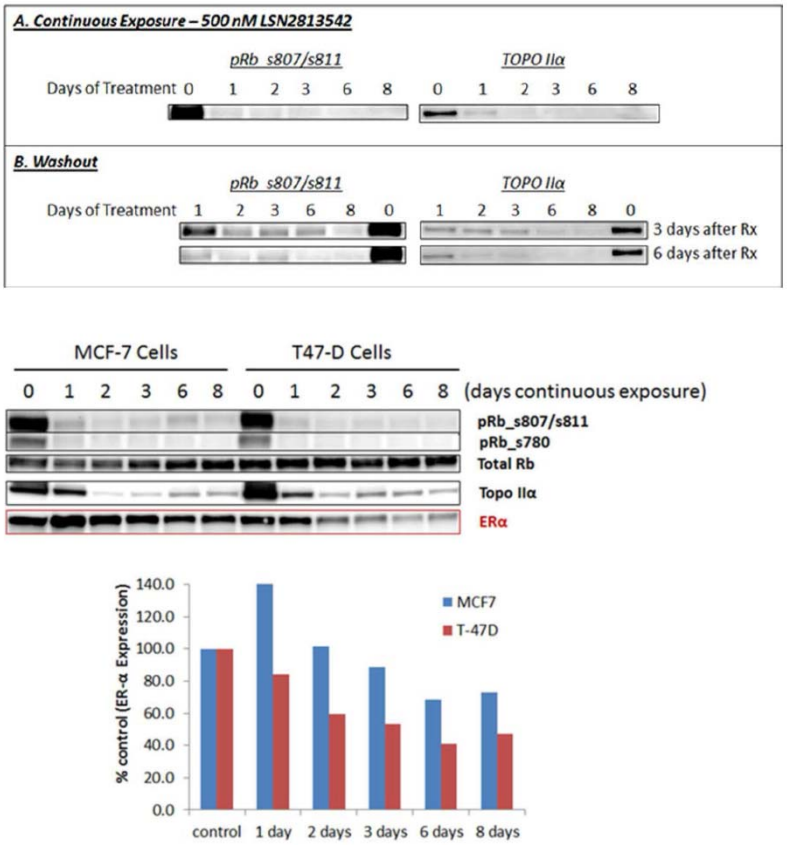
The Applicant tested abemaciclib in various cancer cell lines to evaluate cytotoxicity, biomarkers of response, and mechanisms of action. The Applicant treated a panel of 560 human cancer cell lines with increasing concentrations of abemaciclib for two doubling times prior to measuring cell viability (Study #CCGS292). Abemaciclib inhibited cell growth of 13% of cell lines at IC_{50} values of less than 1 µM. Sensitivity to abemaciclib treatment correlated with expression of wild type Rb, mutations reported to activate D-type cyclins, or amplification of D-type cyclin and Myc family genes. Sensitive cell lines included mantle cell lymphoma, neuroblastoma, medulloblastoma, Burkitt's lymphoma, Ewing's sarcoma, thyroid cancer, and colorectal cancer. Lung and breast cancer cell lines were also sensitive to abemaciclib after longer treatment duration of 10 days, and sensitivity to abemaciclib correlated with wild type Rb expression. In a panel of 46 breast cancer cell lines, abemaciclib treatment for six days resulted in variable cytotoxicity with IC_{50} values in the subnanomolar to micromolar range (Study #CCGS291). The most sensitive cell lines were generally ER+ with luminal histology. As observed with other cancer cell lines, the sensitivity of breast cancer cell lines to abemaciclib treatment correlated with wild type Rb expression, inhibition of Rb phosphorylation, and copy number amplification of the cyclin D1 gene.

To assess the mechanism of action, the Applicant evaluated the effects of abemaciclib on cell cycle progression, senescence, apoptosis, and cell metabolism in ER+ breast cancer cell lines (Study #QSB35, CCG293). Abemaciclib exposure for up to four days inhibited Rb phosphorylation (IC_{50} = 12-67 nM) and DNA synthesis (IC_{50} = 178 nM) and caused G1 cell cycle arrest (IC_{50} = 32-54 nM; Study #QSB35). Cytotoxicity and markers of senescence increased over time and correlated with morphological changes including increased cell size, flattening, and vacuolation (Study #QSB35). Abemaciclib exposure for four or more days resulted in apoptosis measured by increased Annexin V and Tunel staining. Abemaciclib caused maximal inhibition of cell proliferation after three or five doubling times, depending on the cancer cell line. Metabolic profiling demonstrated a concentration and time-dependent decrease in fumarate, malate, alpha-ketoglutarate, and lactate levels, suggesting that abemaciclib treatment attenuates cell metabolism.

To further assess the effects of abemaciclib on senescence, the Applicant treated three ER+/Rb+ breast cancer cell lines, T47-D, MCF-7, and ZR-75-1, with 500 nM abemaciclib (Study #CCGS304). Following eight days of treatment, all three cell lines showed 40 to 58% increase in senescence-associated β-galactosidase activity, a biomarker for senescence. Abemaciclib inhibited Rb phosphorylation and expression of S-phase cell cycle marker Topo IIα by Day 1 of treatment through Day 8 (Figure 1). Continuous abemaciclib exposure prevented rebound of Rb phosphorylation. ERα expression was reduced by up to ~60% of controls in T47-D cells and up to ~30% in MCF-7 cells. Collectively, these findings demonstrate that abemaciclib treatment for up to eight days results in inhibition of Rb phosphorylation and G1 cell cycle arrest, leading to senescence. Abemaciclib treatment had no effect on downstream targets of CDK9 (e.g., MCL

and phosphorylated CTD of RNA polymerase II) at concentrations up to 20 µM, despite showing nanomolar inhibitory activity in CDK9 enzymatic assays (Study #CCGS311).

Figure 1. Effects of Continuous Abemaciclib Exposure on ER+ Breast Cancer Cells



[Excerpted from Applicant's submission]

To characterize the activity profile of major human metabolites, the Applicant conducted in vitro pharmacology studies and compared the activity to abemaciclib (Study #CCGS293). Following a single dose of 150 mg [^{14}C]abemaciclib in healthy subjects, metabolites M2, M18, and M20 were present in plasma at 13%, 5%, and 26%, respectively, of total radioactivity (Study #I3Y-MC-JPBD). In enzymatic assays, abemaciclib and metabolites M2, M18, and M20 demonstrated similar inhibitory activity in the presence of purified CDK4, CDK6, CDK1, and CDK9 (Table 6). As observed with abemaciclib, treatment of lung and colorectal cancer cell lines with major metabolites M2 and M20 for 24 h caused G1 cell cycle arrest and inhibited Rb phosphorylation and expression of cell cycle markers Topo IIα and pHH3. M2 and M20 inhibited growth of breast cancer cells after four to six days of treatment (Figure 2) and increased

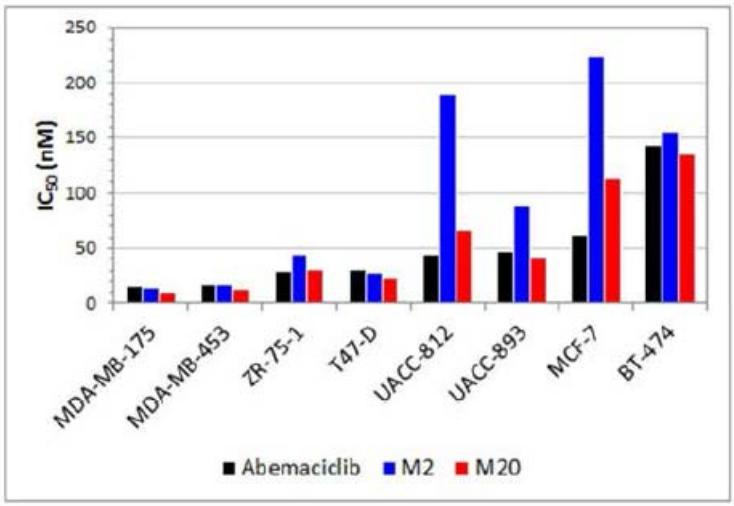
expression of senescence biomarkers after eight days of treatment. In general, M20 activity was comparable to abemaciclib whereas M2 activity was 2 to 5-fold lower than that observed in abemaciclib-treated cells. None of the metabolites had an effect on downstream targets of CDK9, despite showing inhibitory activity in cell-free enzymatic assays.

Table 6. IC50 Values from Cell-free Kinase Assays for Abemaciclib and Human Metabolites

	CDK4/CyclinD1			CDK6/CyclinD1			CDK1/CyclinB1			CDK9		
Compound	**Abs IC_{50} (μM)**	**SD**	**N**	**Abs IC_{50} (μM)**	**SD**	**N**	**Abs IC_{50} (μM)**	**SD**	**N**	**Abs IC_{50} (μM)**	**SD**	**N**
Abemaciclib	0.00157	0.0006	10	0.00202	0.0018	5	0.925	0.65	13	0.035	0.03	7
M2	0.00124	0.0004	7	0.00133	0.0003	4	0.816	0.45	7	0.01	0.00	3
M18	0.00146	0.0002	3	0.00265	0.0008	4	0.706	0.15	4	0.0157	0.00	3
M20	0.00154	0.0002	2	0.00186	0.0005	4	0.869	0.34	4	0.0215	0.01	3
M22	0.425	0.0906	3	0.557	0.2410	3	>20.0	0.00	4	2.01	1.11	3

[Excerpted from Applicant's submission]

Figure 2. Effects of Abemaciclib Metabolites on Inhibiting Growth of Breast Cancer Cells



Cell Line	Abemaciclib (nM)	M2 (nM)	M20 (nM)
MDA-MB-175	15.4	14.5	10.8
MDA-MB-453	17.2	16.7	13.0
ZR-75-1	29.9	44.6	30.5
T47-D	30.9	28.6	22.6
UACC-812	44.3	190.3	66.8
UACC-893	47.2	88.7	41.8
MCF-7	62.8	224.1	113.6
BT-474	143.9	155.6	135.2

[Excerpted from Applicant's submission]

The Applicant evaluated the anti-tumor activity of abemaciclib in mouse xenograft models of ER+/HER2- luminal breast cancer. A few tumor models harbored genetic alterations in the CDK4/6 pathway (e.g., amplification of cyclin D1 gene [CCND1] or activating mutation in CCND1). Doses of 50 or 75 mg/kg abemaciclib daily reduced tumor growth by 65-100% following 28 to 35 days of treatment (Study #CCGS303, #CCGS314, #CCGS319, and #CCGS321). In some tumor models, abemaciclib treatment resulted in tumor regression by up to 50% of initial tumor volume. Tumor analysis demonstrated effects on downstream CDK4/6 targets, including inhibition of Rb phosphorylation and reduced protein expression of cell cycle markers Topo IIα and pHH3 (Study #CCG303). Abemaciclib treatment also reduced tumor mRNA expression of several cell cycle-related genes, including cyclin E, MCM7, CDKN2C (p18), PTEN, Aurora A, cyclin B1, FOXM1, Ki67, and Topo IIα. Abemaciclib treatment had no effect on downstream targets of CDK9, suggesting that its anti-tumor activity is dependent on CDK4/6 inhibition and not CDK9.

The Applicant also evaluated the anti-tumor activity of abemaciclib in combination with hormonal therapies 4-hydroxytamoxifen or fulvestrant in mouse xenograft models of

ER+/HER2- luminal breast cancer (Study #CCGS314, #CCGS319, and #CCGS321). Addition of hormonal therapy to 50 mg/kg abemaciclib further reduced tumor growth by 15 to 50% and prolonged the anti-tumor response compared to abemaciclib alone. Tumor analysis demonstrated a corresponding decrease in mRNA expression of cell cycle-related genes and inhibition of cell cycle markers phosphorylated Rb, Topo IIα, and pHH3 (Study #CCGS319).

Safety Pharmacology

The Applicant evaluated the effects of abemaciclib on hERG channel currents using stably transfected HEK293 cells (Study #090210.FMD). Due to solubility limitations, the highest concentration tested was 1.65 µM abemaciclib, which resulted in 33.7% inhibition of hERG channel currents. The Applicant also assessed the inhibitory activity of human metabolites M2, M18, and M20 (Study #140516.FMD). IC_{50} values for these metabolites were all greater than 10 µM. Abemaciclib and its metabolites are low potency inhibitors of hERG channels, indicating a low risk of hERG channel inhibition.

The effects of abemaciclib on blood pressure, heart rate, and ECG parameters were assessed in a GLP-compliant cardiovascular telemetry study in unrestrained conscious Beagle dogs (Study #692944). Dogs received a single oral dose of 0, 0.3, 1, or 10 mg/kg abemaciclib using a 4x4 crossover design with at least seven days between each dose. ECG tracings were collected prior to each dose and at 1, 2, 4, 6, 24, and 48 h post-dose. Dogs receiving 10 mg/kg abemaciclib demonstrated statistically significant decreases in blood pressure. Abemaciclib caused a decrease in systolic blood pressure up to 7.1% compared to controls at 12 to 14 h and 17 to 19 h post-dose and reduced diastolic pressure up to 8.5% compared to controls at 5, 14, 19, 21, 26, and 45 h post-dose. Decreases in mean arterial pressure up to 7.4% were noted at 5, 12 to 14, 17 to 19, 26, and 45 h post-dose. No adverse findings were observed at ≤1 mg/kg (C_{max} = 24.8 ng/mL; $AUC_{0\text{-}24h}$ = 334 ng·h/mL from Study #8000445).

One dog receiving 10 mg/kg abemaciclib had ventricular premature complexes at 22 to 46 h post-dose and episodes of paroxysmal ventricular tachycardia or accelerated idioventricular rhythm at 22 to 48 h post-dose. The Applicant proposed that these findings may be due to ventricular irritation from the insertion site of the left ventricular pressure transducer or positive ECG electrode; however, this animal did not experience adverse effects after receiving lower dose levels or vehicle control, so this finding is possibly test article-related.

The Applicant evaluated the effect of abemaciclib on respiratory and central nervous system (CNS) function in GLP-compliant studies in male Sprague Dawley rats (Study #692943, 692942). Rats received a single oral dose of 0, 10, 30, or 50 mg/kg prior to respiratory evaluation at 1, 2, 4, 6, 24 and 48 h post-dose and prior to CNS evaluation. Respiratory and CNS function were comparable to vehicle controls at doses up to 50 mg/kg abemaciclib (C_{max}=1330 ng/mL; $AUC_{0\text{-}24h}$=23000 ng·h/mL from Study #803871).

5.4. ADME/PK

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Absorption</td><td></td></tr>
<tr><td>Dose-exposure relationship of LY2835219 in male Sprague Dawley rats following a single oral dose of 5, 15, 40, or 80 mg/kg of LY2835219 and pharmacokinetics following a single intravenous infusion dose of 5 mg/kg of LY2835219 (Study # 8243-263)</td><td>Rat
Plasma PK parameters of abemaciclib following a single oral or IV dose to male rats (n = 3/group):
<table>
<tr><th></th><th>5 mg/mg</th><th>15 mg/kg</th><th>40 mg/kg</th><th>80 mg/kg</th><th>5 IV mg/kg</th></tr>
<tr><td>C_{max} (ng/mL)</td><td>167</td><td>510</td><td>789</td><td>1020</td><td>1610</td></tr>
<tr><td>AUC_{0-48h} (ng·h/mL)</td><td>1380[a]</td><td>7040</td><td>22000</td><td>39300</td><td>4620[b]</td></tr>
<tr><td>$T_{1/2}$ (h)</td><td>3.2</td><td>5.9</td><td>10.3</td><td>NR[c]</td><td>3.25</td></tr>
<tr><td>CL (mL/kg/h)</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td><td>1090</td></tr>
<tr><td>Vd (L/kg)</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td><td>3.56</td></tr>
<tr><td>Bioavailability (%)</td><td>29.9</td><td>50.8</td><td>59.5</td><td>53.2</td><td>NA</td></tr>
</table>
[a]AUC from 0 to last measurable time point (12 h)
[b]AUC from 0 to last measurable time point (24 h)
[c]Not reported due to %CV greater than 100%</td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>In vitro investigation of LY2835219 binding to mouse, rat, dog, and human plasma proteins and human liver microsomes using equilibrium dialysis (Study # N0574)</td><td>Mean protein binding of abemaciclib (% bound):
Mouse: 98-99%
Rat: 98-99%
Dog: 95-97%
Human: 96-98%
Human liver microsomes: 85-91%</td></tr>
<tr><td>In vitro protein binding of LY2835219 metabolites LSN2839567, LSN3106726, and LSN3106729 in mouse, rat, dog, monkey, and human plasma and human liver microsomes (Study # LY2835219-Metab-prelim-pb)</td><td>Mean protein binding of metabolites (% bound)
<table>
<tr><th></th><th>Mouse plasma</th><th>Rat plasma</th><th>Dog plasma</th><th>Human plasma</th><th>Human microsomes</th></tr>
<tr><td>M2</td><td>94</td><td>92</td><td>83</td><td>89</td><td>67</td></tr>
<tr><td>M20</td><td>90</td><td>93</td><td>76</td><td>94</td><td>39</td></tr>
<tr><td>M18</td><td>89</td><td>82</td><td>69</td><td>91</td><td>59</td></tr>
</table></td></tr>
<tr><td>Pharmacokinetics, distribution, metabolism, and elimination of [^{14}C]LY2835219 in male Sprague Dawley and male and female Long Evans rats following a single 10-mg/kg oral dose of [^{14}C]LY2835219 (Study # 8221544PK)</td><td>Rat
- Mean blood-to-plasma ratio = 0.94-1.24
- C_{max} in most tissues occurred at 8 h post-dose.
- Highest maximum concentrations detected in GI tract contents
- Highest tissue concentrations in SD rats were observed in preputial gland, exorbital lacrimal gland,</td></tr>
</table>

Type of Study	Major Findings
	harderian gland, intra-orbital lacrimal gland, thyroid, and pituitary gland. - High peak tissue levels were in the kidney, spleen, liver, salivary gland, and adrenal medulla. - Moderate to low levels were in the testis. - Low levels of radioactivity were in brain tissues up to 8 h post-dose
Metabolism	
Metabolism of LY2835219 in biliary cannulated and intact male Sprague Dawley rats following a single 10 mg/kg oral dose of [^{14}C]LY2835219 (Study # 8221544ME)	**Rat** Following a single oral dose of 10 mg/kg abemaciclib to intact SD rats (% of total parent and metabolites): - Plasma: 74-81% parent, 5-9% M2, 5-9% M13 - Feces: 36% parent, 10% M1, 38% M2, 4% M14 - Urine: <1.5% parent and metabolites Following a single oral dose of 10 mg/kg abemaciclib to cannulated SD rats: - Feces: 13% parent, 19% M2 - Bile: 12% M2, 5% M7, <4% parent and metabolites
Metabolism of LY2835219 in male beagle dogs following a single 3 mg/kg (50-µCi/kg) oral dose or a single 1 mg/kg (15 µCi/kg) intravenous dose of [^{14}C]LY2835219 (Study # 8221545ME)	**Dog** Following a single oral dose of 3 mg/kg abemaciclib to dogs (% of total parent and metabolites): - Plasma: 90-100% parent, 15-18% M2 -Feces: 11% parent, 46% M2, 6% M20, 6% M1, ≤5% M14, M18, M21, and M22 - Urine: <1% parent and metabolites
Excretion	
Pharmacokinetics, distribution, metabolism, and elimination of [^{14}C]LY2835219 in male Sprague Dawley and male and female Long Evans rats following a single 10-mg/kg oral dose of [^{14}C]LY2835219 (Study # 8221544PK)	**Rat** - Following a single oral dose of 10 mg/kg, mean recovery of radioactivity was ~94-96%, with ~90% recovered by 48 h post-dose. - In intact rats, fecal excretion was the major route of elimination with ~91% in feces and ~3% in urine. - In bile duct-cannulated rats, total radioactivity eliminated in feces, bile, and urine was 35%, 51.6% and 6.6%, respectively.
Pharmacokinetics, metabolism, and elimination of [^{14}C]LY2835219 in male beagle dogs following a single 3-mg/kg (50-µCi/kg) oral dose or a single 1-mg/kg (15-µCi/kg) intravenous dose of [^{14}C]LY2835219 (Study # 8221545PK)	**Dog** - Following a single oral dose of 3 mg/kg or IV dose of 1 mg/kg, mean recovery of radioactivity was ~90%. Approximately 84% of total radioactivity was recovered by 72 h post-dose. - Fecal excretion was the major route of elimination with ~86% in feces and ~2-3% in urine.
TK data from general toxicology studies 3-month repeat dose study in rats	**Rat** <u>Abemaciclib</u> - Tmax: 4 to 12 h

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>(Study # 8000444)</td><td>- Accumulation: yes, ~2 to 4-fold
- Dose proportional
<table>
<tr><th>Day</th><th>Sex</th><th>Dose level (mg/kg)</th><th>C_{max} (ng/mL)</th><th>AUC_{0-24} (ng·h/mL)</th></tr>
<tr><td rowspan="6">1</td><td rowspan="3">M</td><td>3</td><td>59.2</td><td>735</td></tr>
<tr><td>10</td><td>194</td><td>2990</td></tr>
<tr><td>30</td><td>606</td><td>10500</td></tr>
<tr><td rowspan="3">F</td><td>3</td><td>102</td><td>1170</td></tr>
<tr><td>10</td><td>277</td><td>3960</td></tr>
<tr><td>30</td><td>711</td><td>13000</td></tr>
<tr><td rowspan="6">91</td><td rowspan="3">M</td><td>3</td><td>210</td><td>3020</td></tr>
<tr><td>10</td><td>574</td><td>10200</td></tr>
<tr><td>30</td><td>1400</td><td>30100</td></tr>
<tr><td rowspan="3">F</td><td>3</td><td>280</td><td>3760</td></tr>
<tr><td>10</td><td>875</td><td>15600</td></tr>
<tr><td>30</td><td>1540</td><td>32000</td></tr>
</table>

<u>Metabolite M2</u> (LD below LLOQ on Day 1)
- Tmax: 2 to 12 h (Day 29), 0.5 to 8 h (Day 91)
- Accumulation: yes, 5.8 to 16.4-fold at ≥10 mg/kg
- Greater than dose proportional
- 4 to 14% of abemaciclib exposure
<u>Metabolite M20</u> (LD, MD below LLOQ on Day 1)
- Tmax: 2 to 12 h (Day 91)
- Accumulation: yes, 3.4-fold at 30 mg/kg
- Dose proportional
- <1% of abemaciclib exposure when calculable</td></tr>
<tr><td>3-month repeat dose study in dogs</td><td>Dog</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>(Study # 8000445)</td><td>
<u>Abemaciclib</u>
- Tmax: 2.7 to 5.3 h
- Accumulation: yes, 1.6 to 2.3-fold
- Dose proportional
<table>
<tr><th>Day</th><th>Sex</th><th>Dose level (mg/kg)</th><th>C_{max} (ng/mL)</th><th>AUC_{0-24} (ng·h/mL)</th></tr>
<tr><td rowspan="6">1</td><td rowspan="3">M</td><td>0.3</td><td>6.2</td><td>73.8</td></tr>
<tr><td>1</td><td>24.8</td><td>334</td></tr>
<tr><td>3</td><td>50.5</td><td>735</td></tr>
<tr><td rowspan="3">F</td><td>0.3</td><td>6.3</td><td>60.2</td></tr>
<tr><td>1</td><td>21.6</td><td>236</td></tr>
<tr><td>3</td><td>46.6</td><td>611</td></tr>
<tr><td rowspan="6">91</td><td rowspan="3">M</td><td>0.3</td><td>11.3</td><td>148</td></tr>
<tr><td>1</td><td>49.0</td><td>743</td></tr>
<tr><td>3</td><td>105</td><td>1730</td></tr>
<tr><td rowspan="3">F</td><td>0.3</td><td>7.8</td><td>98.4</td></tr>
<tr><td>1</td><td>38.5</td><td>488</td></tr>
<tr><td>3</td><td>98.4</td><td>1400</td></tr>
</table>
<u>Metabolite M2</u> (LD below LLOQ)
- Tmax: 2.8 to 5.3 h at ≥1 mg/kg
- Accumulation: yes, 1.6 to 2.6-fold at ≥1 mg/kg
- Greater than dose proportional
- 10 to 33% of abemaciclib exposure when calculable

<u>metabolite M20</u> (LD, MD below LLOQ on Day 1)
- Tmax: 3 to 8 h at ≥1 mg/kg
- Accumulation: yes, 3.3-fold at 3 mg/kg
- Dose proportional
- <7% of abemaciclib exposure when calculable
</td></tr>
<tr><td>TK data from reproductive toxicology studies
Embryo-fetal development study in rats (Study # 8299046)</td><td>
Rat (maternal values)
<u>Abemaciclib</u>
- Tmax: 4 to 12 h
- Accumulation: yes, 1.4 to 1.9-fold
- Greater than dose proportional
-C_{max} and AUC_{0-24h} (GD17)
1 mg/kg: 54.6 ng/mL; 843 ng·h/mL
4 mg/kg: 348 ng/mL; 5250 ng·h/mL
15 mg/kg: 826 ng/mL; 17800 ng·h/mL

<u>Metabolite M2</u> (LD below LLOQ)
- Tmax: 4 to 12 h
- Accumulation: yes, 1.9 to 2.5-fold
- Greater than dose proportional
- 2 to 8% of abemaciclib when calculable

<u>Metabolites M20 and M18</u> were below LLOQ
</td></tr>
</table>

5.5. Toxicology

5.5.2. General Toxicology

Study title/ number: A repeat-dose toxicity and toxicokinetic study in rats given LY2835219 (compound 2835219) by oral gavage for 91 days/8000444

Key Study Findings

- Major target organs were the lymphoid organs, kidney, lung, and small intestine primarily at doses ≥10 mg/kg abemaciclib
- Moderate adverse effects were observed in male reproductive organs at 30 mg/kg abemaciclib.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 3, 10, 30 mg/kg/day

Route of administration: Oral gavage

Formulation/Vehicle: 1% hydroxyethylcellulose, 0.25% polysorbate 80 and 0.05% antifoam 1510-US in purified water

Species/Strain: Sprague Dawley rats

Number/Sex/Group: 10/Sex/Group

Age: 6 weeks old

Satellite groups/ unique design: 3-9/Sex/Group (TK analysis)

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No test article-related deaths
Clinical Signs	Unremarkable
Body Weights	End of dosing (body weight/body weight gain) Males: LD (-5.0%/-7.7%), MD (-17.0%/-23.2%), HD (-32.1%/ -43.1%) Females: LD (-6.5%/-11.5%), MD (-9.1%/-16.5%), HD (-17.8%/

	-33.5%)
Food consumption	Males: Decreased at LD (to -7%), MD (to -10%), HD (to -30%) Females: Decreased at LD (to -10%), MD (to -15%), HD (to -19%)
Ophthalmoscopy	Unremarkable
Hematology	RBC at LD (-5%), MD (-13%), HD (-25%) Hemoglobin at MD (-5%) and HD (to -16%) Hematocrit at MD (-6%) and HD (to -17%) Neutrophils at LD (36%), MD (41%), HD (102%) Monocytes at HD (41%) Eosinophils at LD (-47%), MD (-33%), HD (-47%) APTT at MD (to -14%) and HD (to -19%)
Clinical Chemistry	Decreased total bilirubin at HD (-36%) Increased urea nitrogen (31%) and creatinine (22%) in HD males Decreased creatine kinase at LD (to -25%), MD (to -31%), and HD (to -53%)
Urinalysis	Reduced pH and urine volume (-57%) in HD males
Gross Pathology	Small adrenal gland, prostate gland, seminal vesicle (HD only), and thymus at MD and HD Discoloration of kidney, lymph node, and spleen at HD Lung (pale and raised focus) at HD
Organ Weights	Reduced weights of adrenal, pituitary, prostate, thyroid, liver, spleen, and thymus primarily at MD and HD
Histopathology **Adequate battery:** Yes	See below

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.

Table 7. Summary of Histological Findings in Rats at Scheduled Necropsy

	Males				Females			
Doses (mg/kg/day)	**0**	**3**	**10**	**30**	**0**	**3**	**10**	**30**
Bone marrow, femur								
-Decreased cellularity; hematopoietic								
Minimal				3/10				1/10
Mild				6/10				
Bone marrow, sternum								
-Decreased cellularity; hematopoietic								
Minimal				1/10				5/10
Mild				8/10				3/10
Epididymis								
-Cellular debris								
Marked		1/1						
-Depletion; sperm								
Moderate				1/10				
Marked		1/1						
GALT								
-Decreased cellularity; lymphoid, follicular								
Minimal				1/10				4/10
Mild				7/10				3/10

	Males				Females			
Doses (mg/kg/day)	**0**	**3**	**10**	**30**	**0**	**3**	**10**	**30**
Moderate				1/10				
Heart								
-Cardiomyopathy								
Minimal	3/10			2/10				
Mild				2/10				
Kidney								
-Fibrosis, capsular								
Minimal							1/10	
-Necrosis; medullary								
Minimal				2/10				1/10
-Degeneration/regeneration; tubular								
Minimal	5/10	3/10	2/10	1/10			1/10	4/10
Mild				5/10				1/10
Moderate				2/10				
-Vacuolation; cortical, medullary, tubular								
Moderate				1/10				
-Vacuolation; cortical, tubular								
Mild							1/10	
-Vacuolation; medullary, tubular								
Minimal	1/10			4/10				1/10
Mild	1/10			3/10				8/10
-Vacuolation; tubular								
Minimal				2/10				
-Dilatation; tubular								
Moderate			1/10					
-Dilatation; pelvis								
Minimal			2/10					
Mild				1/10				
-Pigmentation; increased, proximal convoluted tubule								2/10
Mild								
-Cytoplasmic vacuolation/basophilic granules; glomerular								1/10
Minimal				10/10				9/10
Mild								
Liver								
-Vacuolation; hepatocellular								
Marked			1/10					
Lung								
-Accumulation; alveolar, macrophage								
Minimal	1/10		3/10			1/10		
Mild			1/10	5/10				4/10
Moderate				5/10				6/10
-Inflammation; alveolar, interstitial								
Minimal				4/10				7/10
Mild				4/10				1/10

	Males				Females			
Doses (mg/kg/day)	**0**	**3**	**10**	**30**	**0**	**3**	**10**	**30**
Lymph node, mandibular								
-Decreased cellularity; lymphoid, follicular								
Minimal				1/10				2/10
Mild				6/10				4/10
Moderate								3/10
Lymph node, mesenteric								
-Decreased cellularity; lymphoid, follicular								
Minimal				4/10				3/10
Mild				4/10				5/10
Moderate				2/10				2/10
-Erythrocytosis								
Minimal			2/10					1/10
Mild								1/10
Small intestine, duodenum								
-Hyperplasia; crypt								
Minimal				1/10				
Mild			1/10	1/10				1/10
Spleen								
-Fibrosis; capsular								
Mild				1/10				
Testis								
-Degeneration								
Severe		1/1						
-Dilatation; tubular								
Moderate				1/10				
Thymus								
-Decreased cellularity; lymphoid								
Minimal			4/10				8/10	
Mild			3/10				2/10	
Moderate				3/10				5/10
Marked				6/10				3/10
Severe								1/10

Study title/ number: A repeat dose toxicity and toxicokinetic study in the Beagle dog given LY2835219 by oral gavage for 3 months/8000445

Key Study Findings

- The major target organs were the lymphoid organs, adrenal gland, lung, and male reproductive organs.
- Abemaciclib caused cellular debris and oligo/aspermia in the epididymis and seminiferous tubule degeneration/necrosis in the testis at doses ≥0.3 mg/kg (C_{max}=11.3 ng/mL; AUC_{0-24h}=148 ng·h/mL).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 0.3, 1, 3 mg/kg/day

Route of administration: Oral gavage

Formulation/Vehicle: 1% hydroxyethylcellulose, 0.25% polysorbate 80 and 0.05% antifoam 1510-US in purified water

Species/Strain: Beagle dog

Number/Sex/Group: 3/Sex/Group

Age: 8 to 9 months

Satellite groups/ unique design: None

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No unscheduled deaths
Clinical Signs	Red skin at all doses in males Dry skin at all doses in females Single incidence of non-sustained convulsion in 1/3 HD males Tremors in 1/3 MD males and 2/3 HD females Abnormal gait 1/3 HD females Backbone prominent in 1/3 MD and HD females
Body Weights	End of dosing (body weight/body weight gain) Males: LD (-1.3%/-37.8%), MD (-4.6%/-55.6%), HD (-1.3%/0.0%) Females: LD (-4.1%/-60.2%), MD (-4.1%/-60.2%), HD (-6.8%/ -67.5%)
Food consumption	Unremarkable
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Hematology	RBC at LD (to -13%), MD (to -15%), HD (to -16%) Hemoglobin at LD (to -10%), MD (to -12%), HD (to -13%) Hematocrit at LD (to -11%), MD (to -14%), HD (to -18%) Platelets at HD (to -33%) Reticulocytes at LD (to -32%), MD (to -64%), HD (to -72%) WBC at LD (to -26%), MD (to -38%), HD (to -44%)

	Lymphocytes at LD (to -18%), MD (to -36%), HD (to -26%) Neutrophils at LD (to -32%), MD (to -45%), HD (to -48%) Monocytes at LD (to -47%), MD (to -42%) HD (to -55%) Eosinophils at LD (-57%), MD (to -72%), HD (to -70%) Basophils at LD (-52%), MD (to -67%), HD (to -78%)
Clinical Chemistry	Urea nitrogen at HD (to 54%) Cholesterol at LD (to 75%), MD (to 126%), HD (to 192%)
Urinalysis	Unremarkable
Gross Pathology	Adrenal gland (dark discoloration) at LD, MD, and HD Lung (discoloration, pale or dark focus) at MD and HD Spleen (enlargement, pale focus) at LD, MD, and HD Testis (soft abnormal consistency, small) at LD, MD, and HD Thymus (small) at LD, MD, and HD Urinary bladder (thick) at HD
Organ Weights	Reduced thymus weight at all dose levels and testis weight at MD and HD
Histopathology **Adequate battery: Yes**	See below

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.

Table 8. Summary of Histological Findings in Dogs at Scheduled Necropsy

	Males				Females			
Doses (mg/kg/day)	**0**	**0.3**	**1**	**3**	**0**	**0.3**	**1**	**3**
No. examined	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Bone marrow								
-Decreased cellularity; hematopoietic								
Minimal				2				2
Mild				1				
Epididymis								
-Cellular debris								
Minimal		1	1					
Mild			1					
-Oligo/aspermia								
Marked				1				
Severe				2				
-Inflammation, neutrophilic								
Mild				1				
Gallbladder								
-Vacuolation; epithelial								
Minimal	1	2	1		1			
Mild		1		1		1	1	
Moderate				1				
-Macrophage aggregation; lamina propria								
Minimal				1				
Mild				1				

	Males				Females			
Doses (mg/kg/day)	**0**	**0.3**	**1**	**3**	**0**	**0.3**	**1**	**3**
No. examined	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Adrenal gland								
-Vacuolation; cortical, decreased								
Minimal						2	2	
Mild		3	1					
Moderate			2	3			1	3
-Pigment deposit; cortical								
Mild								1
Prostate gland								
-Dilatation; urethra								
Mild				1				
Kidney								
-Inflammation; interstitial								
Minimal								1
Lung								
-Inflammation; alveolar								
Mild			1					
Moderate				1				
-Macrophage aggregation								
Minimal							1	1
-Granuloma								
Minimal							2	1
-Metaplasia; osseous								
Minimal							1	
Lymph node, mesenteric								
-Erythrocytosis								
Mild				1				
Spleen								
-Siderotic plaque								
Minimal	1							
Mild			1			1		
-Pigment deposit; increased								
Minimal			1				1	2
Mild								1
Stomach								
-Hemorrhage; mucosal, pylorus								
Minimal				1				
-Hemorrhage; pylorus								
Minimal						1		

	Males				Females			
Doses (mg/kg/day)	**0**	**0.3**	**1**	**3**	**0**	**0.3**	**1**	**3**
No. examined	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Testis								
-Atrophy								
Minimal		1						
-Degeneration/necrosis; seminiferous tubule								
Minimal		1						
Mild		2	3					
Marked				1				
Severe				2				
Thymus								
-Hemorrhage								
Minimal		1						
-Decreased cellularity; lymphoid								
Mild		2	2				2	
Moderate				2		1		1

General toxicology; additional studies

Study title/ number: A repeat dose toxicity and toxicokinetic study in Sprague-Dawley rats given LY2835219 (Compound 2835219) by oral gavage for 28 days followed by a recovery period of 28 days/ #803871

In a GLP-compliant study, Sprague Dawley rats received doses of 0, 10, 30, or 50 mg/kg/day orally for 28 days followed by a 28-day recovery period. Clinical signs occurred primarily at the mid and high dose level and included salivation, partially closed eyes, dehydration, decreased activity, prominent backbone, thin appearance, fecal changes, thin fur, alopecia, and dry, flaky, red or scabbed skin. Abemaciclib caused a dose-dependent decrease body weight gain up to ~25% relative to controls. Abemaciclib targeted organs with rapidly dividing cells including lymphoid organs, GI tract, and male reproductive organs at doses ≥10 mg/kg (C_{max}=729 ng/mL; $AUC_{0\text{-}24h}$=12415 ng·h/mL). Toxicological findings in the epididymis, testis, prostate, and seminal vesicle occurred at all dose levels and included decreased organ weight, atrophy, intratubular cellular debris, necrosis, germ cell degeneration/depletion, and spermatid retention. Histological findings were also observed in the kidney (tubular vacuolation/ degeneration, inflammation), lung (macrophage accumulation, bronchoalveolar inflammation), mammary gland (glandular atrophy), skeletal muscle (myofiber degeneration/ necrosis), and skin (parakeratosis, epidural hyperplasia, ulceration) primarily at the mid and high dose levels. Hematology analysis showed a reversible decrease in red cell mass, platelets, monocytes, and eosinophils at doses ≥10 mg/kg. An increase in total leukocytes, neutrophils, and basophils at doses ≥30 mg/kg was indicative of inflammation observed in multiple organs.

Study title/ number: A repeat-dose toxicity and toxicokinetic study in Beagle dogs given LY2835219 (Compound 2835219) by oral gavage for 28 days followed by a recovery period of 28 days/ #803872

In a GLP-compliant study, Beagle dogs received doses of 0, 1, 3, and 10 mg/kg/day orally for 28 days followed by a 28-day recovery period. Two dogs receiving 10 mg/kg abemaciclib were euthanized moribund on Day 12 and 15 due to severe GI and hematologic toxicity. Clinical signs were observed primarily at 10 mg/kg and included decreased activity, tremors, cold to touch, dehydration, reduced food consumption, body weight loss, vomiting, weakness, partially closed eyes, and soft, liquid, red, and black feces. On Day 13/14, the Applicant stopped dosing the remaining animals in the 10 mg/kg dose group. The major target organs were the lymphoid organs (decreased cellularity, erythrocytosis/hemorrhage), GI tract (hyperplasia, hemorrhage, atrophy, lymphoid depletion, necrosis), male reproductive organs, lung (bronchoalveolar inflammation), and adrenal glands (immune infiltrates, cytoplasmic eosinophilia, decreased vacuolation). Toxicological findings in the testis and epididymis occurred at all dose levels and included atrophy and degeneration of the seminal epithelium and oligo/aspermia. Clinical pathology analysis showed a reversible decrease in red cell mass and leukocyte populations at all dose levels and an increase in cholesterol up to 3.5-fold. At end of recovery, toxicological findings were still observed in the bone marrow, GI tract, male reproductive organs, lymphoid organs, mammary gland (atrophy), and lung (macrophage accumulation, fibrosis, and hemorrhage).

5.5.3. Genetic Toxicology

Study title/ number: LY2835219 (Compound 2835219) Bacterial mutation test/ #962562
Key Study Findings:

- Abemaciclib was not mutagenic under the conditions tested.

GLP compliance: Yes
Test system: salmonella strains TA1535, TA1537, TA98, TA100 and E. coli strain WP2 *uvrA*; up to 5000 µg/plate abemaciclib; +/- S9
Study is valid: Yes

Study title/ number: LSN3151113 (Metabolite M20): Bacterial reverse mutation assay/ #8323847
Key Study Findings:

- Metabolite M20 (mesylate salt) was not mutagenic under the conditions tested.

GLP compliance: Yes
Test system: salmonella strains TA1535, TA1537, TA98, TA100 and E. coli strain WP2 *uvrA*; up to 5000 µg/plate metabolite M20; +/- S9
Study is valid: Yes

Study title/ number: LSN2839543 (Metabolite M2): Bacterial reverse mutation assay/ #8324137
Key Study Findings:
- Metabolite M2 (mesylate salt) was not mutagenic under the conditions tested.

GLP compliance: Yes
Test system: salmonella strains TA1535, TA1537, TA98, TA100 and E. coli strain WP2 *uvrA*; up to 5000 µg/plate metabolite M2; +/- S9
Study is valid: Yes

In Vitro Assays in Mammalian Cells
Study title/ number: LY2835219 (Compound 2835219) Chromosome aberration test/ #962563
Key Study Findings:
- Abemaciclib was not clastogenic under the conditions tested.

GLP compliance: Yes
Test system: human peripheral blood lymphocytes; up to 12.5 µg/mL in main study; +/- S9
Study is valid: Yes

Study title/ number: LSN3151113 (Metabolite M20): Chromosomal aberrations in Chinese hamster ovary (CHO) cells/ #8323846
Key Study Findings:
- Metabolite M20 (mesylate salt) was not clastogenic under the conditions tested.
- Following 3 hour treatment, M20 caused an increase in the number of cells with endoreplication at 1.97 and 2.32 µg/mL (5.5% and 10.5%, respectively) without S9 activation and at 4.44 and 5.22 µg/mL (13.5 and 22.0%, respectively) with S9 activation. These findings were attributed to mechanism of cell cycle disruption rather than genotoxicity.

GLP compliance: Yes
Test system: Chinese hamster ovary cells; up to 10 µg/mL in main study; +/- S9
Study is valid: Yes

Study title/ number: LSN2839543 (Metabolite M2): Chromosomal aberrations in Chinese hamster ovary (CHO) cells/ #8323848
Key Study Findings:
- Metabolite M2 (mesylate salt) was not clastogenic under the conditions tested.
- M2 caused an increase in the number of cells with endoreplication at 2.95 and 2.47 µg/mL (12.5% and 6.0%, respectively) without S9 activation and at 3.47 and 4.81 µg/mL (6.5% and 17.0%, respectively) with S9 activation. These finding were attributed to mechanisms of cell cycle disruption rather than genotoxicity.

GLP compliance: Yes
Test system: Chinese hamster ovary cells; up to 15 µg/mL in main study; +/- S9
Study is valid: Yes

5.5.4. Carcinogenicity

Not conducted or required to support this NDA application of abemaciclib for patients with advanced cancer

5.5.5. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development
Not conducted or required to support this NDA application of abemaciclib for patients with advanced cancer

Embryo-Fetal Development
Study title/ number: Oral gavage embryo-fetal development and toxicokinetic study for effects with LY2835219 in rats/ #8299046
Key Study Findings

- Doses ≥4 mg/kg abemaciclib given to pregnant rats during the period of organogenesis caused a decrease in fetal weights.
- Skeletal (rib, skull, vertebra, sternebra) and cardiovascular malformations and variations occurred at doses ≥4 mg/kg abemaciclib (C_{max}=348 ng/mL; AUC_{0-24h}=5250 ng·h/mL).

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods
Dose and frequency of dosing: 0, 1, 4, and 15 mg/kg/day
Route of administration: Oral gavage
Formulation/Vehicle: 1% hydroxyethylcellulose (w/v), 0.25% polysorbate 80 (w/v), 0.05% Dow Corning antifoam in reverse osmosis water
Species/Strain: Sprague Dawley rats
Number/Sex/Group: 25 females/Group
Satellite groups: 4 females/Group 1, 12 females/Group 2-4
Study design: Pregnant female rats of approximately 11 to 12 weeks old received 0, 1, 4, or 15 mg/kg/day abemaciclib on GD 6-17. Animals were euthanized on GD 21.
Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	No unscheduled deaths in main study
Clinical Signs	LD: unremarkable MD: unremarkable HD: Rough hair coat 3/25 females, swollen appearance 1/25 females
Body Weights	End of dosing (body weight/body weight gain) LD: unremarkable MD: -3.4%/-11.3% HD: -8.3%/-28.9%
Food consumption	Mean food consumption GD 6-18 LD: unremarkable MD: -7.9% HD: -17.8%
Necropsy findings Cesarean Section Data	LD: unremarkable MD: -7.4% gravid uterine weight HD: -20% gravid uterine weight Corrected body weight: unremarkable Cesarean section data: unremarkable
Necropsy findings Offspring	LD: unremarkable MD: -6.7% fetal weight HD: -18.3% fetal weight See below

LD: low dose; MD: mid dose; HD: high dose

Table 9. Summary of Fetal Rat Malformations and Variations

Doses (mg/kg)	0	1	4	15
External (No. examined litter/fetus)	25/296	24/293	25/304	25/284
Tail M-tail – bent M-tail – filamentous				 1/1 1/1
Visceral variations (No. examined litter/fetus)	25/148	24/148	25/153	25/141
Blood vessel Carotid/innominate arteries – common origin Innominate artery - absent	 1/1	 1/1	 2/2	 1/1 14***/19
Lung Intermediate lobe – absent Lung lobe - small				 1/1 1/1
Visceral malformations (No. examined litter/fetus)	25/148	24/148	25/153	25/141

Doses (mg/kg)	0	1	4	15
Blood vessel				
Aortic arch – absent			1/1	6*/8
Subclavian artery – malpositioned			1/1	5*/7
Subclavian artery - retroesophageal			1/1	7**/9
Skeletal variations (No. examined litter/fetus)	25/148	24/145	25/151	25/143
Rib				
Rib-rudimentary		4/4	1/1	8**/13
Rib – detached				4/4
Rib – nodulated				5*/8
Rib - wavy				3/4
Skull				
Interpariental – incomplete ossification				1/3
Sternebra				
Sternebra – asymmetric ossification		1/1	1/1	1/1
Sternebra – bipartite ossification			1/1	1/1
Sternabra – incomplete ossification				2/2
Sternebra - unossified			2/2	8**/13
Supernumerary rib				
Supernumerary rib – present	4/5	3/3	3/6	7/14
Vertebra – lumbar centrum				
Lumbar centrum – bipartite ossification				2/2
Lumbar centrum – unilateral ossification				1/1
Vertebra – thoracic centrum				
Thoracic centrum – bipartite ossification				8**/12
Vertebral column				
Pre-sacral vertebra				2/2
Skeletal malformations (No. examined litter/fetus)	25/148	24/145	25/151	25/143
Rib				
M-rib – absent				4/5
M-rib – bent				1/1
M-rib - interrupted				1/1

Significant finding, *p<0.05, **p<0.01, ***p<0.001

Study title/ number: A pilot embryo-fetal development study in Sprague-Dawley rats of LY2835219 (Compound 2835219) administered orally (gavage)/ Study #902075

The Applicant assessed the effect of abemaciclib on rat embryo-fetal development in a pilot toxicity study. Pregnant Sprague Dawley rats received doses of 0, 0.3, 1, 5, or 15 mg/kg by oral gavage on gestation Day 6 to 17. Blood samples for toxicokinetic analysis were collected at 0.5, 2, 4, 8, 12, and 24 h post-dose on gestation Day 6 and 17. Additional blood samples were collected at pre-dose, 48, and 72 h post-dose on Day 17. All animals survived to scheduled

necropsy. At a dose of 15 mg/kg, maternal body weight gain was approximately 17% lower than controls with a corresponding decrease in food consumption. Fetal weights were approximately 17-18% lower than controls at 15 mg/kg (C_{max}=760 ng/mL; AUC_{0-24h}=14564 ng·h/mL). The pregnancy rate was 100%, and there were no major external malformations or minor external anomalies noted for any fetuses.

Prenatal and Postnatal Development
Not conducted or required to support this NDA application of abemaciclib for patients with advanced cancer

5.5.6. Other Toxicology Studies

The Applicant evaluated the effect of abemaciclib on phototoxicity in a GLP-compliant toxicology study in Long-Evans pigmented rats. Rats received three consecutive doses of 0, 5, or 40 mg/kg abemaciclib followed by a single exposure to UVR at 2 h post-dose. A second 40 mg/kg dose group received sham UVR. There were no adverse effects on the eyes or skin on Day 1, 2, and 3 following UVR exposure.

The Applicant evaluated abemaciclib for potential dermal toxicity in a GLP-compliant acute toxicity study in Sprague Dawley rats. Rats received a single dermal administration of abemaciclib at 2000 mg/kg body weight. There were no adverse effects on the skin.

The Applicant assessed abemaciclib for ocular irritation in a GLP-compliant bovine corneal opacity and permeability test. Five corneas were treated with 0.75 mL of 20% abemaciclib solution for 4 h. Abemaciclib did not cause adverse effects on opacity measurements or sodium fluorescein permeability.

X X

Tiffany Ricks
Primary Reviewer

Todd Palmby
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The applicant seeks the approval of two different dosing regimens of abemaciclib, one for each proposed indication. As monotherapy, the proposed dosage regimen is 200 mg abemaciclib administered twice daily for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. As combination therapy with fulvestrant, the proposed dosage regimen is 150 mg abemaciclib administered twice daily for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. Abemaciclib can be continuously administered without regard to food based on individual safety and tolerability. The primary evidence of efficacy supporting the 150 mg dose in combination with fulvestrant is based on the demonstrated increase in progression-free survival (PFS) in MONARCH 2, a randomized, double-blind, placebo-controlled trial. Refer to section 7 for further details regarding the supportive evidence of effectiveness for the proposed indications.

The clinical pharmacology review focused on evaluating the acceptability of the different proposed dosage regimens, and adjustment of the starting dose for drug-drug interactions and patients with organ dysfunction.

Recommendations

The Office of Clinical Pharmacology recommends the approval of the NDA 208716 from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	The effectiveness of abemaciclib as monotherapy and in combination with fulvestrant was demonstrated in the MONARCH 1 and 2 trials, respectively. Refer to section 7 for further details.
General dosing instructions	The proposed dosage regimens of abemaciclib 200 mg administered twice daily as monotherapy and 150 mg administered twice daily in combination with fulvestrant are acceptable. The exposure-response analyses support the proposed 200 mg dose of abemaciclib administered twice daily despite the observed incidence of diarrhea (grade 3: 19.7%; all grades 90%) and neutropenia (grade 3: 18.9%; all grades: 37%) given the stage of disease. Over half of the patients treated at the 200 mg dose level remained on the starting dose in the MONARCH 1 trial. A lower

	starting dose would lead to a loss of efficacy based on the positive relationship between tumor shrinkage and the exposure of abemaciclib. On the other hand, the starting dose of abemaciclib was reduced to 150 mg in combination with fulvestrant based on a higher incidence of treatment discontinuation and modifications primarily due to diarrhea observed with the 200 mg dose. The protocol for the MONARCH 2 trial was consequently amended to treat all patients with the 150 mg abemaciclib dose. Although the lower dose improved the tolerability profile of abemaciclib, further dose optimization may be beneficial for patients who can tolerate the higher dose level. Prophylactic antidiarrheal management in the first few treatment cycles may also reduce the incidence of diarrhea-related dose modifications and treatment discontinuations. Of note, modeling and simulations suggest that the risk of severe neutropenia do not significantly differ between the 150 mg and 200 mg abemaciclib doses after the first two treatment cycles. The applicant is currently evaluating the effects of prophylactic antidiarrheal management on the risk-benefit profile of abemaciclib in combination with estrogen suppression therapy. A PMR was also issued to evaluate whether co-administration of abemaciclib with meals improves its tolerability profile with regards to gastrointestinal adverse events.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No adjustment in the starting dose is necessary for patients with mild or moderate hepatic impairment or renal impairment. The terminal half-life of abemaciclib and the systemic exposure of the total active moieties in plasma doubled in subjects with severe hepatic impairment (Child-Pugh category C, n=6) relative to those with normal liver function (n=10). The dosing frequency for the starting dose of abemaciclib in patients with severe hepatic impairment is reduced to once daily. The PK of abemaciclib was not studied in patients with severe renal impairment (CLcr < 30 mL/min) or those with end-stage renal disease requiring dialysis.
Drug-drug interactions	The concomitant administration of strong CYP3A modulators altered the PK of abemaciclib in vivo. Abemaciclib has three major circulating active metabolites, N-desethylabemaciclib (M2), hydroxy-N-desethylabemaciclib (M18), and hydroxyabemaciclib (M20), which respectively account for 13%, 5%, and 26% of the total analytes AUC in plasma. In a dedicated drug-interaction trial (Study JPBE), concomitant use of clarithromycin, (a strong CYP3A4 inhibitor), with a single 50 mg dose of abemaciclib increased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2, M18, and M20) by 1.7-fold relative to abemaciclib alone in

	cancer patients. Conversely, study JPBF reported that the concomitant administration of repeat daily doses of rifampin 600 mg, (a strong CYP3A4 inducer), with a single 200 mg dose of abemaciclib decreased the relative potency-adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2, M18, and M20) by 67% in healthy subjects. Physiologically-based PK (PBPK) models were developed to predict the drug-drug interaction potential of abemaciclib.
	PBPK simulations suggested that the PK of abemaciclib is differentially affected by ketoconazole compared to other strong CYP3A inhibitors, such as clarithromycin and itraconazole. With ketoconazole, the model predicted a 16-fold increase in abemaciclib exposure following a single 50 mg dose of abemaciclib. Overall, the following recommendations regarding the co-administration of strong CYP3A modulators were concluded:
	• Avoid concomitant use of ketoconazole given the predicted up to 16-fold increase of abemaciclib and potential concerns for unknown off-target toxicities.
	• Other strong CYP3A inhibitors:
	  o In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the VERZENIO dose to 100 mg twice daily with concomitant use of other strong CYP3A inhibitors.
	  o In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the VERZENIO dose to 50 mg twice daily with concomitant use of other strong CYP3A inhibitors.
	• Avoid concomitant use of strong CYP3A inducers with abemaciclib.
	A post-marketing requirement was issued to evaluate the effects of moderate CYP3A inducers on the PK of abemaciclib by conducting a dedicated clinical trial or using modeling and simulation.

Labeling	Labeling recommendations were communicated to the applicant. Refer to section 10 for further details.

Post-Marketing Requirements (PMR)

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
☐ PMC ☒ PMR	The effects fasting state on the tolerability and safety of abemaciclib with regards to gastrointestinal adverse events.	The mechanisms of the observed gastrointestinal toxicities of abemaciclib are unknown. Fasting and Fed state differentially affects GI motility and its physicochemical properties which may improve tolerability without significantly altering the systemic exposure of abemaciclib.	The trial should be an open-label, non-randomized, study investigating the incidence of dose reduction and interruptions due to severe diarrhea following dosing of abemaciclib in three different administration conditions: fed, fasted, and without regards to meals. (b) (4)
☒ PMC ☐ PMR	There is insufficient information to determine the starting dose of abemaciclib in patients requiring concomitant treatment with moderate CYP3A inducers.	The effects of moderate CYP3A inducers on the PK of abemaciclib have not evaluated.The systemic exposure of relative potency-adjusted, unbound abemaciclib plus its active metabolites was reduced by 67% following CYP450 induction with repeated rifampin administration, a strong inducer.	Conduct PBPK analysis or a pharmacokinetic trial to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of abemaciclib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations." Submit final report and data sets.

6.2. Summary of Clinical Pharmacology Assessment

Abemaciclib is a weakly basic, small molecule (MW: 506.6 g/mol) which reversibly inhibits cyclin-dependent kinase 4 (CDK4) and cyclin-dependent kinase 6 (CDK6) at respective IC_{50} values ranging from 1.2 to 2.0 nM and 2.0 to 9.9 nM. Of note, the major systemic metabolites of abemaciclib (M2, M18, and M20) are pharmacologically equipotent to the parent drug and present in plasma at similar extent as abemaciclib. Abemaciclib suppresses tumor cellular proliferation through inhibition of CDK4/CDK6-dependent phosphorylation of the retinoblastoma protein thereby thwarting formation of complexes and factors required for transition into the DNA synthesis or S phase of the cell cycle.

Approximately dose proportional and linear pharmacokinetic properties were observed after a single oral administration of abemaciclib at doses ranging from 50 to 600 mg and repeated oral doses ranging from 50 to 200 mg twice daily. The systemic exposure of abemaciclib was highly variable as illustrated by an observed intra- and inter-subject variability of 15%CV and >60%CV, respectively. The estimated geometric mean elimination half-life (CV%) of abemaciclib, M2 or M20 was 18.3 hours (72%), 20.4 hours (67%), and 17 hours (63%), respectively. After five days of repeated twice daily administration, the exposure of abemaciclib reached steady state with an estimated geometric mean accumulation ratio of 3.2 (59% CV). Of note, abemaciclib is almost exclusively eliminated by the liver where it undergoes capacity-limited clearance. Consequently, the unbound intrinsic clearance is the primary determinant of the unbound steady state exposure, and ultimately the pharmacological effects of abemaciclib and its equipotent metabolites.

6.2.1. Pharmacology and Clinical Pharmacokinetics

Absorption: The mean fraction of the administered oral dose of abemaciclib available systemically is 0.45 (19% CV) while the median [range] time to maximal plasma concentration, t_{max}, is 8.00 hours [4.1-24.0]. The t_{max} for the major metabolites typically occurs within 3 to 10 hours following oral administration. Clinically relevant alterations in the extent of abemaciclib absorption from reduction in gastric acid are not expected since the 200 mg drug product remains soluble in 250 mL of aqueous solution at pH 6.8. Thus, a clinical trial investigating the effects of co-administration of gastric acid reducing agents on the exposure of abemaciclib is not warranted. No clinically relevant food effect on abemaciclib exposure was observed following concomitant administration with a high-fat meal (approximately 800 to 1000 calories with 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat).

Distribution: In vitro, abemaciclib binds to human plasma proteins in a concentration-independent manner from 152 ng/mL to 5066 ng/mL. The mean (standard deviation, SD) bound fraction was 96.3% (1.1) for abemaciclib, 93.4% (1.3) for M2, 96.8% (0.8) for M18, and 97.8% (0.6) for M20. The geometric mean systemic volume of distribution is approximately 690.3 L (49% CV).

Metabolism: In humans, the metabolism and elimination of abemaciclib are characterized by intestinal and hepatic biotransformation via oxidative reactions by cytochrome P450 (CYP) 3A4 to several equipotent active metabolites, which primarily include N-desethylabemaciclib (M2), hydroxy-N-desethylabemaciclib (M18), and hydroxyabemaciclib (M20). In plasma, abemaciclib and its major active metabolites M2, M18, and M20 circulated in similar abundance as their AUCs respectively accounted for 34%, 13%, 5%, and 26% of the total abemaciclib-derived radioactivity.

Excretion: Following a 336-hour collection period, biliary excretion was the primary route of elimination of abemaciclib and its derived moieties as 81% and 3% of the orally administered radioactive dose was recovered in feces and urine, respectively. Overall, unchanged abemaciclib and its metabolites respectively accounted for 7% and 47% of the administered dose excreted in feces.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing
The proposed dosage regimens of orally administered abemaciclib 150 mg twice daily in combination with fulvestrant and abemaciclib 200 mg twice daily as monotherapy, without regard to food, are acceptable. Refer to section 6.3.2 for further details and discussion.

Therapeutic Individualization

Organ Dysfunction
Renal function is not expected to impact the exposure of abemaciclib since abemaciclib and its major metabolites are primarily eliminated in the liver. Based on the results of a popPK analysis, no changes in abemaciclib PK were observed in patients with mild (Cockroft Gault creatinine clearance, CLcr≥60 mL/min and <90 mL/min, n=186), or moderate (CLcr≥30 mL/min and <60 mL/min, n=64) renal impairment, relative to those with normal renal function (CLcr ≥ 90 mL/min, n=233). Following the administration of a single 150 mg oral dose of abemaciclib, no clinically relevant changes in the systemic exposure of abemaciclib was noted in subjects with mild (Child-Pugh category A, n=9), or moderate (Child-Pugh category B, n=10) hepatic impairment, relative to those with normal hepatic function (n=10). The terminal half-life of abemaciclib, as well as the systemic exposure of total abemaciclib analytes (abemaciclib + M2 + M18 + M20), were doubled in subjects with severe (Child-Pugh category C, n=6) hepatic impairment relative to those with normal liver function. Consequently, no starting dose adjustment is necessary for patients with mild or moderate hepatic or renal impairment. The recommended dosing frequency for the starting dose of abemaciclib in patients with severe hepatic impairment is once daily.

Drug-Drug Interactions
The concomitant administration of strong CYP3A modulators altered the PK of abemaciclib in vivo. The co-administration of 500 mg twice daily doses of clarithromycin, a strong CYP3A4

inhibitor, with a single 50 mg dose of abemaciclib increased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2, M18, and M20) by 1.7-fold relative to abemaciclib alone in cancer patients.

Conversely, the co-administration of repeated 600 mg daily doses of rifampin, a strong CYP3A inducer, with a single 200 mg dose of abemaciclib decreased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2, M18, and M20) by 67 in healthy subjects. The effect of moderate CYP 3A4 inducers was not determined, and labeling instructions cannot be described.

Physiologically-based pharmacokinetic (PBPK) modelling was used to predict the drug-drug interaction potential of abemaciclib as a victim of the CYP3A metabolic pathway. Based on the results of a PBPK modeling and simulation analysis, the PK of abemaciclib is differentially affected by ketoconazole compared to other strong CYP3A inhibitors. For example, PBPK simulations predicted 5 and 7-fold increases in exposure of abemaciclib following co-administration of a single 200 mg dose of abemaciclib with clarithromycin and itraconazole, respectively, whereas an up to 16-fold increase in the exposure of abemaciclib was predicted with ketoconazole. Overall, labeling recommendations regarding the co-administration of strong CYP3A modulators were:

<u>Ketoconazole</u>

- Avoid concomitant use of ketoconazole given the predicted up to 16-fold increase of abemaciclib and potential concerns for unknown off-target toxicities.

<u>Other Strong CYP3A Inhibitors</u>

- In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the VERZENIO dose to 100 mg twice daily with concomitant use of other strong CYP3A inhibitors.
- In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the VERZENIO dose to 50 mg twice daily with concomitant use of other strong CYP3A inhibitors.

<u>Strong CYP3A Inducers</u>

- Avoid concomitant use of strong CYP3A inducers with abemaciclib.

A post-marketing commitment was issued to evaluate the effects of moderate CYP3A inducers on the PK of abemaciclib by conducting a dedicated clinical trial or by using modeling and simulation.

Outstanding Issues

The remaining clinical pharmacology-related areas of uncertainty remaining for this application are:

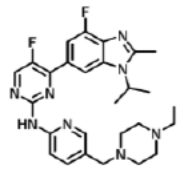
1) Dose optimization with regards to diarrhea-related events
    a. The positive dose-response and lack of exposure response relationships observed for diarrhea in patients treated with abemaciclib support the hypothesis that diarrhea is a localized effect in the gastrointestinal track. Though no exposure related food effect was observed, the potential effects of food on the tolerability of abemaciclib as it pertains to diarrhea incidence is unknown. A PMR was issued to further evaluate this matter.

2) The starting dose of abemaciclib in patients requiring concomitant treatment with a moderate CYP3A4 inducer. The applicant will submit a dedicated drug interaction trial or a PBPK analysis evaluating the effects of concomitant administration of moderate CYP3A inducers on the PK of abemaciclib (PMC issued).

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Table 10 Summary of clinical pharmacology and pharmacokinetics

Physicochemical properties	
Chemical structure and molecular weight	 Chemical structure of abemaciclib, MW: 506.6 g/mol
Aqueous solubility	Abemaciclib exhibits pH-dependent solubility at pH above 7. Its aqueous solubility reduces to 0.002 mg/mL at pH 7.6 from 1.6 mg/mL at pH 6.8 following a 24-hour incubation period at 37 °C. At the highest clinical dose, e.g., 200 mg, abemaciclib is soluble in less than 250 mL at pH 6.8. Thus, a clinically relevant drug interaction from the concomitant administration of gastric-acid reducing agents with abemaciclib is unlikely.
Pharmacology	
Mechanism of action	Abemaciclib inhibits cyclin D1-dependent kinases 4/6 (CDK4/6) at respective IC_{50} values of 1.6 and 2 nM, as measured in cell-free kinase assays.
Active moieties	Similar to abemaciclib, the major active metabolites, M2, M18, and

	M20, exhibit CDK4/6 IC_{50}s ranging from 1.2 to 2.6 nM. Following the oral administration of a single 150 mg radiolabeled abemaciclib dose in healthy subjects, the respective abundance of abemaciclib, M2, M18, and M20 in plasma expressed as a % of total radioactivity $AUC_{0\text{-}INF}$ was 34%, 13%, 5%, and 26%.
QT/QTc prolongation	No large change (that is, >20 ms) in the QTcF interval was detected at the mean steady state C_{max} following a therapeutic dosing schedule.
Pharmacokinetic characteristics	
Bioanalytical assay	Several assays were developed to measure the concentrations of abemaciclib and its major active metabolites in various matrices for studies submitted as part of this application. Refer to appendix section 13.4.2.
Steady state exposure at the proposed regimen	Based on the results of the dose escalation trial JPBA (C1 formulation), the observed geometric mean (CV%) $AUC_{0\text{-}\tau,ss}$ and $C_{max,ss}$ of abemaciclib in patients treated at the 150 mg twice daily dosing regimen is 2390 ng·hr/mL (90%) and 249 ng/mL (86%). Similarly for patients treated at the 200 mg twice daily dose, the observed geometric mean (CV%) $AUC_{0\text{-}\tau,ss}$ and $C_{max,ss}$ of abemaciclib is 3000 ng·hr/mL (69%) and 298 ng/mL (72%), respectively.
Range of effective dose or exposure	The efficacy of abemaciclib was established at starting doses of 150 and 200 mg twice daily. The observed geometric mean steady state trough concentration (CV%) of abemaciclib at the 200 mg twice daily is 197 ng/mL (82%), which is similar to the pre-clinical target trough concentration of 200 ng/mL for tumor growth inhibition reported in a mouse xenograft model.
Dose proportionality	The exposure of abemaciclib was approximately dose proportional following oral administration at single doses ranging from 50 to 600 mg, and repeated oral doses ranging from 50 to 200 mg twice daily.
Accumulation	The exposure of abemaciclib reaches steady state within 5 days of repeated twice daily dosing. The observed geometric mean accumulation ratio of abemaciclib exposure (R_{AUC}) on day 28 relative to day 1 was 2.53 (67% CV) according to the NCA results of trial JPBA.
Variability	The observed intrasubject variability (CV%) in the exposure of abemaciclib is approximately 15%. In clinical trial JPBA, the observed intersubject variability (CV%) in $AUC_{0\text{-}\tau,ss}$ and $C_{max,ss}$ respectively ranged from 69% to 90% and 72% to 86%.
Absorption	
Bioavailability	The absolute bioavailability of abemaciclib is 0.45 (19% CV)
Tmax	The median [range] time to maximal plasma concentration, t_{max}, is 8.00 hours [4.1-24.0]. The t_{max} for the major metabolites typically occurs within 3 to 10 hours following oral abemaciclib administration.
Bioequivalence	C3: late phase capsule formulation used in MONARCH 1 and 2 trials

	T1: proposed commercial formulation		
C3 (3 x 50 mg, Ref) T1(150 mg, Test) T1(3 X 50 mg, Test)	**$AUC_{0\text{-}INF}$ (GMR, 90%CI)**	**C_{max} (GMR, 90%CI)**	**t_{max} (hours) (range)**
	T1, 150 mg 1.02 (0.98,1.06) T1, 3 X 50 mg 1.02 (0.99,1.06)	T1, 150 mg 1.00 (0.96,1.05) T1, 3 X 50 mg 1.03 (0.99,1.08)	C3, 3 X 50 mg 8.00 (4.05 – 24.0) T1, 150 mg 8.00 (6.00 – 24.0) T1, 3 X 50 mg 8.00 (6.00 – 24.0)
	The results of this trial provide evidence of bioequivalence between the tablet and capsule formulation for the 50 and 150 mg tablet strengths.		
Food effect			
Capsule formulation	**$AUC_{0\text{-}INF}$ (GMR, 90%CI)**	**C_{max} (GMR, 90%CI)**	**t_{max} (hours) (range)**
	1.27 (1.18,1.36)	1.35 (1.25, 1.46)	Fed 8.00 (6.00 – 12.0) Fasted 8.00 (6.00 – 12.0)
	The systemic exposure of abemaciclib or total abemaciclib active moieties (abemaciclib + M2 + M20) was marginally altered following the concomitant administration of a single 200 mg oral dose of abemaciclib with the FDA-defined high fat, high calorie meal vs. the fasted condition.		
Tablet formulation	**$AUC_{0\text{-}INF}$ (GMR, 90%CI)**	**C_{max} (GMR, 90%CI)**	**t_{max} (hours) (range)**
	1.13 (1.05,1.22)	1.30 (1.20, 1.40)	Fed 8.00 (4.00 – 10.0) Fasted 8.00 (6.00 – 24.0)
	No clinically relevant food effect was observed on the exposure of abemaciclib or total active analytes (abemaciclib + M2 + M20) following the concomitant administration of single 150 mg abemaciclib tablet (T1 formulation) with the FDA defined high fat, high calorie meal. Given the observed intersubject variability in exposure of 69% CV for steady state AUC at the therapeutic dose, the 13% and 30% increase in AUC and C_{max} respectively, following a single dose, is not expected to clinically affect the safety profile of abemaciclib. Refer to question 6.3.2.2 for further discussion on the assessment of the effects of food on the tolerability of abemaciclib.		
Distribution			
Volume of distribution	The geometric mean (%CV) systemic volume of distribution of		

	abemaciclib is approximately 690.3 L (49%).
Plasma protein binding	The mean (standard deviation, SD) bound fraction was 96.3% (1.1) for abemaciclib, 93.4% (1.3) for M2, 96.8% (0.8) for M18, and 97.8% (0.6) for M20.
Blood to plasma ratio	The blood to plasma ratio for abemaciclib is 0.82, which suggests greater partition into plasma than red blood cells.
Substrate of transporter systems	Abemaciclib and M2 are substrates of P-gp and BCRP in vitro. Based on the high permeability of abemaciclib and M2 and the relative systemic exposure of M2 (13% of total AUC), a clinically relevant drug-transporter interaction resulting from the co-administration of a P-gp or BCRP modulator is not expected.
Elimination	
Elimination half-life and clearance	In patients, the estimated geometric mean (%CV) hepatic clearance of abemaciclib, M2 and M20 was 26.0 L/hr (51%), 23.4 L/hr (50%), and 28.1 L/hr (45%), respectively. Of note, the observed systemic clearance following administration of a single intravenous dose of 0.4 mg of [$^{13}C_8$]-abemaciclib to 8 healthy subjects was similar to the estimated hepatic clearance in patients 24.0 L/hr (27% CV) vs 26.0 L/hr (51% CV). The estimated geometric mean elimination half-life (CV%) of abemaciclib, M2 or M20 was 18.3 hours (72%), 20.4 hours (67%), and 17 hours (63%), respectively.
Metabolism	In vivo, cytochrome P450 (CYP) 3A4/5 metabolizes abemaciclib to several equipotent active metabolites, which primarily include N-desethylabemaciclib (M2), hydroxyl-N-desethylabemaciclib (M18), and hydroxyabemaciclib (M20). In plasma, abemaciclib and its major active metabolites M2, M18, and M20 circulated in similar abundance as their AUCs respectively accounted for 34%, 13%, 5%, and 26% of the total abemaciclib-derived radioactivity.
Excretion	Following a 336-hour collection period, biliary excretion was the primary route of elimination of abemaciclib and its derived moieties as 81% and 3% of the orally administered 150 mg radioactive abemaciclib dose was recovered in feces and urine, respectively. Overall, unchanged abemaciclib and its metabolites respectively accounted for 7% and 47% of the administered dose excreted in feces.
Drug Interaction Studies	
In vitro	Abemaciclib inhibits P-gp, BCRP at IC_{50} values of 0.57 µM and 0.32 µM, respectively. Abemaciclib, M2, and M20 are inhibitors of renal

	uptake transporter OCT2, and renal efflux transporters MATE-1 and MATE-2K at clinical relevant concentrations.	
Clinical Studies		
Strong CYP3A Inducer		
Abemaciclib Abemaciclib + Rifampin	**$AUC_{0\text{-}INF}$ (GMR, 90%CI)**	**C_{max} (GMR, 90%CI)**
Parent	0.05 (0.03, 0.06)	0.08 (0.07, 0.09)
Total Analytes	0.23 (0.21, 0.25)	0.55 (0.49, 0.61)
	The co-administration of repeated oral doses of 600-mg once daily rifampin for 14 days and a single 200-mg abemaciclib dose reduced the plasma $AUC_{0\text{-}INF}$ and C_{max} of abemaciclib by 95.0% and 92.0% respectively in cancer healthy subjects. Similarly, the $AUC_{0\text{-}INF}$ and C_{max} of total abemaciclib analytes in plasma were respectively reduced by 77.0% and 45.0%.	
Strong CYP3A Inhibitor		
Abemaciclib Abemaciclib + Clarithromycin	**$AUC_{0\text{-}INF}$ (GMR, 90%CI)**	**C_{max} (GMR, 90%CI)**
Parent	3.37 (2.85, 3.99)	1.30 (1.10, 1.52)
Total Analytes	2.19 (1.87, 2.56)	0.93 (0.79, 1.09)
	Co-administration of repeated twice daily doses of 500-mg clarithromycin for 5 days and a single 50-mg abemaciclib dose increased the $AUC_{0\text{-}INF}$ and C_{max} of abemaciclib by 3.4 and 1.3 fold respectively in cancer patients. Similarly, the $AUC_{0\text{-}INF}$ and C_{max} of total abemaciclib analytes in plasma respectively increased by 2.2 and 0.9 fold.	
Relevant Concomitant Agent		
Loperamide Abemaciclib + Loperamide	**AUC_{INF} (GMR, 90%CI)**	**C_{max} (GMR, 90%CI)**
Loperamide	1.09 (1.01, 1.18)	1.35 (1.15, 1.59)
	The co-administration of a single 8 mg dose of loperamide with 400 mg abemaciclib increased loperamide plasma $AUC_{0\text{-}INF}$ by 9% and C_{max} by 35% compared to loperamide alone. Conversely, no clinically relevant alterations in abemaciclib exposure were observed following concomitant administration of a single 8 mg dose of loperamide and 400 mg of abemaciclib.	
OCT2 and MATE-1/2K Substrate		

Metformin Abemaciclib + Metformin	**AUC_{0-INF}** **(GMR, 90%CI)**	**C_{max}** **(GMR, 90%CI)**
	1.37 (1.28, 1.46)	1.22 (1.13, 1.30)
	The renal clearance and active tubular secretion of metformin, a substrate of renal uptake transporter OCT2, and tubular efflux transporters MATE-1 and MATE-2K, was respectively reduced by 45% and 62% following co-administration of a single 400 mg dose of abemaciclib with 1000 mg metformin in healthy subjects. Renal function as measured by iohexol clearance and cystatin C was not altered. This clinical study provided conclusive evidence to relate the observed increase in serum creatinine of patients treated with abemaciclib to inhibition of active renal tubular uptake and secretion without impacting renal function.	

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness to justify the proposed abemaciclib starting doses in early and advanced metastatic breast cancer?

Yes. The efficacy results from the registration trials JPBL or MONARCH 2, and JPBN or Monarch 1, along with the clinical pharmacology program collectively provide adequate evidence for the effectiveness of abemaciclib in both early and late line metastatic breast cancer populations.

Dose selection rationale

The maximum tolerated dose (MTD) was determined in a first-in-human dose-finding trial, JPBA, which evaluated abemaciclib doses ranging from 50 to 275 mg administered once or twice daily using an early phase capsule formulation (C1). The maximum tolerated dose (MTD) was identified as the 200 mg twice daily dose based on observed grade 3 fatigue in 2 out of 3 patients treated at 275 mg twice daily. Although the 200 mg twice daily dose level was the recommended phase 2 dose, the applicant conducted further evaluations of the 150 mg twice daily dose based on the preliminary safety and tolerability data from the dose-finding trial. At steady state, the observed average trough plasma concentration of abemaciclib in patients treated at the MTD in the dose finding trial was 197 ng/mL (82% CV), which was similar to the pre-clinical target trough concentration of 200 ng/mL for anti-tumor activity determined with a mouse xenograft model. However, there is minimal clinical relevance for the pre-clinical target trough concentration since the on-target effects of the major metabolites of abemaciclib were not accounted for in this mouse xenograft model, as only the PK of the parent drug was evaluated. Furthermore, the relative composition of circulating active analytes at steady state is likely different in humans compared to mice due to interspecies differences in the metabolism of abemaciclib. The pharmacodynamic analyses from trial JPBN (MONARCH 1) showed a similar

magnitude of inhibition of topoisomerase-II alpha and phosphorylated retinoblastoma protein expression in patients' skin biopsies when comparing the 150 mg and 200 mg dose levels. The applicant also noted that the results from trial JPBA confirmed that these markers were inhibited at all dose levels ranging from 50 to 200 mg. These results suggest that these biomarkers are not predictive of clinical response in patients treated with abemaciclib. The applicant did not include clinical data to assess the efficacy of the continuous administration compared to alternative dosing regimens, e.g., 21 days on and 7 days off. The clinical effectiveness of the continuous administration is rather supported by the observed efficacy and safety results in the two registration trials MONARCH 1 and MONARCH 2. Overall, the clinical pharmacology evidence supported the rationale for selecting 200 mg bemaciclib administered twice daily for further investigation in larger trials.

Rationale for 150 mg abemaciclib starting dose in combination therapy

Of note, the protocol for MONARCH 2 was amended to reduce the starting dose of abemaciclib to 150 mg from 200 mg administered twice daily, following a blinded safety review of early phase trials in the clinical development of abemaciclib. As illustrated in table 6.2 the proposed 150 mg starting dose effectively improved the tolerability profile of abemaciclib as evidenced by a reduction in the incidence of AE-related treatment discontinuation (24.8% vs 12.8%), grade-3 diarrhea (19.0% vs 11.3%), and grade-3 neutropenia (28.9% vs 21.6%) compared to the 200 mg dose in the pre-amendment period. In addition, the median time to first diarrhea event is 120 days for patients treated with fulvestrant alone versus 7.29 days, and 3.96 days, for those treated with the 150 mg, and 200 mg abemaciclib starting dose, respectively.

These observations were consistent with the results of the applicant's time-to-event model which characterized the effects of various factors on the risk of first diarrhea occurrence. The results of the model identified the following parameters as factors that can delay the time to first diarrhea occurrence: treatment with fulvestrant alone and lack of opioid treatment at baseline. As observed in the data, the model also highlighted a shorter time to first diarrhea occurrence for patients treated with the 200 mg abemaciclib starting dose compared to 150 mg. Similar results were obtained from an analysis incorporating a pooled dataset of patients treated in other early phase trials including MONARCH 1 (JPBN). Refer to the Pharmacometrics (PM) review in section 13.4.1 for additional details regarding this analysis. Of note, there is no relationship between the systemic exposure of abemaciclib or its active moieties and incidence of diarrhea, which supports the applicant's hypothesis that the observed diarrhea could be a localized toxicity due to abemaciclib exposure to the intestinal cells.

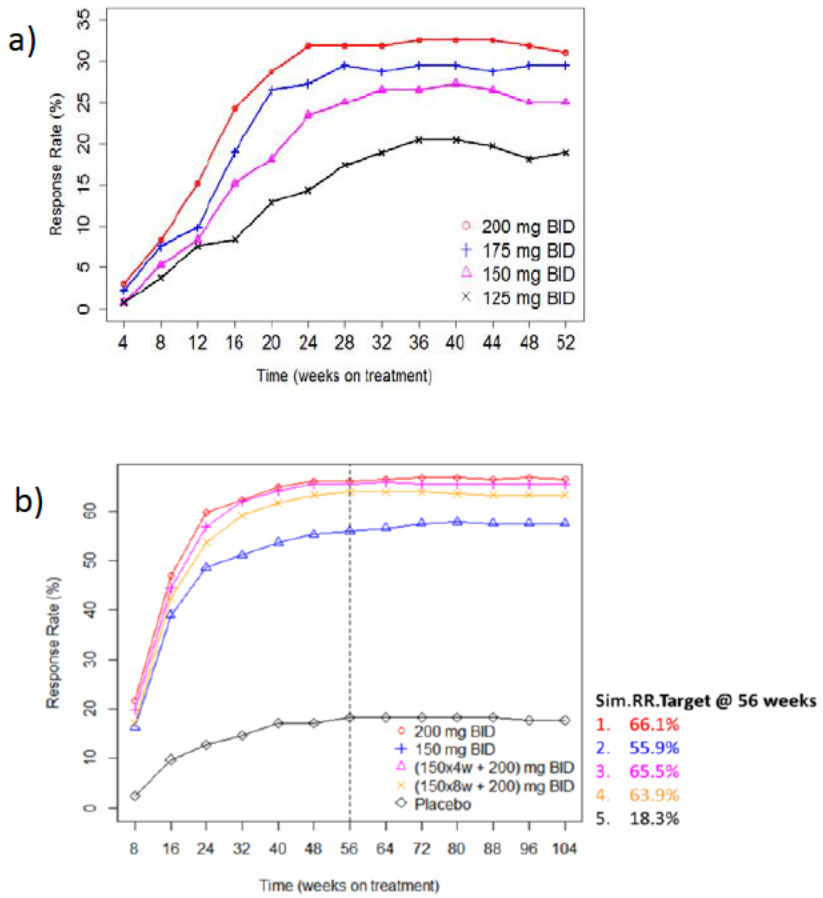
As further supportive evidence for the 150 mg abemaciclib starting dose, the applicant characterized the contribution of abemaciclib to the observed myelosuppressive effects in the trial. The applicant used a semi-mechanistic PKPD model, which identified a positive relationship between the maximal steady state concentration, $C_{max,ss}$ of total active analytes (abemaciclib + M2 + M20) and reduction in neutrophil counts. The model suggests that the highest risk of grade ≥3 neutropenia occurs within 3 to 5 weeks of treatment with abemaciclib in combination with fulvestrant. Similarly, the applicant identified a positive exposure-response

relationship between abemaciclib concentration in plasma and tumor shrinkage using a semi-mechanistic PK/PD model. The implementation of abemaciclib concentration instead of total active analytes as the exposure metric in the tumor shrinkage model is acceptable as the latter would not provide additional useful information since the metabolite-to-parent AUC ratios are time-independent. Hence, the clinical pharmacology program collectively supported the rationale for the dose selection, proposed regimen, and dose reduction strategy for mitigation of adverse events.

6.3.2.2. Do the available clinical pharmacology, safety and efficacy data provide evidence to support further dose optimization to improve the risk-benefit profile of abemaciclib in the proposed indications?

Yes. Further dose optimization may improve the risk-benefit profile of abemaciclib in combination with fulvestrant. For example, the positive ER relationship between abemaciclib concentration and magnitude of tumor shrinkage supports a higher than 150 mg abemaciclib starting dose from an efficacy standpoint (Figure 3). These simulations were conducted in which the response rate was calculated solely based on measurements at the target lesion. Therefore, the simulated response rate is expected to be higher than that was observed in a clinical study at the corresponding dose level. In addition, as only two thirds of the intent-to-treat population in MONARCH 2 had measurable diseases and there appeared to be differences in disease progression dynamics in patients with or without measurable disease, the predicted difference in response rate between different dosing regimens in the early line setting should be interpreted with caution.

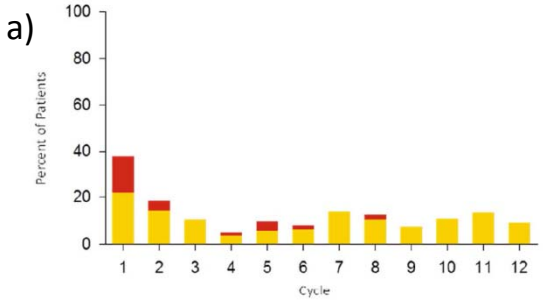
Figure 3. Simulated response rate (target lesion) in MONARCH 1 (a) and 2 (b)



Source: Pharmacometric reviewer's analysis

At the 200 mg starting dose, diarrhea was the primary reason for adverse event-related treatment discontinuations and modifications. Approximately 51% and 57% of patients treated at the 200 mg and 150 mg dose level remained on the starting dose throughout the course of trials MONARCH 1 and MONARCH 2, respectively. During the pre-amendment phase in MONARCH 2, approximately 44% of patients treated with abemaciclib remained on the starting 200 mg dose before the mandatory dose reduction to 150 mg took effect. In both trials, the majority of dose modifications occurred within the first few cycles of therapy which suggests that patients likely reached a stable dose as the treatment course progressed. The incidence (n=total patients) of discontinuation was 7.6% (n=132) and 15.9% (n=441) for patients treated with abemaciclib in the MONARCH 1 and MONARCH 2 trial, respectively. As illustrated in Figure 4, the majority of the grade ≥2 diarrhea occurred over the first two months of treatment in both trials.

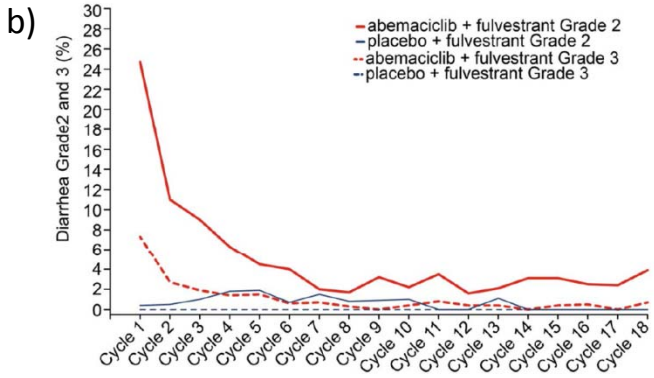
Figure 4. Diarrhea incidence by cycle during (a) MONARCH 1 and (b) MONARCH 2



Source: NDA208716, JPBN CSR MONARCH 1

: Grade 2 : Grade 3

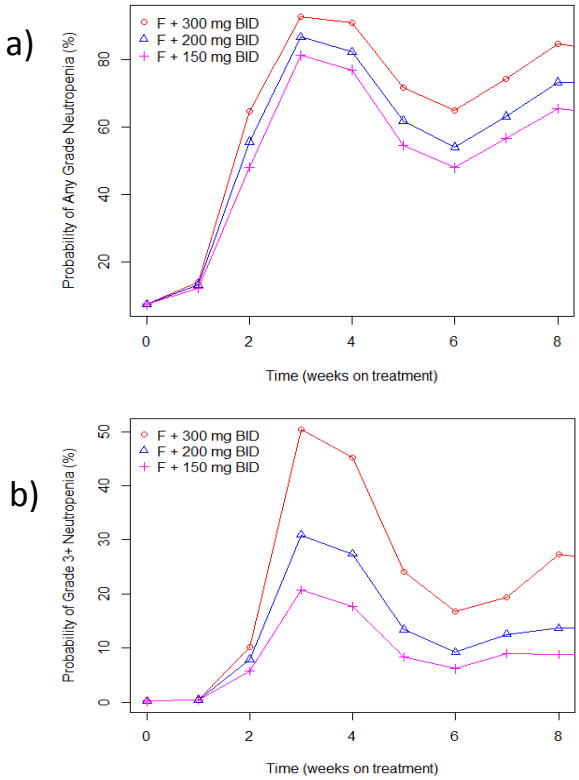
Note: The number of patients starting the cycle is the denominator for that cycle.
Source: smdiav11.rtf.



Source: NDA208716, JPBL CSR MONARCH 2

Thus, patients who are able to tolerate the 200 mg dose may experience incremental benefit if prophylaxis anti-diarrheal management is effective in mitigating the incidence and or severity of diarrhea during the first few months of therapy. Moreover, a 30% increase in the proposed dose from 150 mg to 200 mg translates to a maximum of 10% increase in the risk of grade ≥3 neutropenia, which would likely occur between day 20 to day 35 following onset of abemaciclib treatment. The expected increase in the risk of grade ≥3 neutropenia is less than 6% after the first two months of treatment between the 150 and 200 mg abemaciclib starting dose according to the applicant's model (Figure 5).

Figure 5. Model predictions of probability of (a) any grade and (b) grade ≥3 neutropenia of patients initiating treatment with abemaciclib in combination with fulvestrant



Source: Pharmacometric reviewer's analysis

The collective evidence herein supports the opportunity for further dose optimization to improve the tolerability of abemaciclib during the first few cycles of therapy. Hence, it is plausible that more patients would benefit from a higher abemaciclib starting dose in combination with fulvestrant using an effective prophylaxis anti-diarrheal management. Such an anti-diarrheal management approach would differ from the one implemented by the applicant during the MONARCH 1 and MONARCH 2 trials, such that the preferred anti-diarrheal agent would be initiated with the first dose of abemaciclib and continued up to the first few treatment cycles. Additionally, anti-diarrheal prophylaxis, if effective, over the first few cycles may provide additional benefits in the monotherapy setting by prolonging the time to first dose reduction due to diarrhea, thereby increasing the average steady state abemaciclib concentration which improves its tumor shrinkage effects. Similarly, it is plausible that the co-administration of abemaciclib with food may improve the tolerability of the drug despite the known lack of food effect on exposure. It is likely that food may provide a protective effect for the potentially localized GI irritation effects of abemaciclib.

However, there are several uncertainties and risks with the approach to increase the proposed dose in the combination setting. Although a positive exposure response between abemaciclib concentration and tumor shrinkage in MONARCH 2 was observed, the collected longitudinal target tumor lesion data only included patients with measurable disease whose disease progression and response may not be representative of the typical patient in the early line setting. Notwithstanding the aforementioned discrepancies with the MONARCH 2 analysis, substantiated with data from the majority of patients treated in MONARCH 1. Presently, the mechanisms or reasons for the observed higher incidence of abemaciclib-related diarrhea at the 200 mg dose in combination with fulvestrant compared to when it is administered as monotherapy have not been elucidated. PopPK analyses of abemaciclib PK data in plasma, as well as the known metabolic pathways and properties of fulvestrant do not support any indication for a drug-drug interaction between fulvestrant and abemaciclib. Although unlikely, it is not known whether the PK of the circulating active metabolites is altered in the presence of fulvestrant. Modeling-based analyses support the hypothesis that the diarrhea is a localized effect as the unit dose, instead of the systemic concentration, was predictive of the incidence or median time-to-occurrence of diarrhea. These noted concerns regarding dose optimization were communicated and extensively discussed with the applicant throughout the review cycle. The applicant informed the FDA that the administration of abemaciclib with prophylaxis anti-diarrheal therapy is currently being evaluated as part of the clinical development program of the drug. The applicant agreed to submit these data to the FDA for review upon completion of the trial. The applicant will also investigate whether the co-administration of abemaciclib with food affects the tolerability of the drug with regards to the incidence and/or severity of diarrhea as a post-marketing requirement.

6.3.2.3. Can predicted DDI using PBPK modeling adequately support labeling dosing recommendations?

Abemaciclib has three major circulating active metabolites, N-desethylabemaciclib (M2), hydroxy-N-desethylabemaciclib (M18), and hydroxyabemaciclib (M20), which respectively account for 13%, 5%, and 26% of the total analytes AUC in plasma following a single oral dose of 150 mg abemaciclib in healthy subjects. A dedicated DDI study in healthy subjects, Study JPBE, showed that clarithromycin (500 mg twice daily) increased the systemic exposure of abemaciclib by 3.4-fold and increased the systemic exposure of total analytes (abemaciclib plus three active metabolites (M2, M20, and M18)) by 2.2-fold. Conversely, DDI Study JPBF reported that concomitant use of rifampin, (a strong CYP3A4 inducer), with a single oral dose of 200 mg abemaciclib reduced the systemic exposure of abemaciclib and total analytes by 95% and 77%, respectively. PBPK models were developed to describe the PK profiles (such as AUC) of abemaciclib and its three active metabolites and predict the DDI potential between abemaciclib and CYP3A modulators.

Given abemaciclib and these three active metabolites are generally equipotent for binding to the CDK4/6 target for efficacy and safety with different fraction unbound, the relative potency adjusted unbound AUC was used to determine total effective exposure of abemaciclib and its metabolites (potency adjusted unbound exposure). The potency adjusted unbound exposure was calculated by converting the analyte concentrations to molar units (nmol·h/mL) and accounting for the different fraction unbound and CDK4 IC_{50}s of abemaciclib plus its active metabolites. Table 11 summarized the ratios of simulated exposure of abemaciclib, abemaciclib total analyte, and potency adjusted unbound exposure with and without CYP3A modulators.

Table 11 Simulated geometric mean abemaciclib, total analyte, and potency adjusted unbound exposure change (auc ratio) following a single 200 mg dose of abemaciclib and various CYP3A modulators

	Abemaciclib	Total Analyte	CDK4 IC_{50} Adjusted unbound Exposure
Ketoconazole[a]	↑ 15.73-fold	↑ 6.87-fold	↑ 2.87-fold
Itraconazole[a]	↑ 7.15-fold	↑ 3.78-fold	↑ 2.16-fold
Clarithromycin[a]	↑ 4.95-fold	↑ 2.76-fold	↑ 1.71-fold
Diltiazem[b]	↑ 3.95-fold	↑ 2.41-fold	↑ 1.66-fold
Verapamil[b]	↑ 2.28-fold	↑ 1.63-fold	↑ 1.31-fold
Rifampin[c]	↓ 93%	↓ 71%	↓ 67%
Carbamazepine[c]	↓ 80%	↓ 52%	↓ 38%

[a] Strong CYP3A4 inhibitors; [b] Moderate CYP3A4 inhibitors; [c] Strong CYP3A4 inducers
Summarized from Table A8 of PBPK review (section 6.3.2.3)

Table 11 shows that ketoconazole and itraconazole (strong CYP3A inhibitors) can increase the potency adjusted unbound exposure by 2.87-fold and 2.16-fold, respectively. However, the PK of abemaciclib is differentially affected by ketoconazole in comparison to other strong CYP3A inhibitors. For example, simulations predicted 5.0- and 7.2-fold increases in exposure of abemaciclib following co-administration of a single 200 mg dose of abemaciclib with clarithromycin and itraconazole, respectively. With ketoconazole, the model predicted an up to 16-fold increase in abemaciclib exposure. Given the magnitude of exposure change in the context of the exposure-response relationships for safety and effectiveness observed with abemaciclib plus its active metabolites, the following recommendations are provided with regard to concomitant use of strong CYP3A inhibitors:

- Avoid concomitant use of ketoconazole given the predicted up to 16-fold increase of abemaciclib and potential concerns for unknown off-target toxicities.
- In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the VERZENIO dose to 100 mg twice daily with concomitant use of other strong CYP3A inhibitors.

- In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the VERZENIO dose to 50 mg twice daily with concomitant use of other strong CYP3A inhibitors.
- Examples of other strong CYP3A inhibitors include but are not limited to: boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, troleandomycin, and voriconazole.
- After discontinuation of a strong CYP3A inhibitor, increase the VERZENIO dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the strong inhibitor.

Coadministration of 600 mg daily doses of rifampin (a strong CYP3A inducer) with a single 200 mg dose of VERZENIO decreased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2, M18 and M20) by 67% in healthy subjects. The recommendation is avoidance of concurrent use of strong CYP3A inducers. A postmarketing commitment (PMC) will be requested to conduct PBPK analysis (or a PK trial if the results from the PBPK analysis are inconclusive) to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose PK of abemaciclib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations.

6.3.2.4. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Yes. The plasma exposure of abemaciclib and its active metabolites is altered in subjects with severe hepatic impairment. In a dedicated clinical study, following the administration of a single oral 150 mg dose of abemaciclib, no clinically relevant changes in the systemic exposure of abemaciclib was observed in subjects with mild (Child-Pugh category A, n=9), or moderate (Child-Pugh category B, n=10) hepatic impairment relative to subjects with normal hepatic function (n=10). Based on the results of the covariate assessment from the popPK analysis, the exposure of abemaciclib is not affected by age, body weight, gender, race, the presence of hepatic metastases, or renal function.

<u>Serum creatinine elevation with abemaciclib exposure</u>
Abemaciclib caused exposure-dependent increases in serum creatinine due to its inhibitory effects on renal uptake transporter OCT2, and tubular efflux transporters MATE-1 and MATE-2K. This issue raised clinical concerns regarding the co-occurrence of renal toxicity and diarrhea as well as dose adjustments for patients with renal insufficiency. In trial JPCK, the renal clearance and active tubular secretion of metformin, a substrate of renal uptake transporter OCT2, and tubular efflux transporters MATE-1 and MATE-2K, was reduced by 45% and 62%, respectively following co-administration of a single 400 mg dose of abemaciclib with 1000 mg metformin in healthy subjects. In addition, administration of a single 400 mg dose of

abemaciclib did not alter glomerular filtration rate (GFR) as measured by iohexol clearance and serum cystatin C in this trial. These results provided conclusive evidence to exclude concentration-dependent renal toxicity effects from abemaciclib at the evaluated and proposed clinical dose.

Hepatic impairment

Abemaciclib primarily undergoes capacity-limited hepatic metabolism via CYP3A4 and exits the body through biliary excretion to feces. The exposure ($AUC_{0\text{-}INF}$) and terminal half-life of abemaciclib in plasma increased two-fold in subjects with severe hepatic impairment (Child-Pugh category C, n=6) relative to healthy subjects. The unbound exposure of abemaciclib plus its active metabolites (M2 + M18 + M20) in plasma also doubled in subjects with severe hepatic impairment relative to those with normal liver function. The applicant submitted an analysis incorporating the relative potency-adjusted unbound AUC of abemaciclib plus its active analytes (M2 + M18 + M20) in plasma for the hepatic impairment trial using the unbound fraction results from the ex-vivo samples of the subjects involved in the trial. Compared to the approach of using the total drug exposure in plasma, a similar two-fold increase in the potency-adjusted unbound exposure was observed in subjects with severe hepatic impairment relative to those with normal liver function. Hence, the proposed adjustment to the dosing frequency of the starting dose from twice daily to once daily is adequately justified for patients with severe hepatic dysfunction.

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

Food-drug interaction

No. The exposure of abemaciclib was not altered following co-administration with a high fat meal (approximately 800 to 1000 calories with 150 (15%) calories from protein, 250 (25%) calories from carbohydrate, and 500 to 600 (50%) calories from fat). In trial JPCC, the C_{max} and $AUC_{0\text{-}INF}$ of total abemaciclib analytes increased by 9% and 26%, respectively in the fed state compared to fasted. Based on the exposure-response relationship for neutropenia, a 30% increase in abemaciclib C_{max} would yield a 9% to 15% increase in the inhibitory effects on neutrophil progenitors. These changes are not expected to have clinically meaningful deleterious effects on the tolerability of abemaciclib with regards to myelosuppression. Thus, the applicant's proposal to administer abemaciclib without regard to food, as evaluated in registration trials MONARCH 1 and MONARCH 2, is acceptable. However, it is plausible that co-administration of abemaciclib with meals may improve its tolerability with regards to gastrointestinal adverse events without affecting efficacy. A PMR was issued to investigate the incidence of dose reductions and interruptions due to severe diarrhea following dosing of abemaciclib in three different administration conditions: fed, fasted (b) (4) and without regards to meals.

Drug-drug interaction

Yes. The effects of CYP3A4 modulators were investigated in two dedicated clinical trials and PBPK modeling and simulations. Refer to section 6.3.2.3 and the PBPK review in section 13.4.3 for further details regarding the labeling recommendations.

X X

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7 Statistical and Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

Data from 15 studies were submitted to this NDA. This includes the Phase 3 randomized, double-blind, placebo-controlled, multi-center MONARCH 2 study (I3Y-MC-JPBL) of fulvestrant with or without abemaciclib for women with hormone receptor positive, HER2 negative, locally advanced or metastatic breast cancer and the MONARCH 1 study (I3Y-MC-JPBN), a Phase 2 multicenter, single-arm, open-label study of LY2835219 (abemaciclib) for patients with previously treated HR-positive, HER2 negative metastatic breast cancer. Additional studies submitted including bioavailability study (I3Y-MC-JPBS), a healthy subject bioequivalence study (I3Y-MC-JPCC), 3 healthy subject PK and initial tolerability studies (I3Y-MC-JPBG, I3Y-MC-JPBU, I3Y-MC-JPCA), 2 patient PK and initial tolerability studies (I3Y-MC-JPBA, I3Y-JE-JPBC), 1 intrinsic factor PK study (I3Y-MC-JPBV), 2 extrinsic factor study reports (I3Y-MC-JPBE, I3Y-MC-JPBF), 1 healthy subjects pharmacodynamics and PK/pharmacodynamics study (I3Y-MC-JPBD), 1 clinical study in mantle cell lymphoma (I3Y-MC-JPBB), 1 clinical pharmacology study (I3Y-MC-JPCK).

The primary evidence to support this new drug application is derived from MONARCH 2 and MONARCH 1 as demonstrated in Table 12.

Table 12 Listing of Clinical Trials Relevant to this NDA

Trial Identity	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							
MONARCH2 I3Y-MC-JPBL	Randomized, double-blind, placebo-controlled Phase 3 trial	200 mg orally BID then 150 mg BID with fulvestrant 500 mg IM on day 1 and day 15 of cycle 1 and then on day 1 of cycle 2 and beyond	Investigator assessed PFS	Until disease progression or lack of tolerability	855 patients entered 669 patients were randomized/enrolled into the ITT population	Women with HR+/HER2- locally advanced or MBC who had disease progression following endocrine therapy	145 sites in 19 countries
MONARCH1 I3Y-MC-JPBN	Single-arm, open-label study to evaluate the antitumor activity of abemaciclib	200 mg orally BID	Investigator assessed ORR	Until disease progression or lack of tolerability; Eighteen months after last patient enrolled	184 patients entered 132 patients enrolled and received at least one dose of treatment	Women with HR+/HER2- MBC whose disease had progressed after endocrine therapy and who received 1 or 2 prior chemotherapy regimens in the metastatic setting	35 sites in 4 countries
Studies to Support Safety							
I3Y-MC-JPBA	Multicenter, nonrandomized, open-label, dose-escalation trial of a CDK4/6 dual inhibitor (LY2835219)	50 -225 mg orally every 24 hours, 75-275 mg orally every 12 hours dose escalation evaluation	To evaluate the safety and tolerability of LY2835219 when administered orally to patients with advanced cancer	Until disease progression or unacceptable toxicity; 30 days after the last dose of study drug	33 patients in the dose escalation cohort; 68 in NSCLC, 17 GBM, 47 breast cancer, 26 melanoma, 15 CRC, 19 HR+ breast	Patients with advanced cancer where available standard therapies have ceased to provide clinical benefit or are appropriate for therapy in combination with fulvestrant for part G. For the dose	Three US Sites

						escalation cohort, part A, patients had advanced solid tumors or lymphoma, expansion cohorts included patients with NSCLC, GBM, breast cancer, melanoma, CRC, HR+ breast cancer	
I3Y-MC-JPBB	Multicenter, nonrandomized, open-label, Phase 2 study	200 mg orally BID	To estimate the disease control rate (DCR) for patients who receive abemaciclib for relapsed or refractory MCL	Until disease progression or unacceptable toxicity; 90 days then until patient death or lost to follow up	28 patients with relapsed or refractory mantle cell lymphoma	Patients with relapsed or refractory MCL for whom no standard therapy known to confer clinical benefit was available or tolerable	Eight sites, 3 in France and 5 in Germany
I3Y-JE-JPBC	A single-arm, open-label, dose escalation study	100, 150, and 200 mg orally every 12 hours with dose escalation	To evaluate the safety and tolerability of LY2835219 in patients with advanced cancer up to the MTD as determined in the Phase 1 Study JPBA	Until disease progression or unacceptable toxicity; 30 days after the last dose of study drug	12 patients with advanced cancer	Japanese patients with advanced cancer who have no standard therapy options known to confer clinical benefit	Single Japanese Center
I3Y-MC-JPBE	An open-label, 2-period,	50 mg single dose	The effect of clarithrom		26 patients with	Patients with advanced cancer who	Single US Center

	fixed-sequence study and a safety extension phase		ycin, a CYP3A inhibitor, on the PK of LY2835219 and its metabolites after a single dose.		advanced cancer	have no standard therapy options known to confer clinical benefit for their condition	

7.1.2. Review Strategy

The clinical and statistical review is based on the clinical study report for the randomized phase 3 trial MONARCH 2, I3Y-MC-JPBL, as well as the single-arm phase 2 trial MONARCH 1, I3Y-MC-JPBN. The efficacy and safety reviews were conducted by Dr. Lynn Howie. Statistical review of both the studies was conducted by Dr. Erik Bloomquist.

Data Sources

The review included the following:

1. Literature review of hormone receptor positive metastatic breast cancer in female and male patients, the cyclin D1 CDK 4/6 pathway, and patient reported outcomes
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 data sets for MONARCH 2 (I3Y-MC-JPBL) and MONARCH 1 (I3Y-MC-JPBN).
4. Review of selected case report forms (CRFs) for MONARCH 2 and MONARCH 1.
5. Review of patient narratives for serious adverse events and deaths in MONARCH 2 and MONARCH 1
6. Review of responses to clinical and biostatistical queries sent to the Applicant
7. Review of consultation reports from the Office of Scientific Investigations (OSI)
8. Consultation with the multidisciplinary review team including Biostatistics, Clinical Pharmacology, CMC, and Toxicology reviewers was undertaken.
9. EDR link for electronic data sources is: \\CDESUB1\evsprod\NDA208716\208716.enx
10. SDTM and ADaM datasets were submitted along with software code for data analyses

Data and Analysis 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 was able to be verified through the datasets. The Applicant submitted information regarding 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.

Data were submitted to the Office of Computational Science and Data Fitness assessment found only minor issues with data traceability in the laboratory and vital sign datasets. There were no traceability issues found in the adverse event data sets.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. MONARCH 2

Trial Design and Endpoints

MONARCH2 (I3Y-MC-JPBN) was a Phase 3, multicenter, randomized, double blind, placebo controlled trial of fulvestrant with or without abemaciclib (LY2835219) in women with hormone receptor (HR)-positive , human epidermal growth factor 2 (HER2)-negative (HER2 negative) metastatic breast cancer who have had disease progression on previous endocrine therapy. Patients who had received chemotherapy in the metastatic setting were excluded from participation in this trial.

The primary objective for this study was to evaluate the effect of abemaciclib plus fulvestrant vs. fulvestrant alone on investigator assessed progression free survival. Key secondary objectives include overall survival (OS), OS rate at 1, 2 and 3 years, overall response rate (ORR), duration of response (DoR), disease control rate, clinical benefit rate, safety and tolerability, pain and symptom using patient reported outcomes (PROs), pharmacokinetics of abemaciclib and its metabolites and fulvestrant.

Patient reported outcomes (PROs) were collected for the MONARCH 2 study using the Modified Brief Pain Inventory, Short Form (mBPI-sf), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and Breast Cancer (EORTC QLQ-BR23), and the EQ-5D-5L. These assessments were collected at baseline, cycle 2 day 1, and then beginning with cycle 3 at every second cycle through cycle 13 and then every third cycle after cycle 13. Data were also collected at the short term follow up visit.
In the MONARCH 1 study, PROs were collected using the mBPI-sf and the EORTC QLQ-C30. These assessments were collected at days 1 and 15 of cycle 1 and then with each visit when the patient was at the clinic for other study assessments. Data were also collected at the short term follow up visit. Review of the PRO data is located in section 11.4 on page 214.

Patients who enrolled were initially treated with fulvestrant 500 mg IM on days 1 and 15 of cycle 1 and then on day 1 of subsequent cycles and abemaciclib 200 mg or placebo every 12 hours daily for a 28 day cycle. The dose of abemaciclib was reduced to 150 mg every 12 hours in Protocol Amendment (a) In both arms, pre- and peri-menopausal women received a GnRH agonist such as goserelin which was initiated 28 days prior to cycle 1, day 1. Patients were randomized using the following stratification factors: endocrine therapy naïve (EN) or endocrine therapy pretreated (EP), nature of disease (visceral metasteses vs. bone-only metasteses vs. other), and sensitivity to endocrine therapy (primary resistance vs. secondary resistance). Primary endocrine resistance was defined per European Society for Medical Oncology (ESMO) guidelines as follows: recurrence within the first two years on adjuvant endocrine therapy while on endocrine therapy and in the advanced or metastatic setting, progressive disease within the first 6 months of initiating first line endocrine therapy. Patients

not meeting either of these definitions were considered to have secondary endocrine resistance. Figure 6 demonstrates the MONARCH 2 study schema.

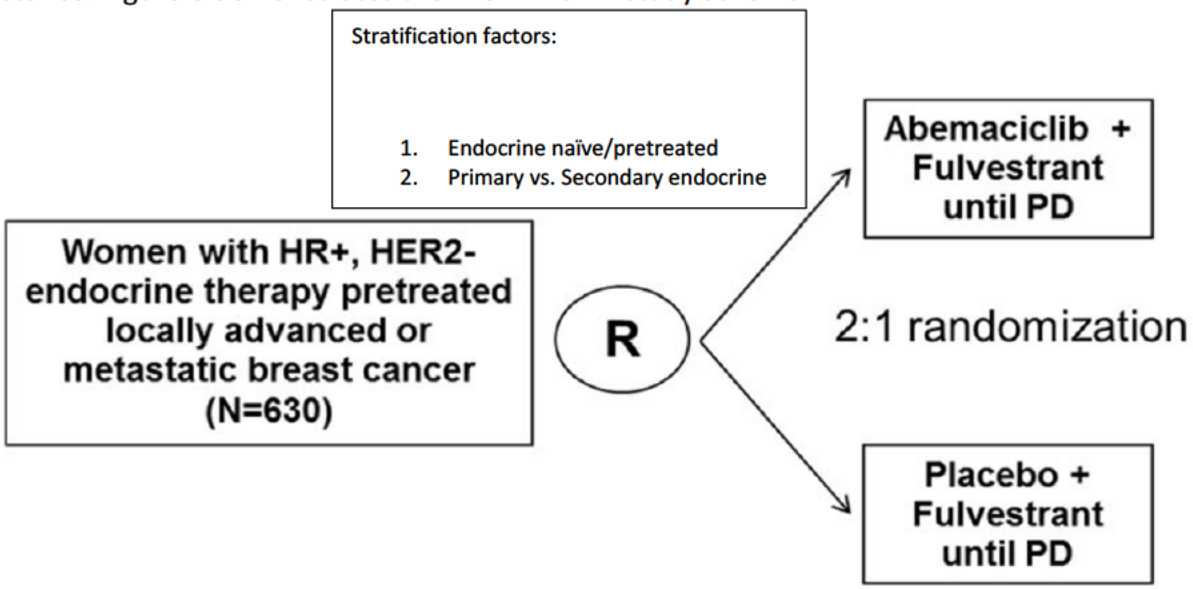

Figure 6. MONARCH 2 Study Schema

Source, MONARCH 2 CSR, page 37

After completing study screening, follow up visits occurred on days 1 and 15 of cycle 1 and day 1 of subsequent cycles. Radiological tumor assessment occurred within 7 days of every other cycle beginning with Cycle 3. CT scans of the chest, abdomen and pelvis or MRI were used to assess progression in all patients. In patients with locally advanced disease, breast MRI was performed at the same interval that other radiographic assessments were performed. Bone scintigraphy was performed at baseline for all patients and was repeated every sixth cycle beginning with cycle 7, when complete response was identified in target disease, or when progression of bone disease was suspected. X-rays, CT/MRI of other regions, and measurement of visible or palpable tumor was performed if clinically indicated and additional imaging was only required if patients had bone lesions identified by bone scintigraphy at baseline. Patient reported outcome (PRO data) were collected using mBPI-sf, the EORTC QLQ-C30, the EORTC QLQ-BR23, and the EQ-5D-5L. PRO data were collected on day 1 and 15 of cycle 1 and subsequently on day 1 of each cycle and at short term post-discontinuation follow up.

Patients were discontinued from study drugs in the event of progressive disease (PD) as defined by RECIST v 1.1, enrollment into another clinical trial not compatible with the study, or based on investigator, sponsor or patient decision.

<u>Study Design and Choice of Control Group</u>

The study design was randomized, controlled, and double-blinded to minimize systematic bias in the selection and assignment of patients to study therapy. Fulvestrant is considered a standard of care in patients with HR-positive, HER2-negative metastatic breast cancer per clinical practice guidelines and choice of this control allowed for direct statistical estimation of benefits and harms of this therapy as well as minimized bias in assessing and interpreting treatment effects. Patients were stratified by factors thought to 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. The initial study included both endocrine therapy naïve(EN) and endocrine therapy pretreated (EP) patients which was subsequently modified after patients were enrolled to exclude those who were EN based (n=44) on feedback from the Agency. The EN patients who were enrolled were not included in the ITT population. This was appropriate given other available therapies for patients with no previous endocrine therapy treatment. Given the known differences in the natural history of patients with visceral vs. bone only disease, as well as those who have rapid progression on endocrine therapies, the randomization stratification factors are appropriate.*

Diagnostic Criteria:

Patients were required to have a diagnosis of HR-positive, HER2-negative breast cancer. 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. While not required, a patient with a new metastatic lesion was recommended for consideration of biopsy when possible to reassess HER2 status prior to study entry if clinically indicated.

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
    - To fulfill the requirement of HR positive disease, a breast cancer must express, by immunohistochemistry (IHC), at least 1 of the hormone receptors (estrogen receptor [ER] or progesterone receptor [PgR]) as defined in the relevant American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guidelines.

  - To fulfill the requirement of HER2-negative disease, a breast cancer must not demonstrate, at initial diagnosis or upon subsequent biopsy, overexpression of HER2 by either IHC or in-situ hybridization as defined by the relevant ASCO/CAP Guidelines.
- Have locally advanced disease not amenable to curative treatment by surgery or metastatic disease. In addition, patients must fulfill one of the following criteria:
  - Relapsed with radiologic evidence of progression while receiving neoadjuvant or adjuvant endocrine therapy, with no subsequent endocrine therapy received following progression
  - Relapsed with radiologic evidence of progression within one year of completion of adjuvant endocrine therapy with no subsequent endocrine therapy received following progression
  - Relapsed with radiologic evidence of progression more than one year of completion of adjuvant endocrine therapy and then subsequently relapsed with radiologic evidence of progression after receiving treatment with either an antiestrogen or an aromatase inhibitor as first-line endocrine therapy for metastatic disease. Patients may not have received more than one line of endocrine therapy or any prior chemotherapy for metastatic disease.
  - Presented with de novo metastatic disease and then relapsed with radiologic evidence of progression after receiving treatment with either an antiestrogen or an aromatase inhibitor as first-line endocrine therapy for metastatic disease. Patients may not have received more than 1 line of endocrine therapy or any prior chemotherapy for metastatic disease
- Postmenopausal status due to either surgical/natural menopause or ovarian suppression (pre/perimenopausal) (initiated at least 28 days prior to Cycle 1, Day 1) with a gonadotropin releasing hormone (GnRH) agonist such as goserelin. Postmenopausal status due to surgical/natural menopause required at least 1 of the following:
  - Prior bilateral oophorectomy
  - Age ≥60 years
  - Age <60 and amenorrheic for at least 12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle stimulating hormone (FSH) and estradiol levels in the postmenopausal range
- Have a negative serum pregnancy test at baseline (within 14 days of randomization) and agree to use medically approved precautions to prevent pregnancy during the study and for 12 weeks following the last dose of abemaciclib if postmenopausal status is due to ovarian suppression with a GnRH agonist.
- Had either measurable disease or nonmeasurable bone-only disease. Measurable and nonmeasurable disease were defined according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). Nonmeasurable bone-only disease may have included any of the following: blastic bone lesions, lytic bone lesions without a measurable soft tissue component, or mixed lytic-blastic lesions without a measurable soft tissue component.

- Are female and ≥18 years of age
- Have given written informed consent prior to any study-specific procedures
- ECOG performance status of 0 or 1
- Adequate organ function including:
    - Hematologic: ANC ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, and hemoglobin level ≥8 g/dL. If the patient required transfusions to maintain their hemoglobin level, treatment could not have begun earlier than the day after the transfusion.
    - Hepatic: bilirubin ≤1.5 x the upper limit of normal and alanine aminotransferase (ALT) level ≤3 x ULN
    - Renal: serum creatinine ≤ 1.5 x ULN
- Willingness to participate for the duration of study and to follow study procedures
- Able to swallow capsules
- Have discontinued previous therapies for cancer including aromatase inhibitors, antiestrogens, chemotherapy, radiotherapy, and immunotherapy for at least 21 days for myelosuppressive agents or 14 days for non-myelosuppressive agents prior to receiving study drug and recovered from the acute effects of therapy (until the toxicity resolves to either baseline or grade 1 except for residual peripheral neuropathy or alopecia)

Exclusion Criteria:

- 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. If patient is currently on a clinical trial involving a non-approved use of a device, then agreement with the investigator and Lilly clinical research physician (CRP) is required to establish eligibility

- Visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis. Visceral crisis was not simply the presence of visceral metastatic disease but implied severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid disease progression

- History of or clinical evidence of central nervous system metasteses. Screening was not required for enrollment

- Previous treatment with chemotherapy (excluding adjuvant/neoadjuvant chemotherapy), fulvestrant, everolimus, or any CDK 4/6 inhibitor

- Have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days prior to randomization to study drug for a nonmyelosuppressive or myelosuppressive agent respectively

- Receipt of recent (within 28 days) yellow fever vaccination

- Major surgery within 14 days prior to randomization of study drug to allow for postoperative healing of surgical wound and sites
- Have a personal history within the past 12 months of any of the following conditions: syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest
- Serious preexisting medical condition that in the judgement of the investigator would preclude participation in the study (for example major surgical resection of stomach or small bowel)
- Inflammatory breast cancer or a history of any other cancer except for non-melanoma skin cancer or carcinoma in situ of the cervix unless in complete remission with no therapy for a minimum of 3 years.
- Have received an autologous or allogeneic stem cell transplant
- Have active bacterial or fungal infection, or detectable viral infection (for example HIV or viral hepatitis). Screening is not required for enrollment
- Pregnant or breastfeeding
- Initiated bisphosphonates or approved RANK-L targeted agents less than 7 days prior to randomization

Reviewer Comment: *The above inclusion and exclusion criteria appear generally acceptable. We currently recommend that patients with stable CNS disease be included in clinical studies. Of note, patients who have had one line of chemotherapy in the metastatic setting were excluded making the patients included in this study potentially less heavily pretreated than those in the other approved CDK4/6 inhibitors in combination with fulvestrant trials. Additionally, inflammatory breast cancer patients were not excluded from this other trials evaluating CDK 4/6 inhibitors in combination with fulvestrant. The included population may have more favorable features than those included in studies for other agents within this same class based on patients who received prior chemotherapy in the metastatic setting or had presented with inflammatory breast cancer being excluded. Male patients are excluded based on the limited data for use of fulvestrant in this population due to biological differences in sex hormone physiology.*

Concomitant Radiotherapy or Surgery

A patient with locally advanced breast cancer may receive surgery ± radiotherapy if the study therapy renders the tumor operable. In this case, the patient should not receive study treatment for at least 7 days prior to surgery and until at least 14 days after surgery ± radiotherapy to allow for tissue healing and recovery. There was no restriction on the duration

of the period without study treatment and after this period ends, study procedures were to resume based on most recent cycle completed prior to surgery ± radiotherapy or the patient should be discontinued from study treatment. A patient who receives surgery ± radiotherapy for locally advanced breast cancer was not considered non-compliant and did not incur a protocol violation.

Palliative radiation was not permitted without permanent discontinuation from study treatment. All patients other than locally advanced patients rendered operable by study treatment were required to discontinue from study treatment and have tumor assessment prior to receiving 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 initially chose the abemaciclib dose regimen of 200 mg every 12 hours based on data from the JPBA study (Table 12) which was a dose escalation study of abemaciclib in patients with advanced cancer. However, as this trial was being initiated, the study JPBH (Table 12), a phase 1b study evaluating abemaciclib in combination with letrozole or anastrazole was underway and there was concern for decreased tolerance of abemaciclib in this setting due to early diarrhea with most patients not completing their first cycle at the 200 mg every 12 hours dosing. A blinded trial level safety review was performed on the MONARCH 2 patients enrolled to that time point and found that of the approximately 89 patients included and considered evaluable for treatment (that is had completed one cycle of study treatment, had discontinued study treatment, or had experienced a dose omission or reduction), that approximately one third of patients required a dose reduction in the first cycle. Based on the 2:1 randomization ratio, it was thought that this may include up to one half of the patients randomized to abemaciclib. Given this, protocol amendment JPBLa reduced the dose of abemaciclib from 200 mg every 12 hours to 150 mg every 12 hours.

Dosing for fulvestrant was based on current standard USPI dosing recommendations.

Reviewer Comments: *It was noted at the time of Protocol Amendment JPBLa that many of the patients who had been randomized to receive abemaciclib 200 mg Q12H had already dose reduced to 150 mg Q12H or lower at the time of the amendment and the remaining patients were dose reduced. Prior to JPBLa, 24% of patients discontinued study drug due to an AE and 56% of patients had dose reductions. There were 178 patients enrolled prior to Amendment A with 121 randomized to the starting dose of abemaciclib 200 mg BID and 57 to matching*

placebo. Given this, along with a brief period of exposure to 200 mg Q12H (median duration of therapy was 34 days), it is unlikely that this brief exposure to a higher dose of therapy affected the primary efficacy endpoint results.

Study Treatments

- Experimental Arm A: abemaciclib 150 mg orally Q12H on Days 1-28 of a 28 day cycle plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond
- Control (Placebo) Arm B: Placebo orally Q12H on Days 1-28 of a 28 day cycle plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond

Pre- and perimenopausal women received a GnRH agonist such as goserelin starting at least 28 days prior to study initiation and received concurrent ovarian function suppression per USPI during the active treatment phase

Reviewer's Comment: *The dose and schedule of fulvestrant is appropriate. Multiple GnRH agonists were used as there was no protocol specification for a single agent with goserelin being the most common agent used.*

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 fulvestrant or placebo plus fulvestrant. Assignment to treatment group was determined by a computer-generated random sequence using the IWRS.

Randomization allocation was 2:1 to the abemaciclib and placebo arms respectively and was stratified by the following: nature of disease (visceral metasteses vs. bone only disease vs. other) and sensitivity to endocrine therapy (primary resistance vs. secondary resistance). Prior to Protocol Amendment JPBL(b), randomization was also stratified by endocrine therapy naïve vs. endocrine therapy pretreated. After this amendment, the endocrine therapy naïve patients were removed from the intention to treat population as goal of the study was to evaluate this therapy in endocrine therapy pretreated patients alone.

Reviewer Comments: *Based on the endocrine therapy status (naïve vs. pretreated) being a stratification factor prior to Amendment B, the discontinuation of enrollment of these 44 patients based on Amendment B and the modification of the SAP to exclude these patients from the ITT population should not have resulted in imbalance between the treatment arms and should not affect the primary efficacy endpoint results.*

Blinding

Abemaciclib and placebo were provided by the Applicant and supplied as capsules with matching size and color. 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 as well as neutropenia associated with this drug that was not experienced in the placebo plus fulvestrant arm, both invetigators and patients were likely not fully blinded.*

Dose Modifications

In the event of significant treatment-related toxicities, dose adjustments were recommended for both abemaciclib/placebo and fulvestrant. When treatment interruption was deemed necessary for one of the study drugs in the combination, treatment with the other agent was continued as planned. As Protocol Amendment JPBL(a)reduced the starting dose of abemaciclib from 200 mg Q12H to 150 mg Q12H, there were two different dose adjustment schedules as demonstrated below. Dose adjustments to fulvestrant were made based on recommendations in the USPI. For patients with moderate hepatic impairment (Child Pugh Class B), including any patient who developed moderate hepatic impairment during the course of the study, fulvestrant should have been administered as a single 250 mg injection. If fulvestrant was discontinued, a patient could have continued to receive blinded study drug.

Table 13 Abemaciclib Dose Levels Prior to Amendment JPBL(a)

Dose Adjustment	Oral Dose	Frequency
0	200 mg	Q12H
1	150 mg	Q12H
2	100 mg	Q12H
3	50 mg	Q12H

Adapted from the MONARCH 2 CSR, page 39

Table 14 Abemaciclib Dose Levels After Amendment JPBL(a)

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

Adapted from the MONARCH 2 CSR, page 39

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 below.

Table 15 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	Persistent or	Dose MAY be	Dose MAY be reduced

Toxicity (except diarrhea)	recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	suspended until toxicity resolves to either baseline or Grade 1	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 2 CSR page 38

Administrative Structure

The Applicant used an external data monitoring committee (DMC) to provide patient safety oversight for the MONARCH 2 study independently of the Lilly Study team and Lilly Global patient safety. Safety analyses were performed every 3 months and the first interim analysis was triggered by the 90th patient enrolling.

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 assist in the evaluation of 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 outcome assessment including PROs
- PK analysis
- Archived tumor sample where available

On Treatment Visits

- Laboratory assessments
- Physical Examination
- Concomitant medications
- Tumor assessment (every second cycle 3-13 [+/- 7 days]and every third cycle [+/- 7 days] after cycle 13)
- ECG
- Adverse event analysis
- Health outcome assessment including PROs
- PK analysis cycles 1-3
- Pharmacogenetic blood sample Cycle 1
- Plasma biomarker sample Cycle 1

Follow-up

- Data on adverse events were collected at the short term follow up visit (approximately 30 days after study therapy discontinuation)
- SAEs attributed to study drug or protocol procedures were evaluated during long term follow up

- Long term follow-up began the day after short-term follow up is completed and continues until the study completion or patient's death. Survival assessment occurred every 12 weeks via telephone contact to the patient or their family during this period

The schedule of activities is shown in

Table below.

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Table 16 MONARCH 2 Study Schedule

			Baseline		Patients on Study Treatment				Postdiscontinuation Follow-Up	
		Cycle	BL		1		2 – 3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]
		Visit	0		1		2 – 3	4 and Beyond (if Applicable)	801	802 - 8XX
		Approximate Duration (days)	28		28		28	28	30	Variable
		Relative day within a cycle	≤28	≤14	1	15±3	1[p]	1[p]		
Procedure Category	**Procedure**	**Protocol Reference**								
Study Entry /Enrollment	Informed Consent Form signed[q]	Section 8.1	X[q]							
	Inclusion/Exclusion evaluation	Section 7		X						
Medical History	Medical History			X						
	Historical illnesses	Section 12.2.4		X						
	Habits assessment	Section 12.2.4		X						
Physical Examination	Height	Section 12.2.4		X						
	Weight	Section 12.2.4		X	X	X	X	X	X	
	Vital Signs (Temp, BP, HR, RR)	Section 12.2.4		X	X	X	X	X	X	
	ECOG performance status	Section 7.1 Attachment 4		X	X	X	X	X	X	
Tumor Assessment	Tumor measurement (palpable or visible)[c]	Section 10.1.1	X[c]				X[c]	X[c]	X[c]	X[c]
	Radiologic imaging according to RECIST[b]	Section 10.1.1 Attachment 5	X[b]				X[b]	X[b]	X[b]	X[b]
	Bone Scintigraphy[i]	Section 10.1.1 Attachment 5	X[i]					X[i]	X[i]	X[i]
	X-ray or CT scan with bone windows or MRI[j]	Section 10.1.1 Attachment 5	X[j]				X[j]	X[j]	X[j]	X[j]

			Baseline		Patients on Study Treatment				Postdiscontinuation Follow-Up	
		Cycle	BL		1		2 – 3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]
		Visit	0		1		2 – 3	4 and Beyond (if Applicable)	801	802 - 8XX
		Approximate Duration (days)	28		28		28	28	30	Variable
		Relative day within a cycle	≤28	≤14	1	15±3	1[p]	1[p]		
Procedure Category	Procedure	Protocol Reference								
Survival Information[d]		Section 10.1							X[d]	X[d]
Adverse Event Collection/CTCAE Grading[f]		Section 10.3		X[f]	X[f]		X[f]	X[f]	X[f]	X[f]
Concomitant Medications (with analgesics)		Section 9.6		X	X		X	X	X	
Lab/ Diagnostic Tests	Central hematology	Attachment 2		X	X	X	X	X	X	
	Central serum chemistry	Attachment 2		X	X	X	X	X	X	
	Local FSH and estradiol levels[n]	Attachment 2		X[n]						
	Local serum pregnancy test[o]	Attachment 2		X[o]						
	Central pharmacokinetic (PK) sampling[m]	Attachment 7			X[m]	X[m]	X[m]			
	Pharmacogenetic blood sample	Section 10.4.2.2			X					
	Biomarker plasma sample	Section 10.4.2.3			X					
	Local ECG[e]	Section 10.3.2.1		X[e]	X[e]	X[e]		X[e]	X[e]	
	Archived Tumor Sample[h]	Section 10.4.2.1			X[h]					

			Baseline		Patients on Study Treatment				Postdiscontinuation Follow-Up	
		Cycle	BL		1		2 – 3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]
		Visit	0		1		2 – 3	4 and Beyond (if Applicable)	801	802 - 8XX
		Approximate Duration (days)	28		28		28	28	30	Variable
		Relative day within a cycle	≤28	≤14	1	15±3	1[p]	1[p]		
Procedure Category	Procedure	Protocol Reference								
Study Drug	Fulvestrant Therapy [g]	Section 9.1			Days 1 and 15 of Cycle 1, then Day 1 of Cycle 2 and beyond[g]					
	Abemaciclib or Placebo Therapy[g]	Section 9.1			Q12H on Days 1 through 28 of every cycle[g]					
Health Outcomes	BPI, EORTC QLQ-C30, EORTC BR23, EQ-5D 5L[k]	Section 12.2.12		X[k]			X[k]	X[k]	X[k]	
	Skeletal-Related Events assessment[l]	Section 12.2.12		X[l]			X[l]	X[l]	X[l]	
	Hospitalization	Section 12.2.12.4		X			X	X	X	
	Transfusion	Section 12.2.12.4		X			X	X	X	

Abbreviations: BL = baseline; Temp = Temperature; BP = Blood Pressure; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; GnRH = gonadotropin-releasing hormone; HR = heart rate; IV = intravenous; PK = pharmacokinetics; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; Q12H = every 12 hours; SAEs = serious adverse events; FSH = follicular stimulating hormone.

a Short-term follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days; the associated study procedures are performed once at the end of this period. Long-term follow-up begins the day after short-term follow-up is completed and continues until the patient's death or overall study completion; the associated study procedures are performed approximately every 12 weeks (± 14 days) for the duration of this period.

Study Schedule, Protocol I3Y-MC-JPBL (continued)

b For patients with inoperable locally advanced breast cancer, MRI scan of the breast is performed locally at baseline (Day -28 to Day -1), between Day 1 and Day 7 of every second cycle beginning with Cycle 3 and continuing through Cycle 13, between Day 1 and Day 7 of every third cycle after Cycle 13, and within 14 days of clinical progression. For all patients, CT or MRI scan of the chest, abdomen, and pelvis is performed locally at baseline (Day -28 to Day -1), between Day 1 and Day 7 of every second cycle beginning with Cycle 3 and continuing through Cycle 13, between Day 1 and Day 7 of every third cycle after Cycle 13, and within 14 days of clinical progression. It is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast whenever possible. If this is not feasible due to hypersensitivity or other conditions, then gadolinium-enhanced MRI is preferred. For patients with known serious allergic reactions to CT contrast material, a CT of the chest without contrast and gadolinium-enhanced MRI of the abdomen/pelvis are encouraged. For patients who discontinue study treatment without objectively measured progressive disease (PD), continue to evaluate tumor response approximately every 8 weeks for the first 12 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 until the patient's death or overall study completion.

c Visible tumor (such as skin lesions) should be documented by photography and each photographic image of the tumor should include a ruler. For patients who discontinue study treatment without objectively measured progressive disease (PD), continue to evaluate tumor response approximately every 8 weeks for the first 12 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, tumor assessments are no longer required and the patient will continue with post-discontinuation follow-up until the patient's death or overall study completion.

d Survival information is collected at baseline and during both study treatment and postdiscontinuation follow-up. During Long-Term Follow-Up, survival information is collected approximately every 12 weeks for the duration of this period. Although preferable to collect during a clinic visit, survival information may be collected by contacting the patient or family directly (for example, via telephone). Long-Term Follow-up data collection may include anticancer therapies.

e A local ECG (no replicates required) should be obtained at baseline (Day -14 to Day -1), 2 to 4 hours after the LY dose on Cycle 1 Day 1, upon arrival at site but prior to fulvestrant dose on Cycle 1 Day 15, 2 to 4 hours after the LY dose on Cycle 4 Day 1, and at the short-term follow-up visit.

f Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System. During Long-Term Follow-Up, only SAEs that are related to study drugs or protocol procedures will be collected. All adverse events possibly related to study drugs or protocol procedures should be followed until they resolve, are no longer considered to be possibly related, become stable or return to baseline, the patient starts a new therapy, the patient expires, or the patient becomes lost to follow-up. The frequency of evaluation is determined according to the judgment of the investigator.

g Blinded study drug should be administered orally Q12H on Days 1 through 28 of each cycle; patients should not consume food beginning 1 hour before and ending 1 hour after taking blinded study drug. Fulvestrant 500 mg should be administered intramuscularly into the buttocks slowly (1 to 2 minutes per injection) as two 250-mg injections, one in each buttock; however, for patients with moderate hepatic impairment (defined as Child-Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250-mg injection.

h Formalin-fixed paraffin-embedded tumor tissue (either block or 15-20 unstained slides) should be requested at the time of randomization. However, if this sample is not available for a patient, it will not constitute a protocol deviation

Study Schedule for the extension period only, Protocol I3Y-MC-JPBL

Perform procedure as indicated.

			Patients on Study Treatment		Extension Period Follow-Up
		Cycle	X-Y		Follow-Up[a]
		Visit	501-5XX		901
		Duration (days)	28		30
		Relative day within a cycle	1	15	
Procedure Category	Procedure	Protocol Reference			
Adverse Events Collection/CTCAE Grading[b]		Section 10.3	X		X
Study Drug	Fulvestrant Therapy[c]	Section 8.1.2	Days 1 and 15 of Cycle 1, then Day 1 of Cycle 2 and beyond[c]		
	Abemaciclib Therapy[c]	Section 8.1.2	Daily Q12H[c]		

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; PK = pharmacokinetics; Q12H = every 12 hours; SAEs = serious adverse events.

a The extension period begins after study completion and ends at the end of trial.

b Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly safety system.

c Abemaciclib should be administered Q12H on Days 1 through 28 of each cycle. Patients should not consume food beginning 1 hour before and ending hour after taking study drug.
Fulvestrant 500 mg should be administered intramuscularly into the buttocks slowly (1 to 2 minutes per injection) as two 250-mg injections, one in each buttock; however, for patients with moderate hepatic impairment (defined as Child-Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250-mg injection.

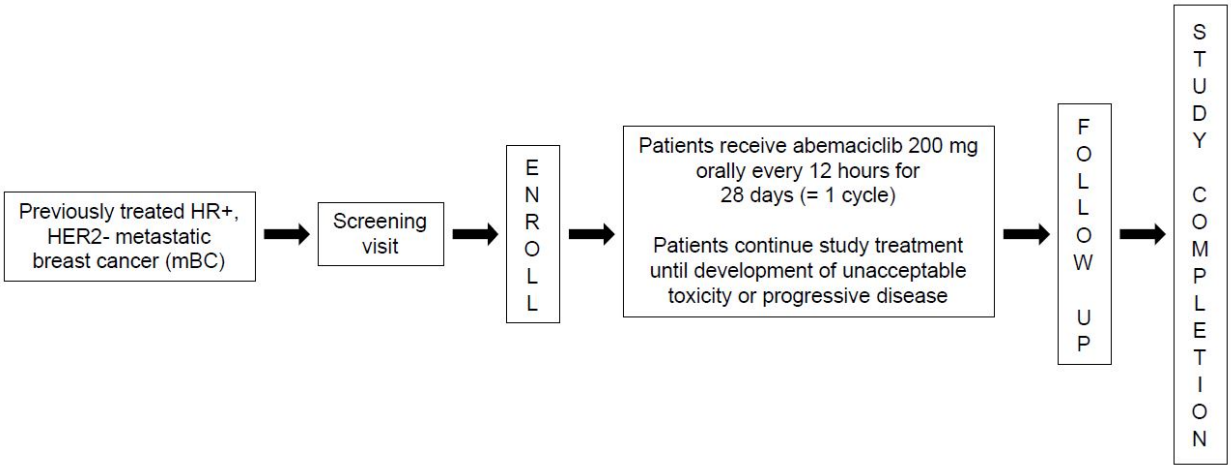
Source: Protocol I3Y-MC-JPBL(d), Appendix 1, pages 76-82

7.2.2. MONARCH 1

Trial Design and Endpoints

MONARCH 1 (I3Y-MC-JPBN) was a phase 2, multicenter, single arm, open label study in patients with hormone receptor positive (HR-positive), human epidermal growth factor receptor 2 negative (HER2-negative) metastatic breast cancer who have had disease progression after endocrine therapy and have received 1 or 2 prior chemotherapy regimens in the metastatic setting. A non-randomized, uncontrolled design was used for this study as there is no standard of care for this patient population, the study therapy was being evaluated as a single agent, and the primary study endpoint was tumor response. Patients who enrolled received abemaciclib orally every 12 ± 2 hours on days 1-28 of a 28 day cycle. Figure 7 demonstrates the MONARCH 1 study schema.

Figure 7 MONARCH 1 Study Schema



Abbreviations: HER2- = human epidermal growth factor receptor negative; HR+ = hormone receptor positive, mBC = metastatic breast cancer.

Source: MONARCH 1 CSR, page 26

After completing study screening, follow up visits occurred on days 1 and 15 of cycle 1 and day 1 of subsequent cycles. Radiological tumor assessment occurred within 7 days of every other cycle beginning with Cycle 3. CT scans of the chest, abdomen and pelvis or MRI were used to assess progression. Nuclear medicine bone scan or PET/CT scan was performed at baseline for all patients with additional imaging if clinically indicated. X-rays, CT/MRI of other regions, and measurement of visible or palpable tumor was performed if clinically indicated and additional imaging was only required if patients had non-measurable bone disease. Patient reported outcomes (PRO data) were collected using the modified Brief Pain Inventory (Short Form) (mBPI-sf) and the European Organization for Research and Treatment of Cancer Quality of Life

Questionnaire (EORTC QLQ-C30). PRO data were collected on day 1 and 15 of cycle 1 and subsequently on day 1 of each cycle and at short term post-discontinuation follow up.

To be eligible for this study, patients must have been females ≥18 years of age who had a diagnosis of HR-positive, HER2-negative breast cancer that was recurrent, locally advanced, unresectable, or metastatic disease. Patients must have progressed either on or after antiestrogen therapy. Patients must have had prior treatment with at least 2 chemotherapy regimens: at least one of these regimens must have been administered in the metastatic setting, at least one regimen must have contained a taxane, and these regimens could have included capecitabine, eribulin, gemcitabine, an anthracycline, or vinorelbine. Patients must have received no more than 2 prior chemotherapy regimens in the metastatic setting.

Key eligibility criteria included:

- A diagnosis of HR-positive+, HER2-negative breast cancer
    - Expression of at least one of the hormone receptors (ER or progesterone receptor PR) by immunohistochemistry
    - No demonstration at initial diagnosis or on subsequent biopsy of overexpression of HER2 by either IHC or in –situ hybridization. Though not a required protocol procedure, a patient with a new metastatic lesion amenable to biopsy should have been considered for this to reassess HER2 status prior to study entry if clinically indicated
- ECOG performance status of 0 or 1
- Adequate organ function including:
    - Hematologic: ANC ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, and hemoglobin level ≥8 g/dL. If the patient required transfusions to maintain their hemoglobin level, treatment could not have begun earlier than the day after the transfusion.
    - Hepatic: bilirubin ≤1.5 x the upper limit of normal and alanine aminotransferase (ALT) level ≤3 x ULN
    - Renal: serum creatinine ≤ ULN
- Measurable disease as defined by RECIST version 1.1 criteria
- Have discontinued all previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, and endocrine therapy) for at least 21 days for myelosuppressive agents or 14 days for nonmyelosuppressive agents and recovered from the acute effects of therapy with toxicity resolving to baseline or grade 1 except for residual alopecia and peripheral neuropathy

Key exclusion criteria included:

- A history of central nervous system (CNS) metastesis or evidence of CNS metastesis on magnetic resonance imaging of the brain obtained at baseline
- Previous therapy with a CDK 4/6 inhibitor

- Treatment with a drug without regulatory approval for any indication within 14 (non-myelosuppressive agent) or 21 (myelosuppressive agent) days of the initial dose of study drug.
- Personal history of syncope, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest
- A history of any other 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
- Had initiated approved bisphosphonates or approved RANK ligand targeted agents such as denosumab ≤28 days prior to Cycle 1, Day 1.

Reviewer Comments: *The Agency generally prefers that patients with stable CNS metasteses be included in clinical studies.*

<u>MONARCH 1 Objectives</u>

Primary Objective

- The primary objective is to evaluate abemaciclib with respect to ORR (complete response [CR] + partial response [PR]) based on tumor assessments and Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 in patients with HR+, HER2- MBC

Secondary Objectives

- Safety and tolerability of abemaciclib using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03
- Overall survival (OS)
- Progression-free survival (PFS)
- Disease control rate (DCR) (CR + PR + stable disease [SD])
- Clinical benefit rate (CBR) (CR + PR + SD ≥6 months)
- Impact on pain, disease symptoms, and overall quality of life using the modified Brief Pain Inventory-Short Form (mBPI-sf) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
- Pharmacokinetics of abemaciclib and its metabolites

Exploratory Objectives

- To explore biomarkers, including, but not limited to, those related to the Rb pathway, CDK 4 and 6, cell cycle, and/or the pathogenesis of breast cancer

Dosing of abemaciclib was 200 mg by mouth every 12 hours based on data from the JPBA study which was a dose escalation study of abemaciclib in patients with advanced cancer. In this study, the MTD was established as 200 mg every 12 hours as 1 patient experienced a dose

limiting toxicity of grade 3 fatigue at this dose with 2 patients with Grade 3 fatigue as a dose limiting toxicity at the 275 mg dose level. Safety review at this dose level demonstrated that the rate of Grade 1 diarrhea in this population was 30%, Grade 2 16%, and Grade 3 5%. The dose in this study was briefly reduced to 150 mg every 12 hours as there was evidence of antitumor activity at this dose level, however was increased to the MTD of 200 mg every 12 hours as diarrhea was found to be manageable with standard supportive therapy.

Dose reductions were outlined for three dose levels: the first to 150 mg every 12 hours, the second to 100 mg every 12 hours, and the third to 50 mg every 12 hours. Dose reduction and dose interruption guidelines were specified for diarrhea (grade 3-4 or requiring hospitalization), grade 3-4 non-hematological toxicities other than diarrhea, recurrent grade 3 hematological toxicity, and grade 4 hematological toxicity.

Reviewer Comments: *The trial design is acceptable given that there is no accepted standard of care for patients with metastatic HR-positive, HER2-negative for this line of therapy. Eribulin and capecitabine are both approved in this setting with ORRs of 12% and 25.6%. Capecitabine is the only oral chemotherapy available in this setting and most patients included in this study (55%) had already received this agent, making this agent an additional oral therapy option for patients with metastatic disease. While male patients are excluded, it is unclear that there would be any significant difference in efficacy between male and female patients as postmenopausal status was not required for female patients.*

Concomitant Radiotherapy or Surgery

Palliative radiation was not permitted without permanent discontinuation from study treatment. All patients other than locally advanced patients rendered operable by study treatment were required to discontinue from study treatment and have tumor assessment prior to receiving radiotherapy.

Dose Selection

The Applicant chose the abemaciclib dose regimen of 200 mg every 12 hours based on data from the JPBA study which was a dose escalation study of abemaciclib in patients with advanced cancer. The dose was chosen based on the safety, clinical activity, PK and pharmacodynamics data in patients with advanced cancer enrolled in this study. The maximum tolerated dose established in this study was 200 mg twice daily.

Based on an interim safety analysis of this study, diarrhea was the most frequently observed toxicity with 29 of 56 patients experiencing this, including 17 Grade 1 events, 9 Grade 2 events, and 3 Grade 3 events. Given this, along with data that demonstrated activity at doses of 150 mg every 12 hours, the initial starting dose in the expansion phase was reduced to 150 mg

Q12H. However, it was returned to 200 mg Q12H after the diarrhea was found to be manageable with standard supportive therapy.

For patients with HR+ in the expansion cohort of JPBA, the confirmed ORR was 33.3% and estimated median PFS was 8.8 months. Based on these data, the dose of 200 mg Q12H was chosen for this study.

Reviewer Comments: *Based on the improvement in ORR seen with higher dosing as well as the improvement in diarrhea related symptoms with standard supportive therapy, the 200 mg BID dose in the MONARCH 1 study of abemaciclib as a single agent appears appropriate. Based on the increased incidence and severity of diarrhea observed at higher doses, we have modified labeling to reflect the importance of patients and prescribers actively managing this adverse event.*

Study Treatments

- Abemaciclib 200 mg orally every 12 (± 2) hours on Days 1-28 of a 28 day cycle

Abemabciclib was supplied as capsules for oral administration and the capsule strength was 50 mg per capsule.

Reviewer's Comment: *The dose and schedule of abemaciclib is appropriate.*

Assignment to Treatment

Patients who met study eligibility criteria were assigned to receive abemaciclib in this study. An identification code was assigned by the investigator to each patient to protect the patient's identity.

Reviewer Comments: *This is appropriate for a single arm, open label study.*

Blinding

Not applicable.

Dose Modifications

Dose adjustments and delays for toxicity were recommended while the patient was felt to continue to receive clinical benefit from the therapy. For patients who required a dose reduction, increase to a previous dose level was permitted only after consultation with the Applicant. If a patient required >25% of doses to be omitted during a cycle due to tolerability,

the patient could have continued treatment as long as the investigator determined that the patient was receiving clinical benefit.

Table 17. Abemaciclib Dose Levels

Dose Adjustment	Oral Dose	Frequency
0	200 mg	Q12H
1	150 mg	Q12H
2	100 mg	Q12H
3	50 mg	Q12H

Source: MONARCH 1 CSR, page 34

The pre-specified dose reductions for treatment associated toxicities are demonstrated in Table 18 below.

Table 18 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 1 CSR page 33

Administrative Structure

Safety analyses were conducted every 6 months by the study team including the study statistician, Clinical Research Scientist/CRP, Global Patient Safety physician, and Medical Director.

Blinded independent central review (BICR) of the primary endpoint was performed as an auditing tool to corroborate the results of the ORR analysis and assist in the evaluation of 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 outcome assessment including PROs
- Archived tumor sample where available

On Treatment Visits
- Laboratory assessments
- Physical Examination
- Concomitant medications
- Tumor assessment (every second cycle beginning with cycle 3)
- ECG
- Adverse event analysis
- Health outcome assessment including PROs
- PK analysis
- Exploratory Pharmacogenetic blood sample
- Survival information

Follow-up
- Data on adverse events were collected at the short term follow up visit (approximately 30 days after study therapy discontinuation)
- SAEs attributed to study drug or protocol procedures were evaluated during long term follow up
- Long term follow-up within 90 days for survival information

The schedule of activities is shown in Table below.

Table 19 MONARCH 1 Study Assessments

Baseline Assessments

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤7	Comments
Informed Consent	X			Informed consent form signed (prior to performance of any protocol-specific tests/procedures)
Radiological Tumor Assessment	X			Imaging studies (CT or MRI scan of the chest, abdomen, and pelvis) are performed locally (Day -28 to Day -1) at baseline. It is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast, whenever possible. If this is not feasible/advisable secondary to hypersensitivity or other conditions, then gadolinium enhanced MRI is preferred. For patients with known serious allergic reactions to CT contrast material, a CT of the chest without contrast and contrast-enhanced MRI of the abdomen/pelvis are encouraged.
Bone Scintigraphy (preferred) or PET Scan or PET component of PET/CT Scan	X			One of these studies (bone scintigraphy [preferred], PET scan, or PET component of PET/CT scan) is performed locally (Day -28 to Day -1) at baseline. (An available prior Bone Scintigraphy or PET scan obtained within 45 days before Cycle 1 Day 1 is acceptable.)
X-ray or CT scan with bone windows or MRI	X			Required only for patients with nonmeasurable bone disease. One or more of these studies (X-ray, CT scan with bone windows, or MRI) is performed locally (Day -28 to Day -1) at baseline to characterize all bone lesions identified by bone scintigraphy, PET scan, or PET component of PET/CT scan.
MRI of Brain	X			Required for all patients. Performed locally (Day -28 to Day -1) at baseline.
Medical History		X		Including alcohol/tobacco use and other relevant habits assessments
Physical Exam, Vital Signs, Height, and Weight		X		Vital signs include temperature, blood pressure, pulse rate, and respiration rate.
Performance Status		X		ECOG
ECG		X		Central ECG with 3 replicates should be obtained at baseline (Day -14 to Day -1)
Hematology		X		Central Lab Sample collected. Although local sample results can be used for clinical management, a central sample must still be submitted.
Serum Chemistry		X		Central lab sample collected. Although local sample results can be used for clinical management, a central sample must still be submitted.
Tumor Measurement (Palpable or Visible)		X		

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤7	Comments
CTCAE v 4.0 Grading (Preexisting conditions)		X		To be reported only after study eligibility is confirmed. See Section 12.2.11 for reporting expectations.
Concomitant Meds		X		
Archived Tumor Samples		X		Formalin-fixed paraffin-embedded tumor must be requested after study eligibility is confirmed. The absence of an available specimen of the patient's tumor does not constitute a protocol deviation.
Pregnancy Test			X	Females with child bearing potential must have a negative serum pregnancy test within 7 days of the first dose of study drug (that is, Day -7 to Day -1).
mBPI-sf and EORTC QLQ-30		X		Patient completes prior to extensive interaction at site.

Abbreviations: CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; IV = intravenous; mBPI-sf = modified Brief Pain Inventory-Short Form; Meds = medications; MRI = magnetic resonance imaging; PET = positron emission tomography.

Assessments During Treatment and the Post-Study Treatment Discontinuation Period

	Cycle 1		Cycle 2-N	Post Discontinuation Follow-Ups		Comments
				Short Term[a]	Long Term[d]	
Relative Day Within a Cycle	1	15	1			
Abemaciclib	X	X	X			Abemaciclib is taken every 12 (± 2) hours on Days 1 through 28 of each cycle. Patients should not consume food beginning 1 hour before and ending 1 hour after taking study drug.
Physical Exam, Vital Signs, and Weight	X	X	X	X		Vital signs include temperature, blood pressure, pulse rate, and respiration rate
ECG	X	X	X	X		Central ECG with 3 replicates should be obtained at the following times: 4-6 hrs after abemaciclib dose on C1D1, upon arrival at site on C1D15, 3 ± 0.5 hrs after abemaciclib dose on C2D1, on D1 of every cycle thereafter, and at the short-term postdiscontinuation visit.
Hematology	X	X	X	X		Central lab sample collected (within 3 days prior). Although local sample results can be used for clinical management, a central sample must still be submitted
Serum Chemistry	X	X	X	X		Central lab sample collected (within 3 days prior). Although local sample results can be used for clinical management, a central sample must still be submitted.
Stored DNA Genotyping Blood Sample	X					
CTCAE v 4.0 Grading	X	X	X	X	X	Throughout study as needed. All drug- or procedure-related AEs and SAEs should be followed until they resolve, are no longer considered to be drug- or procedure-related, become stable or return to baseline, the patient starts a new therapy, the patient dies, or the patient becomes lost to follow-up. Refer to Section 12.2.11 for reporting guidelines.
Concomitant Meds	X	X	X	X		Throughout study as needed

	Cycle 1		Cycle 2-N	Post Discontinuation Follow-Ups		Comments
				Short Term[a]	Long Term[d]	
Relative Day Within a Cycle	1	15	1			
ECOG PS	X	X	X	X		
PK Sampling	X	X	X			Refer to Attachment 7 for PK sampling schedule.
Survival Information	X	X	X	X	x	
Tumor Measurement (Palpable or Visible)	X		X	X		
Radiological Tumor Assessment			X			Imaging studies (CT or MRI scan of the chest, abdomen, and pelvis) are performed locally on Day 1 (within 7 days prior to beginning of cycle) of every other cycle beginning with Cycle 3. It is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast, whenever possible. If this is not feasible/advisable secondary to hypersensitivity or other conditions, then gadolinium enhanced MRI is preferred. For patients with known serious allergic reactions to CT contrast material, a CT of the chest without contrast and contrast-enhanced MRI of the abdomen/pelvis are encouraged.
Bone Scintigraphy (preferred) or PET Scan or PET component of PET/CT Scan			X			Additional postbaseline bone scintigraphy or PET, if clinically indicated
X-ray or CT scan with bone windows or MRI			X			Required only for patients with nonmeasurable bone disease. One or more of these studies (X-ray, CT scan with bone windows, or MRI), identical to the study obtained at baseline, is performed locally on Day 1 of every other cycle beginning with Cycle 3, to monitor all nonmeasurable bone lesions identified by bone scintigraphy, PET scan, or PET component of PET/CT scan.

	Cycle 1		Cycle 2-N	Post Discontinuation Follow-Ups		Comments
				Short Term[a]	Long Term[d]	
Relative Day Within a Cycle	1	15	1			
mBPI-sf, EORTC QLQ-30	X	X	X	X		Collect at each visit and follow-up period when patient is at clinic for labs, tumor assessments, etc.
Tumor Markers, if applicable			X	X		Record results for any previously tested clinical tumor markers in eCRF.
Exploratory Pharmaco-genomic Blood Sample	X[b]	X		X[c]		
Additional Tissue Sample, if applicable	X					If a patient participating in this study elects to have a surgical procedure that involves removal of tumor, then FFPE tumor from that procedure may also be requested.

Abbreviations: AE = adverse event; BP = blood pressure; BSA = body surface area; C = cycle; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FFPE = formalin-fixed, paraffin-embedded; HR = heart rate; hrs = hours; mBPI-sf = modified Brief Pain Inventory-Short Form; Meds = medications; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography; PK = pharmacokinetic; PR = pulse rate; RR= respiration rate; SAE = serious adverse event.

[a] Follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days.

[b] Collect sample prior to drug administration.

[c] Collect sample at time of discontinuation.

[d] Interval follow-up will be within 90 days.

Study Schedule for the extension period only, Protocol I3Y-MC-JPBN
Perform procedure as indicated.

			Patients on Study Treatment	Extension Period Follow-Up
		Cycle	2 – n	Follow-Up[a]
		Visit	501-5XX	901
		Duration (days)	28	30
		Relative day within a cycle	1	
Procedure Category	**Procedure**	**Protocol Reference**		
Adverse Events Collection/CTCAE Grading[b]		Section 10.3.1	X	X
Study Drug	Abemaciclib[c]	Section 9	X	
Serum Chemistry[d]		Attachment 2	X	
Hematology[d]		Attachment 2	X	

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; CT = computed tomography; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetics; SAEs = serious adverse events.

a The extension period begins after study completion and ends at the end of trial.

b Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly safety system.

c Abemaciclib is to be administered every 12 (± 2) hours on Days 1 through 28 of each cycle. Patients should not consume food beginning 1 hour before and ending hour after taking study drug.

d Central lab sample collected.

Note: Efficacy assessments will be done at the investigator's discretion based on the standard of care.

Source: MONARCH 1 CSR Appendix Protocol, pages 57-61

Statistical Analysis Plan

MONARCH 2 (I3Y-MC-JPBL)

The primary study objective for I3Y-MC-JPBL (MONARCH 2) is to compare abemaciclib plus fulvestrant versus placebo plus fulvestrant with respect to progression-free survival (PFS) as assessed by local investigator. To do this, the study initially enrolled two strata of patients based on previous treatment with endocrine therapy: endocrine therapy pretreated (EP) and endocrine naïve (ND) patients. The primary statistical analysis was planned to be performed on randomized patients within the EP stratum. The initial study protocol specified enrollment of 450 EP patients.

The initial statistical analysis plan (SAP) provided for a 2-look group-sequential design of the primary endpoint of investigator assessed PFS. There was one interim analysis and one final analysis for PFS in the EP patient population with the interim analysis planned after approximately 265 (70% of the 378 planned) investigator assessed PFS events have occurred. The final PFS analysis was to be performed after 378 PFS event occurred which corresponds to a 40% censoring rate given the anticipated 630 patients enrolled in the EP stratum. The cumulative 1-sided type I error rate of 0.025 will be maintained using a nominal alpha level of 0.00001 at the interim analysis with the remaining alpha being spent at the final analysis of PFS. Assuming a hazard ratio of 0.703, 378 events at the final PFS analysis gives approximately 90% statistical power to detect superiority of the abemaciclib plus fulvestrant arm over the placebo plus fulvestrant arm using a 1-sided log rank test and type I error of 0.025. If the true median PFS for the placebo plus fulvestrant arm is 6.5 months, then the HR of 0.703 would translate to an approximately 2.75 month (42%) improvement in median PFS for the abemaciclib plus fulvestrant arm with the additional assumption of exponential survival distribution.

Stratification factors for the primary and secondary analyses are:

- Visceral metastatic disease vs. bone only metastatic disease vs. other
- Primary vs. secondary endocrine resistance

The SAP for MONARCH 2 had four versions. Versions 2 through 4 were approved after the first patient was enrolled.

SAP version 2 was finalized on November 9, 2015 prior to the first interim analysis for efficacy and prior to sponsor unblinding. This version allowed for additional safety analyses based on the dose reduction of abemaciclib from 200 mg every 12 hours to 150 mg every 12 hours, modified the sample size and primary analysis population given the exclusion of endocrine naïve patients per Protocol Amendment (b) (March 30, 2015), and updated the interim analysis plan and analysis of OS based on Protocol Amendment (c) (October 27, 2015), which modified the statistical stopping boundary for the first interim analysis of efficacy corresponding to an HR of <0.56.

SAP version 2 amendment modified the study sample size of EP patients so as to include 450 EP patients who were initially treated at the 150 mg every 12 hour dosing. At the time of SAP version 2, there were 180 EP patients enrolled at the dose of 200 mg every 12 hours. Given this, the estimated final sample size of the EP stratum was 630 patients. Additionally, this version indicated that blinded independent central review will be performed on all patients rather than a random subset of patients allowing for a simpler analysis plan.

SAP version 3 was finalized on April 26, 2016 prior to interim analysis for efficacy and prior to sponsor unblinding. This version updated the interim analysis plan and analysis of OS based on Protocol Amendment (d) which modified the timing of the primary efficacy analysis to occur

earlier and removed the planned second interim analysis of efficacy based on the results of another CDK4 and CDK6 inhibitor demonstrating efficacy with fulvestrant.

Reviewer Comments: *The Applicant modified the study design based on Agency comments about the inclusion of endocrine naïve patients confounding results. Based on this cohort being a randomization stratification factor, there should not have been imbalance created by the removal of those patients. To determine what if any affect this had on study results, a sensitivity analysis was performed including these patients.*

MONARCH 1 (I3Y-MC-JPBN)

To evaluate the primary objective of MONARCH 1 which was to estimate the antitumor activity, as measured by tumor response rate, in patients with HR-positive, HER2-negative MBC, there was a planned enrollment of approximately 128 eligible patients. The study was designed to evaluate the null hypothesis (H_0) that the true response rate of abemaciclib was ≤15% versus the alternative hypothesis (H_a) that the true response rate was >15% using a binomial exact test. The H_0 was based on historical data to estimate the ORR for approved therapies in this setting. The final efficacy analysis of ORR was performed 12 months after the last patient had entered treatment. An interim efficacy analysis of the primary endpoint was planned and completed at 8 months after the last patient entered treatment. The 1-sided alpha spend was 0.000008 for the interim efficacy analysis and 0.024992 for the final efficacy analysis. Should exactly 128 patients enroll and 39 responses be observed at the interim which would correspond to an ORR of 30.5%, the H_0 would be rejected at a significance level of 0.000008. If exactly 128 patients enrolled and 28 responses were observed corresponding to an ORR of 21.9%, the H_0 would have been rejected at a significance level of 0.024992. Assuming a true response rate of 25%, this design provides 82% power at an overall 1-sided alpha level of 0.025.

Reviewer Comments: *The choice of response rate of 15% appears appropriate based on existing therapies. However, on review of existing therapies, it was noted that response rates ranged from 11-30%, though these agents were tested in various histological subtypes including HR positive and HR negative making the expected ORR of existing therapies in HR positive, HER2 negative patients who have received 1-2 previous chemotherapies in the metastatic setting more difficult to interpret. The use of a single arm trial with response rate was agreed upon with the agency given the lack of standard comparator in this setting. For a single arm study, efficacy based on ORR is supported by both the magnitude of ORR and a clinically meaningful duration of response.*

Protocol Amendments/Addenda

MONARCH 2 (I3Y-MC-JPBL)

The MONARCH 2 protocol was initially finalizedby the Applicant on April 1, 2014 and submitted to the Agency on April 3, 2014. It was amended four times. Amendment JPBL(a) was finalized by the Applicant on January 12, 2015 and submitted to the Agency on January 16, 2015and

modified the starting dose of study drug from abemaciclib 200 mg every 12 hours to 150 mg every 12 hours or placebo. Additionally this amendment mandated that those who were currently receiving 200 mg every 12 hours have a dose reduction to 150 mg every 12 hours. This was not due to safety signal but was rather due to evidence from patients in JPBA and JPBH that tolerability of treatment with abemaciclib concomitantly administered with endocrine therapy agents was improved at a reduced dose.

Amendment JPBL(b), finalized by the Applicant on March 30, 2015 and submitted to the Agency on April 3, 2015, removed the inclusion of endocrine therapy naïve patients, increased the sample size for endocrine therapy pretreated patients, and updated the statistical analysis plan to include interim analyses. Endocrine therapy pretreated patients were defined as those who had disease progression on or within 12 months of completing adjuvant endocrine therapy or patients who had progressed on or after first-line endocrine therapy for metastatic disease. Previously included endocrine therapy naïve patients were excluded from the primary ITT analysis. Note that the agency conducted a sensitivity analysis that included all randomized patients, and this exclusion has only a negligible difference when compared to the full ITT population. More details on this analysis can be found later.

Amendment JPBL(c), finalized by the Applicant on October 27, 2015 and submitted to the Agency on November 9, 2015, updated guidance for dose adjustments in the setting of hematologic toxicity and diarrhea as well as guidance for the use of blood cell growth factors. Additionally, it modified the statistical stopping boundary for the first interim analysis of efficacy corresponding to an HR of <0.56.

Amendment JPBL(d), finalized by the Applicant and submitted to the Agency on April 26, 2016, removed the second planned interim analysis of efficacy and changed the primary efficacy analysis to occur earlier given Phase 3 study results of fulvestrant in combination with another CDK 4/6 inhibitor.

Reviewer Comments: *Protocol Amendment A for the MONARCH 2 study reduced the dose of abemaciclib from 200 mg Q12H to 150 mg Q12H based on lack of tolerability observed in the JPBH study evaluating the combination of non-steroidal aromatase inhibitors and abemaciclib. At the time of the protocol amendment, 178 patients were enrolled with 121 randomized to the abemaciclib arm. Over half of those patients had a dose reduction due to an AE (56.2%) and 24% of these patients discontinued. Efficacy evaluations of the preamendment and postamendment populations were consistent. Safety evaluations demonstrated a higher incidence of diarrhea and other gastrointestinal toxicities and an increased incidence of neutropenia.*

Since the exclusion of randomized endocrine therapy patients has only a negligible effect on the primary analysis results, the exclusion does not appear to introduce bias.

MONARCH 1 (I3Y-MC-JPBN)

The MONARCH 1 protocol was amended twice and there were two protocol addenda. The initial protocol was submitted to the Agency on April 3, 2014. Protocol Amendment JPBN(a) was finalizedby the Applicant on March 26, 2015 and submitted to the Agency on March 30, 2015. Protocol Amendment JPBN(a) included modification of the planned interim analysis and statistical methods in the synopsis to include interim efficacy analysis information and to change the final efficacy analysis of ORR from 8 months to 12 months after the last patient has entered treatment and the efficacy analysis of ORR at 8 months was considered an interim efficacy analysis. The rationale for changing the time of the ORR analysis was to allow for adequate response data and to ensure that there were adequate data regarding the durability of response available for analysis while the interim efficacy analysis at 8 months allowed for an earlier assessment of efficacy.
Additional changes includedmodification of statistical sections for clarity, addition of interim efficacy analysis information, and clarification of the final analysis, addition of Attachment 9 for supportive management for diarrhea, updating of the language and assessments used for the analysis of health outcomes, and the addition of windows for laboratory measurements and scans so that labs could be collected within 3 days of the cycle and imaging could occur within 7 days prior to the start of the next cycle.

Protocol Amendment JPBN(b) was finalized by the Applicant on October 16, 2015 and submitted to the Agency on October 21, 2015. This amendment updated the dosing guidance for cases of hematological toxicity and diarrhea and standardized guidance for the use of blood cell growth factors consistent with ASCO guidelines. Additionally, it incorporated standard dose adjustments and delays for toxicity, clarifying the dose suspension and dose reduction associated with Grade 3 hematologic toxicity and growth-factor administration and dose reduction in the setting of recurrent diarrhea.

Additionally there were two protocol addenda, the firstfinalized by the Applicant on June 23, 2014 to clarify the need for use of reliable contraception and inclusion of additional pregnancy tests based on nonclinical study findings. The second was submitted on July 8, 2014 and was an assessment of abemaciclib and its metabolites on the activity of CYP3A by measuring endogenous renal cortisol 6b-hydroxylation clearance. This analysis was not conducted due to insufficient sample collection. Both addenda were submitted to the agency on July 15, 2014.

Reviewer Comments: *The protocol amendments are not thought to have a significant impact on interpreting the primary efficacy result of ORR in the MONARCH 1 study.*

The submission contains all required components of the eCTD. The overall quality and integrity of the application appear acceptable. Requests for additional information from the Applicant were addressed in a timely fashion.

The Applicant additionally indicated that to ensure data quality that they provided instructional

materials and training sessions, monitored study sites, reviewed and conducted data quality reviews and audits.

7.2.3. Study Results

Compliance with Good Clinical Practices
According to the Applicant, both MONARCH 2 (I3Y-MC-JPBL) and MONARCH 1 (I3Y-MC-JPBN) 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 2 (I3Y-MC-JPBL) and MONARCH 1 (I3Y-MC-JPBN) studies. Of the 1615 investigators listed for the MONARCH 2 study, certification was provided by 1615. Of the 554 investigators listed for the MONARCH 1 study, certification was provided by 551.

Study I3Y-MC-JBPL (MONARCH 2) included 165 principle investigators and 1450 subinvestigators. Study I3Y-MC-JPBN (MONARCH 1) included 36 principle investigators and 518 subinvestigators. One had financial information to disclose and this information is summarized in the table below (Table 20).

Table 20. Summary of Financial Disclosures for MONARCH 2

Clinical Site Number	Investigator Name (PI or SI)	Study I3Y-MC-JBPL Patient Enrollment at Site	Disclosure
(b) (6)		(b) (4)	$29,108.28

Reviewer Comments: *There was only one investigator with a significantly disclosable financial interest reported. There were two study participants enrolled at that site making up 0.3% of the total study population. This is not likely to affect the results of the study.*

Patient Disposition

MONARCH 2 (I3Y-MC-JPBL)
A total of 855 patients were consented for the MONARCH 2 study at 145 sites in 19 countries. Of these patients, 142 patients were not randomized and 44 patients were enrolled into the endocrine therapy naïve population per the interactive web response system (IWRS).

From August 7, 2014, to December 29, 2015, a total of endocrine pretreated 669 patients were enrolled and randomized. Four hundred forty six patients were randomized to receive abemaciclib plus fulvestrant, of whom 441 were treated, while 223 patients were randomized to and received placebo plus fulvestrant.

At the time of the primary analysis of PFS with a data cutoff of February 14, 2017, 271 (60.8%) patients in the abemaciclib plus fulvestrant arm and 178 (79.8%) patients in the placebo plus fulvestrant arm had discontinuted study treatment. Table 21 below summarizes the patient disposition for MONARCH 2.

Table 21. MONARCH 2 Patient Disposition as of February 14, 2017

	Abemaciclib plus Fulvestrant N (%)	Placebo plus Fulvestrant N (%)	Total N (%)
Endocrine therapy pretreated patients randomized to study treatment	446 (66.7)	223 (33.3)	669 (100)
Randomized and not treated	5 (0.7)	0	5 (0.7)
Randomized and treated	441 (65.9)	223 (33.3)	664 (99.3)
Discontinued	271 (40.5)	178 (26.6)	449 (67.1)
Discontinued abema/placebo	35 (5.2)	1 (0.1)	36 (5.4)
Ongoing at cutoff date	170 (25.4)	45 (6.7)	215 (32.1)
Reason for discontinuation			
Progressive disease	195 (29.1)	156 (23.3)	351 (52.5)
Adverse event[a]	64 (9.6)	6 (0.9)	70 (10.5)
Patient withdrawal	23 (3.4)	9 (1.3)	32 (4.8)
Physician decision	10 (1.5)	4 (0.6)	14 (2.1)
Death	7 (1.0)	2 (0.3)	9 (1.3)
Noncompliance with study drug	4 (0.6)	0	4 (0.6)
Protocol violation	1 (0.1)	0	1 (0.1)
Other[a]	2 (0.3)	1 (0.1)	3 (0.4)

[a] Included in the reason for discontinuation for the EP population are the reasons for discontinuation of study drug for the 36 patients who discontinued study drug/placebo but continued on fulvestrant. Thirty-three patients discontinued due to adverse effects while one patient discontinued study drug based on their decision. Three patients discontinued study drug/placebo for the reason "Other" which was not further specified.

Source: Modified from Figure JPBL.10.1 in the MONARCH 2 I3Y-MC-JPBL CSR on page 83, Table JPBL.10.1 on page 18 of the CSR Addendum for Endocrine Therapy-Naïve Advanced Breast Cancer and from analysis using adsl.xpt and adds.xpt

Reviewer Comments: *It is noted that more patients in the abemaciclib plus fulvestrant arm discontinued study treatment due to adverse events. Based on the protocol, patients were allowed to continue on fulvestrant in the setting of abemaciclib discontinuation. There were a numerically greater number of patient deaths in the abemaciclib plus fulvestrant arm as well which will be discussed further in the safety portion of this review. At the time of the 90 day safety update which is through May 5, 2017, an additional 19 patients had discontinued therapy on the abemaciclib plus fulvestrant arm with 16 discontinuing due to progressive disease, 1 patient withdrawal, 1 lost to follow up and 1 patient death. Eight additional patients had discontinued from the placebo plus fulvestrant arm, all due to progressive disease.*

MONARCH 1 (I3Y-MC-JPBN)

From June 10, 2014, to April 30, 2015, a total of 184 patients were consented for participation at 35 sites in 4 countries. Of these patients, 52 patients did not receive study treatment. One hundred thirty two patients were enrolled and received at least one dose of study treatment.

At the time of data cut off for the final analysis of the primary endpoint, April 30, 2016, 119 (90.2%) had discontinued treatment. Table 22 below summarizes the patient disposition for MONARCH 1.

Table 22. MONARCH 1 Study Disposition as of April 30, 2016

	Abemaciclib 200 mg N=132 n (%)
Enrolled, but never treated	0
Treated	132 (100)
On treatment	13 (9.8)
Off treatment	119 (90.2)
Reason treatment discontinued	
Progressive disease	100 (75.8)
Adverse event	10 (7.6)
Withdrawal by patient	4 (3.0)
Death	2 (1.5)
Noncompliance with study drug	2 (1.5)
Physician decision	1 (0.8)
On post-treatment discontinuation follow-up	70 (53.0)
Continue with protocol procedures	9 (6.8)
Continue only for survival status	57 (43.2)
In short-term follow up	4 (3.0)
Off post-treatment discontinuation follow up	49 (37.1)
Reasons for end of postdiscontinuation follow-up	
Death	45 (34.1)
Lost to follow up	3 (2.3)
Withdrawal by patient	1 (0.8)

Source: MONARCH 1 CSR page 63. Reviewer analysis using adds.xpt

Reviewer Comments: *Most patients on the MONARCH 1 study discontinued study therapy due to progressive disease. There were a similar proportion of patients who discontinued due to adverse event. This suggests that this therapy is reasonably tolerable in a pretreated patient population.*

Protocol Violations/Deviations

MONARCH 2 (I3Y-MC-JPBL)

In the MONARCH 2 study, a total of 349 (80.5%) patients in the abemaciclib plus fulvestrant arm and 181 (81.2%) patients had one or more major protocol deviations. Table 23 below demonstrates incidence of major protocol deviations by type inthe intention to treat population.

Table 23 Major Protocol Deviations in the MONARCH 2 ITT Population

Deviation Category	Abemaciclib N=446 n (%)	Placebo N=223 n (%)	Total N=669 n (%)
Patients with ≥1 major protocol deviation	359 (80.5)	181 (81.2)	540 (80.7)
Key measurements not collected properly	235 (52.7)	114 (51.1)	349 (52.2)
Incorrect stratification factors for IWRS	164 (36.8)	83 (37.2)	247 (36.9)
Inclusion/Exclusion criteria not met	73 (16.4)	38 (17.0)	111 (16.6)
Improper treatment discontinuation	46 (10.3)	37 (16.6)	83 (12.4)
Improper administration of informed consent	55 (12.3)	21 (9.4)	76 (11.4)
Incorrect dose adjustments	33 (7.4)	9 (4.0)	42 (6.3)
Inappropriate handling of the investigational product	24 (5.4)	12 (5.4)	36 (5.4)
Other	12 (2.7)	5 (2.2)	17 (2.5)
Use of prohibited concomitant medications	2 (0.4)	2 (0.9)	4 (0.6)

Source MONARCH 2 CSR, page 85 with additional review of Table JPBL.14.2

Reviewer Comments: *There were multiple major protocol deviations. Most of the key measurement deviations were that the post-baseline tumor assessments were performed outside of the window. While the incidence was similar across treatment arms, there were a proportionally greater number of patients in the abemaciclib plus fulvestrant arm (33% vs. 28%) who had evaluations outside of the window. The incidence of incorrect stratification factors was similar across both treatment arms and incorrect inclusion exclusion criteria were similar across treatment arms. Proportionally greater numbers of patients continued on the placebo plus fulvestrant arm for ≥10 days post progression than did on the abemaciclib arm (16% vs. 10%). Overall, the incidence of protocol deviations was similar across treatment arms and is not thought to have a significant impact on interpreting the primary endpoint.*

MONARCH 1 (I3Y-MC-JPBN)

In the MONARCH 1 study, a total of 87 patients (65.9%) had a protocol deviation. Major protocol deviations occurred in Major protocol deviations occurred with respect to study eligibility criteria, study drug administration/treatment, issues with key measurement

collection, and submission of AEs. The major protocol deviations in this study are listed in Table 24 below.

Table 24 MONARCH 1 Protocol Deviations

Deviation	Abemaciclib 200 mg N=132 n (%)
Patients with ≥1 major protocol deviation	22 (16.7)
Improper treatment discontinuation	7 (5.3)
Inclusion/exclusion criteria not met	5 (3.8)
Key measurement not collected properly	8 (6.1)
Noncompliance with study regimen	1 (0.8)
Late submission of SAE	1 (0.8)
Study therapy dispensed without lab results	2 (1.5)

Source: MONARCH 1 CSR page 65, table modified by Reviewer

Reviewer Comments: *The major protocol deviations were low in this study, likely due to the single arm design, small sample size, and small number of study sites. Two patients had the imaging modality changed during the course of the study though this is not likely to have had a significant impact on study results.*

Table of Demographic Characteristics

MONARCH 2

Demographic data for the intention to treat population for the MONARCH 2 study are included below inTable 25.

Table 25. MONARCH 2 Demographic Data

	Abemaciclib plus Fulvestrant N=446 n (%)	Placebo plus Fulvestrant N=223 n (%)	Total N=669 n (%)
Sex			
Female	446 (66.7)	223 (33.3)	669 (100)
Age			
Median (range)	59 (32-91)	62 (32-87)	60 (32-91)
Age <65 years	291 (65.2)	133 (59.6)	424 (63.4)
Age 65-74 years	114 (25.6)	60 (26.9)	174 (26.0)
Age ≥75 and <85 years	38 (8.5)	28 (12.6)	66 (9.9)
Age ≥85 years	3 (0.7)	2 (0.9)	5 (0.7)
Race			
White	237 (53.1)	136 (61.0)	373 (55.8)
Black or African-American	9 (2.0)	5 (2.2)	214 (32.0)
American Indian or Alaska Native	18 (4.0)	8 (3.6)	26 (3.9)
Asian	149 (33.4)	65 (29.1)	214 (32.0)
Multiple	2 (0.5)	0	2 (0.3)
Missing	31 (7.0)	9 (4.0)	40 (6.0)
ECOG			
0	264 (59.2)	136 (61.0)	400 (59.8)
1	176 (39.5)	87 (39.0)	263 (39.3)
2	1 (0.2)	0	1 (0.1)
Missing	5 (1.1)	0	5 (0.7)
Geographic Region			
US (inc PR)	83 (18.6)	42 (18.8)	125 (18.7)
Canada	10 (2.2)	4 (1.8)	14 (2.1)
Mexico	27 (6.1)	12 (5.4)	39 (5.8)
Europe	179 (40.1)	100 (44.8)	279 (41.7)
Asia	147 (33.0)	65 (29.1)	212 (31.7)
Menopausal Status			
Postmenopausal	371 (83.2)	180 (80.7)	551 (82.4)
Natural	197 (66.6)	148 (66.4)	445 (66.5)
Surgical	74 (16.6)	32 (14.3)	106 (15.8)
Pre/peri (on ovarian suppression)	72 (16.1)	42 (18.8)	114 (17.0)
Missing	3 (0.7)	1 (0.4)	4 (0.6)

Source: MONARCH 2 CSR page 88 and Reviewer analysis using adsl.xpt dataset

Reviewer Comments: *The treatment arms were relatively balanced across various demographic groups. Notably, there were proportionately more patients older than age 75 in the placebo plus fulvestrant arm as compared to the abemaciclib plus fulvestrant arm. Patients over the age of 65 were generally well represented in this trial, though the numbers decrease when older than 75. This was an international study with most patients recruited in Europe and Asia. The largest racial subgroup included was Asian. Small numbers of Black or African-American patients were included in this trial as has been seen in other trials. Missing data for race is primarily due to patients from France who participated given that France does not report race reporting.*

MONARCH 1

Demographic data for the MONARCH 1 study are included in Table below.

Table 26. MONARCH 1 Demographic Data

	Abemaciclib 200 mg **N=132** **n, %**
Sex	
Female	132, 100%
Age	
Median (Range)	58 (36-89)
Age <65 years	90, 68.2%
Age 65-74 years	32, 24.2%
Age ≥75 years	10, 7.8%
Race	
White	112, 84.8%
Black or African-American	6, 4.5%
Asian	2, 1.5%
Missing	12, 9.1%
ECOG	
0	73, 55.3%
1	59, 44.7%
Geographic Region	
US	70, 53.0%
Europe (Belgium, Spain, France)	62, 47.0%

Source: MONARCH 1 CSR page 67 and Reviewer analysis using adsl.xpt dataset

Reviewer Comments: *This was a small study conducted in the US and Europe. Most patients were Caucasian and there were few Asian patients in this study. Numbers of Black or African-American patients were low as well. Reasons for missing data include that France does not allow for race reporting.*

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

MONARCH 2 (I3Y-MC-JPBL)

Disease characteristics for patients in the ITT population in the MONARCH 2 study are included in Table 27 below.

Table 27. MONARCH 2 Baseline Disease Characteristics

Pretreatment Disease Characteristic	Abemaciclib (n=446) n (%)	Placebo (n=223) n (%)	Total (n=669) n (%)
Duration of disease in months			
Mean (Std Dev)	77.8 (68.7)	81.5 (72.6)	79.0 (70.0)
Median (Q1-Q3)	61.3 (27.3, 109.3)	59.8 (27.1, 110.0)	61.0 (27.1, 109.5)
Min, Max	0.4, 447.4	1.5, 354.7	0.4, 447.4
Initial Stage at diagnosis			
Stage 0	5 (1.1)	1 (0.4)	6 (0.9)
Stage I	52 (11.6)	24 (10.8)	76 (11.3)
Stage II	167 (37.5)	94 (42.1)	261 (39.0)
Stage III	113 (25.4)	51 (22.9)	164 (24.5)
Stage IV	86 (19.3)	45 (20.2)	131 (19.6)
Missing	13 (2.9)	2 (0.9)	15 (2.2)
Study Entry Disease Stage			
Recurrent locally advanced	16 (3.6)	2 (0.9)	18 (2.7)
Metastatic	427 (95.7)	221 (99.1)	648 (96.9)
Unknown	3 (0.7)	0	3 (0.4)
Histology at diagnosis			
Invasive ductal carcinoma	306 (68.6)	160 (71.7)	466 (69.7)
Invasive lobular carcinoma	58 (13.0)	17 (7.6)	75 (11.2)
Other	69 (15.5)	44 (19.7)	113 (16.9)
Missing	13 (2.9)	2 (0.9)	15 (2.2)
Grade at Initial Diagnosis			
GX	95 (21.3)	49 (22.0)	144 (21.5)
G1	38 (8.5)	19 (8.5)	57 (8.5)
G2	188 (42.2)	94 (42.2)	282 (42.2)
G3	100 (22.4)	53 (23.8)	153 (22.9)
Missing	25 (5.6)	8 (3.6)	33 (4.9)
Endocrine therapy sensitivity			
No prior endocrine therapy	6 (1.3)	2 (0.9)	8 (1.2)
Primary resistance	111 (24.9)	58 (26.0)	169 (25.3)

Secondary resistance	326 (73.1)	163 (72.1)	489 (73.1)
Missing	3 (0.7)	0	3 (0.5)
Nature of disease			
Visceral	245 (54.9)	128 (57.4)	373 (55.8)
Bone only	123 (27.6)	57 (25.6)	180 (26.9)
Other	75 (16.8)	38 (17.0)	113 (16.9)
Missing	3 (0.7)	0	3 (0.4)
Measurable disease			
Yes	318 (71.3)	164 (73.5)	482 (72.0)
No	128 (28.7)	59 (26.5)	187 (28.0)

Source, Adapted from MONARCH 2 CSR page 90, 92.

Hormone receptor status for patients included in the MONARCH 2 ITT population is in Table 28 below.

Table 28. MONARCH 2 ITT Population Hormone Receptor Status

Receptor Status	Abemaciclib N=446 n (%)	Placebo N=223 n (%)	Total N=669 n (%)
Hormone receptor positive	443 (99.3)	223 (100.0)	666 (99.6)
ER+/PgR+	333 (74.7)	169 (75.8)	502 (75.0)
ER+/PgR-	96 (21.5)	44 (19.7)	140 (20.9)
ER+/PgR unknown	8 (1.8)	8 (3.6)	16 (2.4)
Missing	3 (0.7)	0	3 (0.4)
HER2 Status			
Negative	443 (99.3)	221 (99.1)	664 (99.3)
Missing	3 (0.7)	2 (0.9)	5 (0.7)

Source, MONARCH 2 CSR page 91

Table 29 below is a summary of the preexisting conditions in ≥10% of Patients in the Safety Population of MONARCH 2

Table 29. Summary of Preexisting Conditions in 10% or more of Patients in the MONARCH 2 Safety Population

	Abemaciclib N=441 n (%)	**Placebo N=223 n (%)**	**Total N=664 n (%)**
Patients with ≥ 1 preexisting condition	414 (93.9)	209 (93.7)	623 (93.8)
Musculoskeletal and connective tissue disorders	200 (45.4)	100 (44.8)	200 (45.2)
Back pain	54 (12.2)	28 (12.6)	82 (12.3)
Osteoporosis	48 (10.9)	21 (9.4)	69 (10.4)
Vascular disorders	198 (44.9)	114 (51.1)	312 (47.0)
Hypertension	159 (36.1)	98 (43.9)	257 (38.7)
Social Circumstances	193 (43.8)	97 (43.5)	289 (43.5)
Menopause	193 (43.8)	96 (43.0)	289 (43.5)
Metabolism and nutrition disorders	119 (27.0)	66 (29.6)	185 (27.9)
Hypercholesterolemia	62 (14.1)	29 (13.0)	91 (13.7)
Psychiatric disorders	108 (24.5)	61 (28.3)	171 (25.8)
Insomnia	54 (12.2)	31 (13.9)	85 (12.8)
Anxiety	41 (9.3)	26 (11.7)	67 (10.1)
General disorders and administration site conditions	84 (19.0)	42 (18.8)	126 (19.0)
Fatigue	46 (10.4)	29 (13.0)	75 (11.3)
Patients with ≥1 preexisting pain condition	197 (44.7)	94 (42.2)	291 (43.8)

Source: Adapted from MONARCH 2 CSR, page 95-96

Stratification Factors

In the MONARCH 2 study, patients were stratified by endocrine therapy status (naïve vs. pretreated), nature of disease (visceral vs. bone only vs. other), and endocrine therapy resistance status (primary resistance vs. secondary resistance). As discussed previously, after Protocol Amendment (B), patients who were endocrine therapy naïve were no longer enrolled and not included in the ITT population. Stratification factors were well balanced between treatment arms as seen below in Table 30.

Table 30. Stratification Factors for MONARCH 2

	Abemaciclib N=446 n (%)	Placebo N=223 n (%)	Total N=669 n (%)
Based on Randomization			
Nature of disease			
Visceral	256 (57.4)	128 (57.4)	384 (57.4)
Bone only	129 (28.9)	65 (29.2)	194 (29.0)
Other	61 (13.7)	30 (13.5)	91 (13.6)
Endocrine therapy			
Primary resistance	182 (40.8)	90 (40.4)	272 (40.7)
Secondary resistance	264 (59.2)	133 (59.6)	397 (59.3)
Based on CRF			
Nature of disease			
Visceral	245 (54.9)	128 (57.4)	373 (55.8)
Bone only	123 (27.6)	57 (25.6)	180 (26.9)
Other	75 (16.8)	38 (17.0)	113 (16.9)
Missing	3 (0.7)	0	3 (0.4)
Endocrine therapy			
No prior endocrine therapy	6 (1.3)	2 (0.9)	8 (1.2)
Primary resistance	111 (24.9)	58 (26.0)	169 (25.3)
Secondary resistance	326 (73.1)	163 (72.1)	489 (73.1)
Missing	3 (0.7)	0	3 (0.5)

Adapted from MONARCH 2 CSR, page 92 and 126

Reviewer Comments *As noted in the summary of protocol deviations and in* Table *above, there was a marked discrepancy between the randomization endocrine therapy sensitivity indication and the documented endocrine therapy sensitivity in the CRFs. Given this, an unstratified sensitivity analysis was performed to ensure that results were consistent and, as noted below, demonstrated consistent results in favor of the abemaciclib plus fulvestrant arm.*

Table 31 below summarizes post discontinuation therapies and procedures.

Table 31. MONARCH 2 Post-Treatment Discontinuation Therapies and Procedures

	Abemaciclib N=446 n (%)	Placebo N=223 n (%)	Total N=669 n (%)
Patients remaining on treatment	170 (38.1)	45 (20.2)	215 (32.1)
Patients off treatment as of 2/14/17	271 (60.8)	178 (79.8)	449 (67.1)
Systemic therapy			
Overall	200 (44.8)	141 (63.2)	341 (51.0)
Chemotherapy	138 (30.9)	97 (43.5)	235 (35.1)
Endocrine	110 (24.7)	77 (34.5)	187 (28.0)
Other	25 (5.6)	15 (6.7)	40 (6.0)
Targeted	65 (14.6)	54 (24.2)	119 (17.8)
First subsequent line			
Chemotherapy	109 (24.4)	74 (33.2)	183 (27.4)
Endocrine	89 (20.0)	66 (29.6)	155 (23.2)
Other	17 (3.8)	12 (5.4)	29 (4.3)
Targeted	51 (11.4)	39 (17.5)	90 (13.5)
Surgical procedure	14 (3.1)	3 (1.3)	17 (2.5)
Radiotherapy	37 (8.3)	26 (11.7)	63 (9.4)

Source: MONARCH 2 CSR page 119.

Reviewer Comments: *This table demonstrates the post-discontinuation therapies received by patients after discontinuing abemaciclib or placebo plus fulvestrant. More patients discontinued treatment in the placebo arm than did in the abemaciclib arm. For those that did discontinue therapy, 200/271 (73.8%) of the abemaciclib plus fulvestrant arm and 141/178 (79.2%) of the placebo plus fulvestrant arm went on to receive further systemic therapy. There was a numerically larger number of patients who went on to receive a surgical procedure in the abemaciclib plus fulvestrant arm which is consistent with the numerically higher difference in patients in this arm who had locally advanced disease.*

MONARCH 1 I3Y-MC-JPBN

Disease characteristics for patients in the enrolled population of the MONARCH 1 study are included in Table 32 below.

Table 32. MONARCH 1 Baseline Disease Characteristics

Characteristic		Abemaciclib 200 mg N=132 n(%)
Initial Disease Stage	Stage 0	1 (0.8)
	Stage I	21 (15.9)
	Stage II	53 (40.2)
	Stage III	28 (21.2)
	Stage IV	19 (14.4)
	Missing	10 (7.6)
Initial Pathological Diagnosis	Invasive Ductal Carcinoma	92 (69.7)
	Invasive Lobular Carcinoma	12 (9.1)
	Other	28 (21.2)
Initial Pathological Disease Grade	G1	9 (6.8)
	G2	64 (48.5)
	G3	34 (25.8)
	GX	22 (16.7)
	Missing	3 (2.3)
Study Entry Disease Stage	Stage IV	132 (100)
Study Entry Pathological Diagnosis	Invasive Ductal Carcinoma	65 (49.2)
	Adenocarcinoma, breast	23 (17.4)
	Other	44 (33.3)
Study Entry Disease Grade	G1	9 (6.8)
	G2	44 (33.3)
	G3	33 (25.0)
	GX	41 (31.1)
	Missing	5 (3.8)
Time from initial diagnosis to diagnosis of Stage IV disease (months)	Mean	72.8
	Median (range)	56.5 (0-301.3)
Duration of initial diagnosis (months)	Mean	113.9
	Median (range)	99.2 (13.3-414.0)
Duration of Stage IV disease (months)	Mean	41.9
	Median (range)	27.6 (0.1-228.9)
Baseline ECOG performance status	0	73 (55.3)
	1	59 (44.7)
Nature of Disease		
	Visceral disease	119 (90.2)
	Bone only disease	3 (2.3)
	Other	10 (7.6)
Disease Sites		
	Liver	93 (70.5)

	Bone	82 (62.1)
	Nodal	51 (38.6)
	Lung	31 (23.5)
	Pleura	21 (15.9)
	Peritoneum	9 (6.8)
	CNS (nonbrain)	2 (1.5)
	Brain	1 (0.8)
Organs involved		
	1 organ	24 (18.2)
	2 organs	59 (44.7)
	≥3 organs	49 (37.1)

Source MONARCH 1 CSR page 69-70 and reviewer analysis using adsl.xpt dataset

***Reviewer Comments**: The baseline disease characteristics for patients enrolled in the MONARCH 1 study was representative of patients with metastatic disease at this point in therapy, however the performance status was likely better than most patients in the general population as only patients with ECOG 0 or ECOG 1 performance status were included. Most patients had organ involvement suggesting that the study population was representative of patients known to have a poorer prognosis given the differing natural histories of visceral metastatic disease and bone only metastatic disease.*

Hormone receptor status for patients included in the MONARCH 1 enrolled population is in Table 33 below.

Table 33. MONARCH 1 Hormone Receptor Status

	Abemaciclib 200 mg N=132 n (%)
Hormone receptor positive	132 (100)
ER+/PgR+	94 (71.2)
ER+/PgR-	35 (26.5)
ER+/PgR unknown	2 (1.5)
Missing	1 (0.8)
HER2 Status	
Negative	132 (100)

Source MONARCH 1 CSR page 71

***Reviewer Comments:** These data demonstrate that the enrolled population reflects the intended population for evaluation: patients with hormone receptor-positive, HER2- negative disease.*

Preexisting medical conditions and diagnoses in the MONARCH 1 study population are described in Table 34 below.

Table 34. MONARCH 1 Preexisting Conditions

	Abemaciclib 200 mg N=132 n (%)
Patients with ≥1 pre-existing condition	123 (93.2)
Endocrine disorders	27 (20.5)
Hypothyroidism	25 (18.9)
Gastrointestinal disorders	54 (40.9)
Constipation	17 (12.9)
Gastroesophageal reflux disease	14 (10.6)
General disorders and administration site conditions	63 (47.7)
Fatigue	43 (32.6)
Pain	25 (18.9)
Metabolism and nutrition disorders	46 (34.8)
Hypercholesterolemia	24 (18.2)
Musculoskeletal and connective tissue disorder	68 (51.5)
Back pain	16 (12.1)
Bone pain	19 (14.4)
Osteoporosis	28 (21.2)
Nervous system disorders	44 (33.3)
Neuropathy	34 (25.8)
Psychiatric disorders	59 (44.7)
Anxiety	31 (23.5)
Depression	19 (14.4)
Insomnia	30 (22.7)
Respiratory, thoracic, and mediastinal disorders	44 (33.3)
Dyspnea	19 (14.4)
Vascular disorders	56 (42.4)
Hypertension	38 (28.8)
Patients with ≥1 Preexisting Pain Condition	68 (51.5)

Source adapted from MONARCH 1 CSR pages 73-74

Prior systemic therapies received by patients in the MONARCH 1 study are summarized in Table 35 below.

Table 35. MONARCH 1 Prior Therapy

	Abemaciclib 200 mg N=132 n (%)
Prior systemic therapy	132 (100)
Any intent	
1 regimen	0
2 regimens	7 (5.3)
3 regimens	20 (15.2)
≥4 regimens	105 (79.5)
Mean (std dev)	5.4 (1.95)
Median (min, max)	5 (2, 11)
Metastatic	
1 regimen	15 (11.4)
2 regimens	33 (25.0)
3 regimens	25 (18.9)
≥4 regimens	59 (44.7)
Mean (std dev)	3.4 (1.61)
Median (min, max)	3 (1, 9)
Prior endocrine therapy	132 (100)
Any intent	
1 regimen	20 (15.2)
2 regimens	34 (25.8)
3 regimens	34 (25.8)
≥4 regimens	44 (33.3)
Mean (std dev)	3.0 (1.41)
Median (min, max)	3 (1, 7)
Metastatic	115 (87.1)
1 regimen	48 (36.4)
2 regimens	25 (18.9)
3 regimens	24 (18.2)
≥4 regimens	18 (13.6)
Mean (std dev)	2.1 (1.22)
Median (min, max)	2 (1, 6)
Prior chemotherapy	132 (100)
Any intent	
1 regimen	3 (2.3)
2 regimens	74 (56.1)
3 regimens	42 (31.8)
≥4 regimens	13 (9.8)

Mean (std dev)	2.5 (0.70)
Median (min, max)	2 (1, 4)
Metastatic	132 (100)
1 regimen	67 (50.8)
2 regimens	64 (48.5)
3 regimens	1 (0.8)
≥4 regimens	0
Mean (std dev)	1.5 (0.52)
Median (min, max)	1 (1, 3)

Source: MONARCH 1 CSR page 76

Reviewer Comments: *While the eligibility criteria specified that patients enrolled could have only received 1-2 prior chemotherapy agents in the metastatic setting, the median number of previous therapies in the metastatic setting (both endocrine and chemotherapy) was 3 with a range of 1-8 previous therapies. This demonstrates that the MONARCH 1 study population was heavily pretreated and had few standard therapy options available to them.*

Table 36. Prior Systemic Therapy in the Metastatic Setting Reported by ≥10% or of Particular Interest in MONARCH 1

	Abemaciclib 200 mg N=132 n (%)
Endocrine therapy	
Fulvestrant	67 (50.8)
Exemestane	59 (44.7)
Letrozole	51 (38.6)
Tamoxifen	38 (28.8)
Anastrazole	26 (19.7)
Chemotherapy	
Any taxane	91 (68.8)
Capecitabine	73 (55.3)
Any anthracycline	16 (12.1)
Cyclophosphamide	18 (13.6)
Gemcitabine	10 (7.6)
Vinorebine	9 (6.8)
Eribulin	6 (4.5)
Ixabepilone	0
Other therapies	
Everolimus	37 (28.0)
Investigational drug	16 (12.1)

Source: MONARCH 1 CSR page 78

Reviewer Comments: *Most patients had received the most common chemotherapy agents, taxanes and capecitabine, in the metastatic setting prior to entering the MONARCH 1 study. This demonstrates a study population that has limited treatment options and where other treatment options tend to be intravenous systemic therapy which can affect patient quality of life in a palliative therapy setting.*

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
MONARCH 2 I3Y-MC-JPBL

Treatment Compliance

Treatment compliance of abemaciclib or placebo was measured by pill counts and summarized. Fulvestrant was administered in the clinic. Table 37 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 37. FDA Reviewer Analysis of Treatment Compliance in MONARCH 2

	Abemaciclib N=441 (%)	**Placebo N=223 (%)**
Compliance[a]		
Median	98.1	98.8
Q1-Q3	94.1-100.0	96.6-100.0
Min, Max	35.7, 700.0	63.8, 400.0
Mean (Std Dev)	99.4 (39.3)	100.8 (22.4)
Reviewer analysis excluding patients with >150% adherence		
Compliance[a]		
Median	97.9	98.6
Q1-Q3	93.8-99.9	96.6-100.0
Min, Max	35.7, 143.6	63.8, 133.3
Mean (Std Dev)	96.1 (10.3)	98.7 (6.7)

[a]Dose compliance was calculated as total amount of drug taken/total amount prescribed x 100
Dose adjustments were taken into account in order to measure compliance

Source MONARCH 2 CSR page 103 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 >150% compliance recorded were excluded from analysis. Measuring treatment compliance with pill counts is difficult, however it is notable that a numerically larger difference between groups occurred when outliers were discarded as it was noted those with higher compliance rates had discontinued study therapy and not returned study drug. The numerical difference persisted if patients who had >110% compliance recorded were excluded from analysis. Of note, at this point, there were 14 patients excluded from the placebo arm and 21 patients excluded from the abemaciclib arm which may have also affected the analysis. Review of the box and whisker plot distributions demonstrated that the data in the abemaciclib arm were left skewed as compared to the placebo arm. This suggests that treatment compliance may have been a greater issue in the abemaciclib arm, likely related to treatment toxicities and tolerability.*

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 course of the study were antidiarrheals, analgesics, and bone modifying agents. Concomitant medications that were more frequently used in the abemaciclib plus fulvestrant arm as compared to the placebo plus fulvestrant arm were antidarrheals, antiemetics, and hematopoietic growth factors. Table 38 below demonstrates concomitant therapies by treatment arm. Patients who were premenopausal were treated with GnRH agonists as indicated in Table 25 above.

Table 38. Concomitant Therapies in MONARCH 2

	Abemaciclib (n=441) n (%)	**Placebo (n=223) n (%)**
Patients with ≥1 antidiarrheal	333 (75.5)	40 (17.9)
Patients with ≥1 analgesic	292 (66.2)	139 (62.3)
Opioid	159 (36.1)	74 (33.2)
Non-opioid	246 (55.8)	119 (53.4)
Patients with ≥1 bone modifying agent	201 (45.6)	111 (49.8)
Patients with ≥1 antiemetic or antinauseant	69 (15.6)	15 (6.7)
Patients with ≥1 G-CSF or GM-CSF	31 (7.0)	2 (0.9)
Patients with ≥1 erythropoietic agent	9 (2.0)	1 (0.4)

Source Reviewer Modified from MONARCH 2 CSR page 102

Reviewer Comments: *As noted above, there was a marked difference in the use of antidiarrheal therapies between treatment arms which is consistent with the high incidence of diarrhea. 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. A similar proportion of patients in the abemaciclib plus fulvestrant and the placebo plus fulvestrant arms received bone modifying agents which are known to have benefits in patients with bony metastatic disease.*

MONARCH 1 I3Y-MC-JPBN

Treatment Compliance

Treatment compliance of abemaciclib was measured by pill counts and summarized. As was noted in their analysis, there were abnormally high levels of compliance that were due to patients discontinuing study therapy and not returning their medications. Table 39 is the

Applicant's analysis of treatment compliance followed by the reviewer's analysis leaving these outliers out to better understand treatment compliance.

Table 39. Analysis of Treatment Compliance in MONARCH 1

	Abemaciclib N=132 n (%)
Applicant Analysis	
Compliance[a]	
Median	98.96
Q1-Q3	95.79-100.12
Min, Max	74.02, 966.67
Mean (Std Dev)	111.87 (83.96)
Reviewer Assessment excluding patients with >150% compliance recorded	
Compliance[a]	
Median	98.8
Q1-Q3	95.7-100.0
Min, Max	74.0, 145.3
Mean (Std Dev)	98.5 (8.4)

Source: Reviewer Analysis using adex.xpt dataset and review of Applicant analysis tables from the MONARCH 1 CSR on page 79.

Reviewer Comments: *As seen in the tables above, the estimates of compliance were slightly lower when patients who had >150% compliance recorded were excluded from analysis. Measuring treatment compliance with pill counts is difficult. When those with >101% compliance were excluded, the median was 98% and the mean was 96% with a standard deviation of 5.0. Notably abnormally high numbers reflect treatment non-compliance not due to overdose but due to patients discontinuing early and not returning all of their study drug.*

Concomitant Medications and Rescue Medications

All patients enrolled in the MONARCH 1 study had one or more concomitant medications. Medications reported for >25% of patients included loperamide (57.6%), benzodiazepines (43.2%), opioid analgesics (31.8%), denosumab (28.8%), and paracematol (28.0%). Eighty-four patients (63.6%) were listed as being on a medication for supportive care and 90 patients (68.2%) received a concomitant medication for the treatment of an adverse event. These drugs included antidiarrheals, antiemetics, and antibiotics.

Reviewer Comments: *While it is difficult to assess the attribution of these medications to adverse events associated with study therapy given that this is a single arm trial, it is notable that all patients were taking at least one medication in addition to abemaciclib and that there*

was a large proportion of patients who required antidiarrheal therapy including, but not limited to loperamide. This is likely similar to other agents that would be used in this line of therapy, however, as there are varying toxicities of available systemic therapies depending on which agent is used.

Efficacy Results – Primary Endpoint

MONARCH 2 (I3Y-MC-JPBL)

The primary endpoint in MONARCH 2 was PFS assessed by the local investigator. The primary analysis was conducted when 379 progression events had occurred (378 events were planned for). The primary analysis results are displayed in Table 40 below. Figure **8** shows a Kaplan-Meier plot of the primary analysis results.

The results displayed in Table 40 correspond to the final PFS analysis. As described in the Statistical Analysis Plan section, the Applicant also conducted an interim analysis of PFS when 265 progression events had occurred. Based upon the results of the interim analysis, however, the study did not cross the pre-determined efficacy boundary, and the study continued until the final PFS analysis.

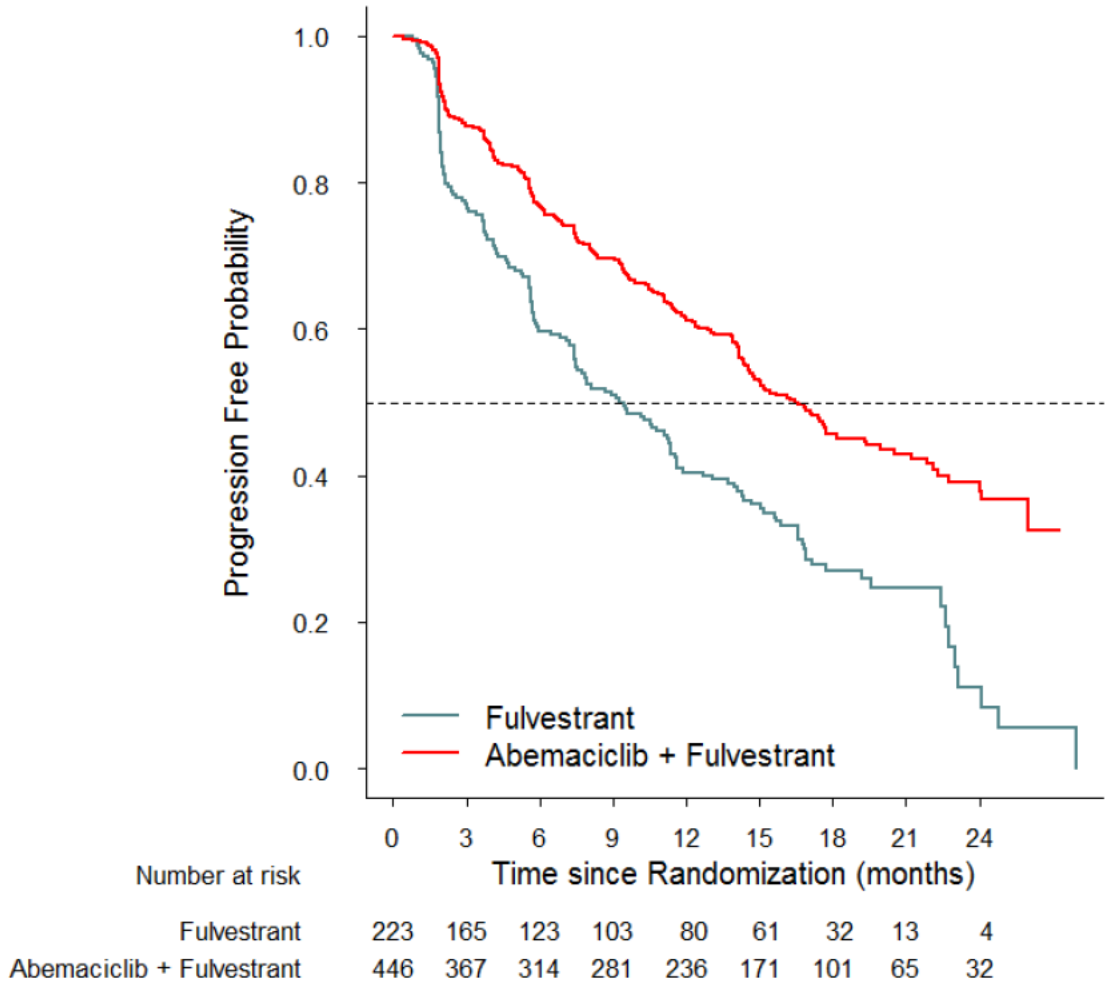
Table 40. MONARCH 2 Primary Endpoint Results (PFS by local investigator)

	Abemaciclib plus Fulvestrant N = 446	**Placebo plus Fulvestrant N = 223**
Events, n (%)	222 (49.8)	157 (70.4)
Censored, n (%)	224 (50.2)	66 (29.6)
Median, months (95% CI)	16.4 (14.4, 19.3)	9.3 (7.4, 11.4)
Hazard ratio, estimate (95% CI)	0.553 (0.449, 0.681)	
p-value*	< 0.0001	

Source: CSR Table JPBL.11.15. The data cutoff for this analysis was February 17, 2017.

**The alpha level for this analysis was 0.24999.*

Figure 8. Kaplan-Meier plot of primary analysis results (PFS by local investigator)



Source: Reviewer's Analysis (dataset: adtte.xpt)

In addition to the primary analysis of PFS as assessed by the local investigator, the Applicant subjected the PFS data to an independent review committee (BICR). The Applicant conducted a full BICR review. The results of this analysis are shown inTable 41.

Table 41. MONARCH 2 Supportive PFS Results (PFS by BICR)

	Abemaciclib plus Fulvestrant N = 446	**Placebo plus Fulvestrant N = 223**
Events, n (%)	164 (36.8)	124 (55.6)
Censored, n (%)	282 (63.2)	99 (44.4)
Median, months (95% CI)	22.4 (18.3, NE)	10.2 (5.8, 14.0)
Hazard ratio, estimate (95% CI)	0.460 (0.36, 0.58)	
p-value	< 0.0001	

Source: CSR Table JPBL.14.17. NE=not estimable

The BICR results showed good concordance with the primary PFS results. To examine this more rigorously, we estimated the early discrepancy rate (EDR) and late discrepancy rate (LDR) for each arm. The EDR and LDR are two ways to measure the differences between the primary investigator results and the secondary BICR results. By estimating the rates on each arm and then computing the difference, we can get a sense whether investigator bias exists in the primary results.

The EDR rate difference (control – treatment) was -12% and the LDR rate difference was 11%. Both of these differences favor the result of no bias.

Reviewer Comments: *The primary endpoint of investigator assessed PFS demonstrated a statistically and clinically significant improvement in PFS with the addition of abemaciclib to fulvestrant. In addition, the BICR results showed good concordance with the primary PFS results.*

MONARCH 1

The primary endpoint in MONARCH 1 was investigator assessed ORR. For investigator assessed ORR, the response rate was 19.1% (26/132) (95% CI: 13.3, 27.5). Of the 26 responses, all were partial responses with no complete responses. ORR as assessed by a BICR was used as supportive endpoint. For BICR assessed ORR, the response rate was 17.4% (23/132) with a 95% CI = (11.4, 25.0). Again all of the 23 responses were partial responses. Note that only confirmed responses were considered for the primary endpoint.

Reviewer Comments: *Single agent use of abemaciclib shows activity in the advanced metastatic breast cancer setting.*

Efficacy Results – Secondary and other relevant endpoints

MONARCH 2

For MONARCH 2, the secondary endpoints included ORR, DoR, CBR and DCR, and overall survival. For the ITT population, the ORR consisting of both complete and partial responses was greater in the abemaciclib and fulvestrant arm with a rate of 35.2% (95% CI: 30.8, 39.6) as compared to the placebo and fulvestrant arm with a rate of 16.1% (95% CI: 11.3, 21.0). The ORR for patients with measurable disease was 48.1% (95% CI: 42.6, 53.6) in the abemaciclib plus fulvestrant arm (n=318) versus 21.3% (95% CI: 15.1, 27.6) for the placebo plus fulvestrant arm.

The estimated median time to response was 3.7 months (1.7-16.9 months) in the abemaciclib plus fulvestrant arm and 4.0 months (1.9-14.7 months) in the placebo plus fulvestrant arm. For the 157 patients in the abemaciclib plus fulvestrant arm with an investigator assessed CR or PR, there have been 49 progression events and 3 deaths observed. The estimated median DoR for patients in this arm of the study has not been reached (95% CI, 18.05 months, NR). At the time of the analysis, 90 responders (57.3%) were continuing on treatment. One subject on treatment and one subject on control had observed responses beyond 2 years.

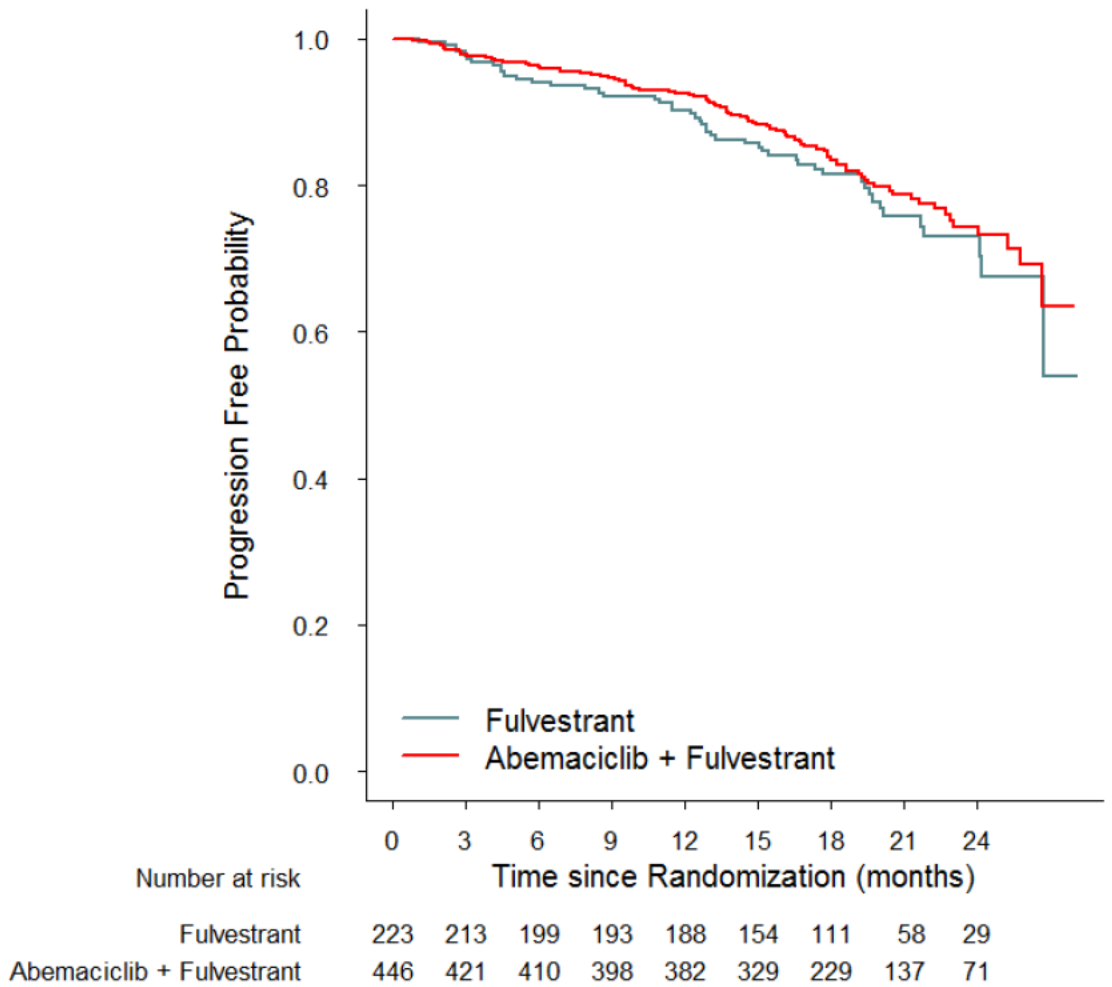
Overall survival results were immature at the time of primary PFS analysis. In total, 133 patients had died at the February 17, 2017 cutoff, representing only 30% of the events required for the final OS analysis (441 events). The results of the OS analysis are shown inTable 42. A Kaplan-Meier plot is shown in Figure 9.

Table 42. MONARCH 2 Overall Survival Results

	Abemaciclib plus Fulvestrant N = 446	**Placebo plus Fulvestrant N = 223**
Deaths, n (%)	85 (19.1)	48 (21.5)
Censored, n (%)	361 (80.9)	175 (78.5)
Median, months (95% CI)	NE (26.7, NE)	NE (26.8, NE)
Hazard ratio, estimate (95% CI)	0.854 (0.598, 1.221)	
p-value	0.38	

Source: CSR Table JPBL.11.18. NE=not estimable

Figure 9. MONARCH 2 Kaplan-Meier plot of Overall Survival results



Reviewer Comments: *The OS data are too immature at this point to make any definite conclusions. Nonetheless, there does not appear to be a detriment to survival at this point.*

MONARCH 1

A major secondary endpoint was Duration of response. For investigator assessment, the estimated median duration of response was 8.6 months (95% CI: 5.8, 10.2 months). For the BICR assessment, the estimated median duration of response was 7.4 months (95% CI: 5.6, Not estimable). Note that of the 26 patients with a response (investigator), 15 had a response longer than 6 months. The estimated median time to response was 3.7 months (95% CI: 1.1 months, 14.2 months).

After 18 months of follow-up, estimated median time to death was 22.3 months (95% CI: 17.7 months, not estimable). Note that since this is not a randomized trial, it is difficult to interpret the overall survival data.

Reviewer Comment: *The duration of response data further support the activity of single agent abemaciclib in the advanced metastatic setting.*

Additional Analyses Conducted on the Individual Trials
MONARCH 2

Additional sensitivity analyses were done to assess the robustness of the PFS primary endpoint. An unstratified analysis of the primary endpoint gave a HR equal to 0.577 (95% CI: 0.45, 0.68). When patients were censored for receiving new anti-cancer therapy, the HR equaled to 0.53 (95% CI: 0.42, 0.65). Finally, when excluding patients randomized to the 200mg starting dose of abemaciclib, the HR equaled 0.598 (0.480, 0.75).

Subgroup analysis results by age, race, and country for the primary PFS endpoint are shown inTable 43. The results were consistent across the demographic subgroups analyzed.

Patient reported outcome data is analyzed in Section 11.4

Table 43. MONARCH 2 Subgroup Analysis of Primary Endpoint

	N	HR	95% CI
Age			
< 65 Years Old	453	0.54	0.42, 0.70
>= 65 Years old	260	0.60	0.44, 0.83
Race			
White	400	0.62	0.47, 0.80
Asian	228	0.51	0.36, 0.73
Other	85	0.47	0.24, 0.93
Region			
USA	136	0.62	0.39, 0.99
Rest of World	577	0.54	0.43, 0.67

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

Reviewer Comments: *As discussed above, there were discrepancies between the IWRS stratification of endocrine therapy sensitivity and that which was documented in the case report forms. The unstratified analysis of the primary endpoint revealed a HR of 0.577 and the 95% CI did not include 1 which further supports the efficacy of this agent.*

Additional subgroups of interest are shown in Table 44. For the "other" group in nature of disease, the hazard ratio was 0.82 (95% CI: 0.49, 1.38). However, when entering an interaction term with nature of disease and treatment in a Cox regression model, the effect is not statistically significant. Therefore the difference seen in the "other" group may be due to chance alone.

Reviewer Comments: *The effect seen in the primary analysis is consistent across the subgroups shown in* Table 44*.*

Table 44. MONARCH 2 Subgroup Analysis of Primary Endpoint

	N	HR	95% CI
Endocrine Resistance			
Primary	169	0.45	0.30, 0.67
Secondary	489	0.59	0.46, 0.76
Naive	49	0.54	0.23, 1.25
Nature of Disease			
Visceral	373	0.50	0.38, 0.65
Bone Only	180	0.52	0.34, 0.81
Other	113	0.82	0.49, 1.38
Menopausal Status			
Post-menopausal	551	0.58	0.46, 0.73
Pre-menopausal	114	0.45	0.26, 0.75

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

MONARCH 1

Unconfirmed ORR by the investigator was also considered. For this endpoint, the ORR was 30/132 (22.7%), 95% CI: (15.9, 30.8). Subgroup analysis results by age, race, and country for the primary ORR endpoint are shown in Table 45. Patient reported outcome data is analyzed in Section 11.4.

Table 45. MONARCH 1 Subgroup Analysis of Primary Endpoint

	N	ORR	95% CI
Age			
< 65 Years Old	90	23.3%	15.0, 33.4
>= 65 Years old	42	11.9%	4.0, 25.6
Race			
White	112	19.6%	12.7, 28.2
Other	8	25%	3.2, 65.1
Region			
USA	70	21.4%	12.5, 32.8
Rest of World	62	17.7%	12.0, 33.7

Source: Reviewer's analysis (dataset: adrs.xpt).

Reviewer Comment: *The additional analyses support the conclusions of the primary endpoint.*

7.3. Integrated Review of Effectiveness

7.3.1. Assessment of Efficacy Across Trials

Primary Endpoints
Not applicable since each trial is supporting a different indication.

Secondary and Other Endpoints
Not applicable since each trial is supporting a different indication.

Subpopulations
Not applicable since each trial is supporting a different indication.

Additional Efficacy Considerations

7.3.2. Integrated Assessment of Effectiveness

MONARCH 1 has shown activity of single-agent abemaciclib against metastatic breast cancer in the advanced setting, and MONARCH 2 has shown the activity of abemaciclib, in conjunction with fulvestrant, in the endocrine resistant setting. Both trials have demonstrated efficacy. No pooled analysis can be made however due to the inherent differences between the trials.

The improvement in PFS demonstrated in the MONARCH 2 study with the use of abemaciclib in combination with fulvestrant as compared to placebo combined with fulvestrant is both statistically significant and clinically meaningful. Overall survival data are immature, however demonstrate no compelling evidence of harm to overall survival at this point.

While the MONARCH 1 study of abemaciclib as a single agent demonstrated a response rate of 19.7%, the lower bound of the 95% CI was slightly below the prespecified analysis value of 15%. However, given the paucity of treatment options in this setting that are also associated with significant toxicities, and the oral availability of this agent in a setting where over half of the patients included had already been treated with the only other orally available chemotherapy, capecitabine, this drug demonstrates similar efficacy with good duration of response and permits another treatment option be available for patients with metastatic HR positive, HER2 negative breast cancer who have few treatment options available to them.

7.4. Review of Safety

7.4.1. Safety Review Approach

For this NDA, the Applicant submitted safety data from MONARCH 2, a Phase 3 trial of abemaciclib plus fulvestrant versus placebo plus fulvestrant in patients who had progressed on

previous endocrine therapy and MONARCH 1, a single arm, open label Phase 2 trial of abemaciclib as a single agent in patients who had received 1-2 prior chemotherapy regimens in the metastatic setting. Four hundred forty one (441) patients received at least one dose of abemaciclib in MONARCH 2 (446 randomized) and 132 patients received at least one dose of abemaciclib in MONARCH 1. Adverse events were assessed at baseline and during the study treatment period and for at least 30 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, days 1 and 15 of Cycle 1, and then day 1 of each subsequent cycle. Hematology labs included a complete blood cell count with differential. Serum chemistries include liver function evaluation, renal function evaluation, and electrolytes. There were no clinical holds for safety during the development of abemaciclib.

Table 46 includes the safety studies submitted to the NDA as well as the data cut-offs for the Initial Submissions and the 90-Day Safety Update.

Table 46. Summary of Safety Population Data Submitted with this NDA

Study[1]	Design	Population	N	Status	Cutoff at time of submission	Extended follow up cutoff
I3Y-MC-JPBL (MONARCH 2)	Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without abemaciclib	Female patients with HR+, HER2 negative locally advanced or metastatic breast cancer who have progressed on prior endocrine therapy	441	Ongoing	February 14, 2017	May 5, 2017
I3Y-MC-JPBL (MONARCH 2)	Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without abemaciclib	Female patients with HR+, HER2 negative locally advanced or metastatic breast cancer,	27	Ongoing	February 14, 2017	May 5, 2017

		endocrine therapy naïve population				
I3Y-MC-JPBN (MONARCH 1)	Phase 2, Single Arm	Female patients with HR+, HER2 negative MBC who had progressed after 1-2 lines of chemotherapy in the metastatic setting	132	Ongoing	April 30, 2016	October 30, 2016
I3Y-MC-JPBA	Phase 1, Single Arm Dose escalation trial	Patients with advanced cancer and included tumor-specific expansion (Parts B-F)	206	A: Completed B-F: Completed	May 29, 2015	October 30, 2016
JPBA Part G	Phase 1, Single Arm Dose escalation trial	Cohort expansion in patients with advanced or metastatic HR+ breast cancer in combination with fulvestrant	19	Completed	May 29, 2015	October 30, 2016
I3Y-JE-JPBC	Phase 1, Single Arm, Open Label Dose Escalation Study	Japanese patients with advanced cancer	12	Completed	April 1, 2015	October 30, 2016
I3Y-MC-JPBB	Phase 2, multicenter nonrandomized, open-label study	Relapsed or refractory mantle cell lymphoma (MCL)	28	Completed	September 28, 2015	October 30, 2016
I3Y-MC-	Phase 1, open	Patients with	26	Completed		June 9,

JPBE	label, 2-period, fixed-sequence study to investigate the impact of CYP3A inhibition by clarithromycin on the metabolism of abemaciclib	advanced or metastatic cancer				2016
I3Y-MC-JPCD	Expanded Access	Advanced or metastatic breast cancer in patients with disease progression on prior therapies	3	Ongoing	May 5, 2017	N/A

[1]Healthy volunteer studies and investigator initiated research studies are not included in this table though data were reviewed.

At the time of data cutoff of May 5, 2017, the Lilly Safety System contained 3621 patients who had been treated with at least one dose of abemaciclib. Of these, 339 were healthy subjects and 3282 were cancer patients. The majority of these patients are breast cancer patients (n=1991). The safety data supporting this application include the completed studies of abemaciclib as a single agent, expansion cohort G of JPBA of abemaciclib in combination with fulvestrant and the data from the phase 3 study JPBL were submitted this included over 891 patients who received at least one dose of abemaciclib in Eli Lilly-sponsored clinical. Of these, 487 patients received abemaciclib in combination with fulvestrant with 468 patients receiving abemaciclib plus fulvestrant with or without ovarian function suppression in the randomized, double blind, phase 3 MONARCH 2 study. One hundred seventy nine patients with advanced or metastatic breast cancer received abemaciclib as a single agent with 132 of these patients being treated in the single arm, open label, phase 2 MONARCH 1 trial.

The 90 Day Safety Update provided cumulative safety information as of May 5, 2017, for the JPBL MONARCH 2 study and data as of October 30, 2016, for the additional studies. Additionally, this summary provided additional information on patients in the included trials as well as information about an event that occurred among one of the three patients enrolled in the Expanded Access Program.

7.4.2. Review of the Safety Database

Overall Exposure

The duration of exposure to abemaciclib or placebo plus fulvestrant in the MONARCH 2 (JPBL) study are summarized in Table 47 below. As of May 5, 2017, 34.2% of patients in the abemaciclib plus fulvestrant arm and 16.6% of patients in the placebo plus fulvestrant arm continued to receive protocol directed therapy. The median daily dose of abemaciclib was 271 mg per day (range 76.56-2100). The median duration of abemaciclib exposure was 51.9 weeks (range 0.14-131).

Table 47. Summary of Drug Exposure and Dose Intensity for Abemaciclib or Placebo in MONARCH 2 (JPBL)

	Abemaciclib N=441	**Placebo N=223**
Cycles received per patient		
Median	13.00	9.00
Q1-Q3	4.00-22.00	4.00-19.00
Min, max	1.00-33.00	1.00-30.00
Mean (Std Dev)	13.25 (9.4)	11.27 (8.42)
Duration of therapy (weeks)		
Median	51.86	34.14
Q1-Q3	14.57-89.00	13.00-75.29
Min, max	0.14-131.00	1.00-121.29
Mean (Std Dev)	54.56 (39.58)	44.84 (34.64)
Cumulative dose (mg)		
Median	77350.00	72150.00
Q1-Q3	25750.00-145600.00	27000.00-151300.00
Min, max	150.00-294600.00	1650.00-263650.00
Mean (Std Dev)	92252.85 (72115.83)	93508.52 (71276.34)
Dose intensity (mg/day)		
Median	271.43	297.86
Q1-Q3	200.31-296.35	289.46-313.99
Min, max	76.56-2100.00	103.13-1200.00
Mean (Std Dev)	259.64 (138.89)	309.16 (75.30)
Relative dose intensity	79.8%	97.4%

From 90 day safety update provided 8/2/2017, page 13, Information Request with Applicant response on July 20, 2017

Reviewer Comments:

It was noted that there were three patients in the dataset who had outlier values for dose

intensity that were >400 mg/day. An information request was sent to the Applicant requesting additional information regarding these outliers. The response received on September 1, 2017 indicated that the abnormally large values were due to early treatment discontinuation by study patients without return of study medication. An FDA analysis of the data was performed leaving out the outliers (those who were recorded as having a dose intensity ≥500 mg/day and is found in Table 48 *below.)*

Table 48. FDA Analysis of Dose Intensity Excluding Outliers

	Abemaciclib N=441	**Placebo N=223**
Dose intensity (mg/day)		
Median	272.5	298.3
Q1-Q3	202.4-295.9	289.3
Min, max	76.6, 466.7	103.1, 491.23
Mean (Std Dev)	251.1	304.6
Relative dose intensity	79.8%	97.4%

Source: Reviewer analysis using adexsum.xpt dataset

Reviewer Comments: *Analysis excluding outliers changed the numbers slightly and continued to demonstrate that the dose intensity of abemaciclib was slightly lower than placebo with the median dose intensity being somewhere between 100 mg twice daily and 150 mg twice daily.*

Relevant characteristics of the safety population:

Demographic information for the patients included in the safety database from the MONARCH 2 and MONARCH 1 studies is included in Section 7.2.3 above. Baseline characteristics of the patients in the two treatment arms of the MONARCH 2 study were well-balanced. All patients in both studies were female and the majority of patients were white. Approximately one third of patients in the MONARCH 2 study were of Asian descent. In the MONARCH 2 study, the median age in the abemaciclib plus fulvestrant arm was 59 (32-91) and in the placebo plus fulvestrant arm was 62 (32-87). The median age was 58 (36-89) in the MONARCH 1 study. All patients had received prior systemic therapy. Over half of patients in the MONARCH 2 study had visceral metastatic disease while over 90% of patients in the MONARCH 1 study did. Most patients in both studies had one or more comorbid conditions including hypertension and hyperlipidemia. Over half the patients in both the MONARCH 2 and MONARCH 1 studies had an ECOG PS of 0 at study entry.

Based on these data, the patients included in the safety database from the MONARCH 2 and MONARCH 1 studies are younger and healthier than the population of women with metastatic HR positive, HER2 negative breast cancer in the overall population.

Adequacy of the safety database:

The safety database from the 573 patients treated in the MONARCH 2 and MONARCH 1 studies is adequate. Additionally, as noted above, over 3,200 cancer patients have received this drug in studies across the abemaciclib clinical development program. The age and sex of the patients is expected for patients with breast cancer. No male patients were included in either of these studies. While the MONARCH 2 study included a large number of Asian patients, Black or African American patients were underrepresented in both trials. Patients included in these studies likely have an improved performance status than patients with metastatic breast cancer as a whole, particularly those who were included in the MONARCH 1 study who were more heavily pretreated patients than those in MONARCH 2. Based on these data, the patients included in the safety database from the MONARCH 2 and MONARCH 1 studies are younger and healthier than the population of women with metastatic HR positive, HER2 negative breast cancer in the overall population.

7.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality
Overall the data quality for this study was acceptable. Case report forms (CRFs) were reviewed and compared to the datasets and patient narratives. The data in the CRFs and AE datasets was generally consistent with any exceptions noted within the course of the review.

Categorization of Adverse Events

MONARCH 2 (I3Y-MC-JPBL)

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. Attribution of the relationship of events to study therapy was not consistent with differences in AE incidence in the treatment arms that are likely due to study therapy. Given this, the safety review was performed of TEAEs regardless of investigator assessment of attribution.*

MONARCH 1 (**I3Y-MC-JPBN)**

AEs were reported by investigators using a verbatim AE term and a CTCAE version 4.0 term for serverity for all AEs. Preexisting conditions were defined as AEs beginning before the first dose of abemaciclib. A TEAE was defined as any AE beginning on or after the day of the first dose of abemaciclib or any preexisting condition that increased in CTCAE grade on or after the day of the first dose of abemaciclib.

Serious adverse events were events that resulted in death, initial or prolonged hospitalization, were life-threatening, caused persistent or significant disability or incapacity, congenital anomaly or birth defect, or were considered significant by the investigator for any other reason.

The relationship of the AE to study drug was also determined by the investigator. Any AE or SAE thought "related" or "possibly related" to study drug was defined as related to abemaciclib.

All hematology and chemistry laboratory values were graded according to CTCAE version 4.0. Calculated grades were summarized by maximum postbaseline grade over the course of the study.

Reviewer Comment: *The attribution of events as related or unrelated to study drug by investigator assessment can be problematic. As discussed above, given this, the safety review was performed of TEAEs regardless of investigator assessment of attribution.*

Routine Clinical Tests
MONARCH 2 (I3Y-MC-JPBL)

In MONARCH 2, routine laboratory testing including CBC with differential (WBC, absolute

neutrophil count, absolute lymphocycte count, hemoglobin, hematocrit and platelets), serum chemistries (creatinine, BUN, sodium, potassium, calcium, ALT, AST, alkaline phosphatase, total bilirubin, albumin) were collected at baseline, Cycle 1 Day 1 and Day 15, and subsequently each cycle. Serum pregnancy testing was completed at baseline for patients receiving ovarian function suppression with a GnRH antagonist. 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, no replicates required, was performed at baseline, Cycle 1 Day 1 and Day 15, and at the short term follow-up visit.

MONARCH 1 (I3Y-MC-JPBN)

In MONARCH 1, routine laboratory testing including CBC with differential (WBC, absolute neutrophil count, absolute lymphocycte count, hemoglobin, hematocrit and platelets), serum chemistries (creatinine, BUN, sodium, potassium, calcium, ALT, AST, alkaline phosphatase, total bilirubin, albumin) were collected at baseline, Cycle 1 Day 1 and Day 15, and subsequently each cycle. Serum pregnancy testing was completed at baseline. Vital signs including temperature, 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. Central ECG with three replicates was to be obtained at baseline and additional ECGs were to be obtained as triplicates on Cycle 1 Day 1 and Day 15, Cycle 2 Day 1 and day 1 of each subsequent cycle and at the short term follow-up visit.

Reviewer Comment: *The frequency of laboratory assessments was appropriate,* (b) (4)

7.4.4. Safety Results

Deaths
MONARCH 2 (I3Y-MC-JPBL)

In the MONARCH 2 study, at the time of 90 day safety update (May 5, 2017), there were 16 deaths on therapy or within 30 days of treatment discontinuation in the abemaciclib plus fulvestrant arm and 10 deaths in the placebo plus fulvestrant arm. Of these deaths, 7/16 (44%) on the abemaciclib plus fulvestrant arm were attributed to progressive disease while 7/10 (70%) on the placebo plus fulvestrant arm were attributed to this. Nine of 14 deaths on the abemaciclib plus fulvestrant arm and 2/10 deaths on the placebo plus fulvestrant arm were attributed to adverse events. A review of the narratives of the 24 patients who died during this period was performed. Table 49 below is the Applicant's summary of deaths on treatment or

within 30 days of treatment discontinuation.

Table 49. Applicant Analysis of Deaths On Treatment or Within 30 Days of Treatment Discontinuation (Data cutoff May 5, 2017)

	Abemaciclib N=441 n (%)	**Placebo N=223 n (%)**
All deaths	98 (22.2)	58 (26.0)
Deaths on therapy or within 30 days of treatment discontinuation	18 (4.1)	10 (4.5)
Reason for Death		
Adverse event	9 (2.0)	2 (0.9)
Sepsis	3 (0.7)	0
Cerebral infarction	1 (0.2)	0
Hepatic failure	1 (0.2)	0
Hepatic function abnormal	1 (0.2)	0
Lung infection[b]	1 (0.2)	0
Multiple organ dysfunction syndrome	1 (0.2)	0
Pneumonitis	1 (0.2)	0
Decreased appetite	0	1 (0.4)
Cardiac arrest	0	1 (0.4)
Study Disease	7 (1.6)	7 (3.1)
Not reported	2 (0.5)	1 (0.4)[c]

[a]Cerebral infarct was coded as embolism per CTCAE term
[b]Cryptogenic organizing pneumonia was coded as lung infection per CTCAE term
[c]Patient died after discontinuing treatment due to progressive disease and there was no additional information regarding the cause of death.
Source: Adapted from Applicant Response to Information Request Received September 6, 2017

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

I3Y-MC-JPBL-110-01487 62-year-old female with a past medical history significant for tobacco abuse, anemia, anxiety, arthritis, depression, lower extremity edema, GERD, IBS, osteopenia, fatigue, anorexia, dyspnea on exertion, wheezing, nausea, vomiting, and allergic rhinitis. She presented with initial metastatic disease and was enrolled on this trial after disease progression on letrozole. She was on study for approximately 6 months. Approximately one month into the study, she had a treatment interruption due to the development of noncardiac chest pain and bradycardia. During that evaluation, she was noted to have a low TSH and methocarbamol and ropinerol were discontinued. Approximately six months into therapy, on (b) (6) she began feeling unwell at home, developed diarrhea and became progressively confused. Her last dose

of study therapy was 10/13/15. She was taken to the ER via ambulance and there was found to be febrile to 106 F, tachycardic with a heart rate of 135, tachypneic with a respiratory rate of 28, and had a GCS of 13. Her WBC at that time was 0.5. Broncheoalveolar lavage revealed *E. coli* and *Klebsiella pneumoniae.* The patient was intubated and transferred to the ICU with severe sepsis and community acquired pneumonia. CT of the chest revealed bilateral pneumonia. She was placed on broad spectrum antibiotics, however overnight condition continued to worsen and was unresponsive on the morning of (b) (6) and at that time had no pulse or spontaneous respirations. Cause of death was severe sepsis due to aspiration pneumonia. The Investigator assessed this event as not related to blinded study drug. The Applicant noted the patient to be neutropenic and given this is a known adverse effect of abemaciclib, indicated that this may be related to blinded study drug.

Reviwer Comment: *This reviewer agrees with the Applicant's assessment that this death may be related to study drug in the setting of neutropenia, infection, and diarrhea which were all noted to be increased in the abemaciclib plus fulvestrant arm of the study.*

I3Y-MC-JPBL-113-01135 57-year-old female with a history of COPD on home oxygen, pulmonary embolism, previous tobacco abuse, who initiated therapy with blinded study drug (abemaciclib) and fulvestrant on 12/2/14. Patient last received study drug on 8/16/16. She was hospitalized on (b) (6) with hypoxic and hypercapnic respiratory failure, encephalopathy, and hypoglycemia. The patient was withdrawn from study protocol on 10/3/16. The patient passed away on (b) (6) as mechanical ventilation was withdrawn and she was transferred to inpatient Hospice care. The Investigator's assessment is that the cause of death was due to respiratory failure and was not thought related to study drug. Based on the Applicant's assessment, there was no clear relationship of this death to study drug given the patient's underlying pulmonary disease and concomitant narcotic pain medication use.

Reviewer Assessment: *This patient was a part of the endocrine naïve patient population. The patient had a significant tobacco history and COPD with a history of PE as well as pleural effusion. Her hypoxic respiratory failure was likely multifactorial given her underlying pulmonary disease and use of narcotic pain medications and does not appear to be related to abemaciclib.*

I3Y-MC-JPBL-130-01021 67-year-old female with metastatic breast cancer, hip osteoarthritis, hyperlipidemia, fatigue, and back pain who died due to pericardial effusion with tamponade in the setting of progressive metastatic disease. The investigator and Applicant attributed the cause of death to study disease.

Reviewer Comment: *While there was not cytological confirmation of the pericardial effusion as a definite malignant pericardial effusion, this was in the setting of progressive disease and this reviewer concurs that the cause of death was due to study disease.*

I3Y-MC-JPBL-150-01144 53-year-old female with metastatic lobular carcinoma and a history of

hypokalemia who initiated study therapy on 11/25/14 and developed nausea and diarrhea. The last dose of study drug was received on 12/27/14. She developed significant vomiting and on (b) (6) she presented to her local ER with nausea, vomiting, decreased oral intake and dehydration. Her potassium was 2.6 mmol/L. ECG showed a QT/QTc of 638/668, which was prolonged. She was treated with IV hydration and electrolyte replacement. She was discharged and on (b) (6), she underwent MRI of the brain which demonstrated leptomeningeal enhancement. On (b) (6), she had an out of hospital arrest and was brought to the ER with CPR in progress. She was asystolic on arrival and remained asystolic. Based on the Investigator and Applicant's assessment, the underlying cause of death was metastatic breast carcinoma with leptomeningeal and liver metasteses.

Reviewer Comments: *While the patient experienced either a cardiac or respiratory arrest, the underlying cause of death was most likely progressive disease based on this reviewer's clinical assessment. Leptomeningeal metasteses can cause nausea and vomiting in patients and could have led to either a cardiac or respiratory arrest due to this. Based on the patient's history, she may have had a cardiac arrest in the setting of electrolyte imbalances which prolonged her QT interval, or she may have had a respiratory arrest in the setting of aspiration. Regardless of the particular event, the underlying cause of death was progressive metastatic breast cancer with leptomeningeal involvement.*

I3Y-MC-JPBL-182-01092 57-year-old female with a history of hypothyroidism, depression, GERD, hyperlipidemia, neuropathy, anxiety, cellulitis, rash and bone metasteses who began taking study drug in November of 2014. In August 2015, the patient developed L arm cellulitis and was treated with antibiotics. Laboratory studies had been within normal limits until February 2015 when ALT rose to 47, AST became elevated to 35. Scans were stable until November 2015 when her scans reported hepatomegaly with fatty infiltration. In August 2016, her LFTs continued to rise with an ALT of 84, AST of 90, total bilirubin of 1.6 and direct bilirubin of 0.7. Last dose of study drug was received 9/23/16. Hepatitis A and Hepatitis B antibodies were negative. CT scan in September revealed trace ascites and on 9/29/16 liver biopsy was performed which demonstrated steatohepatitis with cirrhosis and acute cholangitis. The pathology report indicated that the differential included drug induced liver injury as well as metastatic carcinoma. The patient's bilirubin continued to rise. MRI of the abdomen was consistent with fatty infiltration. (b) (6) the patient was admitted to the hospital with altered mental status and worsening hepatic failure. She expired on (b) (6). In review of this case, the death was considered by the Investigator to be possibly related to study drug. Review by the Applicant noted that the patient was 233 pounds and 68 inches with a BMI of 35.4, was noted to be on a statin and have fluctuating blood glucoses that may be related to fatty liver disease. The patient had been on study drug for 2 years and 4 months prior to this developing. It was also noted that the patient had a UTI and was on nitrofurantoin starting 9/23-10/1/2016 which has associated hepatotoxicity as well. Given the timing and the overall clinical picture, there is insufficient evidence to attribute this to study drug.

Reviewer Comment: *The relationship between this adverse event and abemaciclib is unclear. There has not been significant hyperbilirubinemia associated with abemaciclib, though elevated transaminases have been noted. Additionally fulvestrant is known to have hepatoxicity. It is likely that this event was multifactorial given the patient's body habitus and possible non-alcoholic fatty liver disease, the use of multiple medications with associated hepatotoxicity including nitrofurantoin, fulvestrant, and abemaciclib, and may be in the setting of progressive disease that was not identified on biopsy.*

I3Y-MC-JPBL-201-01720 42-year-old female with metastatic disease to the bone, lung, liver, and skin with asthma, cough, and bone pain who began taking study drug on July 2, 2015. She had study drug held on multiple occasions in May, July, and August for anemia and neutropenia. Study drug was restarted on August 11, 2016, and last dose of study drug was September 12, 2016. On (b) (6), she presented to the ED with nausea, vomiting, diarrhea, and shortness of breath. She was febrile, hypotensive, tachycardic and tachypneic. Blood cultures revealed gram negative bacilli, her ANC was 1.5. She was admitted to the ICU with acute kidney injury, lactic acidosis, septic shock, and myocardial dysfunction. She was given broad spectrum antibiotics and IV fluid resuscitation. She had a cavitary pneumonia in the left upper lobe. She required multiple vasopressors and developed acute lung injury. She subsequently died on (b) (6). Autopsy revealed diffuse metastatic disease in the liver, bones, and lymph nodes. BAL grew out *pseudomonas aeruginosa* and *pneumocystis jiroveci.* Cause of death was septic shock in the setting of metastatic breast cancer. Given that the patient was neutropenic at the time of admission and was on study drug until the day prior to admission, the Investigator assessed that there may be a relationship of study drug to the patient's death. The Applicant did not think this was reasonably related to study drug given that septic shock is an anticipated complication of pneumonia in the setting of advanced malignancy.

Reviewer Comments: *The reviewer does think this event was reasonably related to study drug in the setting of recurrent neutropenia, a known adverse effect of abemaciclib, and diarrhea, an additional adverse effect of abemaciclib.*

I3Y-MC-JPBL-202-01652 75-year-old female with a history significant for CAD, MI, osteoporosis, arthritis, hypothyroidism, CABG, former tobacco use who began study therapy on 6/15/15. Study therapy was discontinued on 6/18/15 and the patient experienced chest pain and shortness of breath on 6/20/15 and presented to the hospital on (b) (6) with an NSTEMI. On (b) (6), she developed bilateral DVTs. The patient died on (b) (6) and the cause of death was reported by the Investigator and Applicant as study disease.

Reviewer Comments: *Based on the patient's history, this event may be related to abemaciclib as it was noted that there was an imbalance in VTE/Pulmonary Embolism events across the abemaciclib clinical development program. Attributing this single event to study drug is unclear however, as the patient's underlying metastatic cancer additionally predisposed the patient to increased risk of VTE/PE.*

I3Y-MC-JPBL-202-01975 68-year-old female who began treatment on 10/14/15 and ended treatment on 1/5/17 due to progressive disease in the liver with worsening LFTs and ascites. Cause of death reported by Investigator and Applicant as progressive study disease.

Reviewer Comments: *The reviewer concurs with the underlying cause of death being study disease.*

I3Y-MC-JPBL-203-02049 68-year-old female who began treatment with fulvestrant and study drug on 11/5/15. Her medical history included osteopenia, adrenal insufficiency, germ cell tumor in 1979, pneumonia, severe motor vehicle accident in 2012 and current alcohol use. She had received previous chemotherapy with Adriamycin, paclitaxel, doxorubicin, and bleomycin. She had pulmonary metasteses. She discontinued study therapy on July 12, 2016. In August, she was noted to have an increase in interstitial changes on exam. She was hospitalized for dyspnea and had a fever, chills, and cough. She was started on ceftriaxone and azithromycin. The patient was unable to tolerate a lung biopsy. She had increased lymphadenopathy and bilateral pleural effusions which were thought related to disease progression. Autopsy was not performed. Cause of death was reported as cryptogenic organizing pneumonia. In the opinion of the Investigator, the event of crypotogenic organizing pneumonia was related to blinded study drug (abemaciclib). Based on the Applicant's assessment, given the concern for disease progression, and the duration of time off of study therapy, there is insufficient evidence to attach a causal relationship between the study drug and patient death.

Reviewer Comments: *The patient's cause of death was likely multifactorial and there may be some contribution to the event of cryptogenic organizing pneumonia to study therapy, however there was not an imbalance of pulmonary events seen across the abemaciclib clinical development program. This patient had previous therapy with multiple agents that could have contributed to pulmonary toxicity incluing paclitaxel and bleomycin. Additionally there was concern for progressive disease and this picture could be consistent with lymphangitic spread of underlying disease. This reviewer finds insufficient evidence to attribute this event to study drug.*

I3Y-MC-JPBL-322-01790 61-year-old female who was initiated on study therapy and fulvestrant in August 2015 and was last treated (b) (6) when she was hospitalized for anorexia and nausea. On (b) (6), the patient was hospitalized for abdominal pain and this was reported due to progressive disease which was 24 days after last dose of study drug. On (b) (6) the patient died. The cause of death as reported by the Investigator and the Applicant was study disease.

Reviewer Comment: *Given that the patient had discontinued study therapy 24 days prior to death, it is most likely due to study disease.*

I3Y-MC-JPBL-324-01525 59-year-old who initially presented with stage IV disease with

Reference ID: 4159689

metasteses to the liver, bone, and lungs in November 2014. She was previously treated with anastrazole. She began taking study drug in May 2015. In (b) (6), she underwent CT scans with new pulmonary infiltrates and the radiologist questioned possible iatrogenic pneumonitis. She had no history of chemotherapy or radiation. Her physician was not aware of these results and on (b) (6), she was hospitalized for grade 4 dyspnea and sinus tachycardia. She was treated with antibiotics and steroids for pneumonitis. CT demonstrated no PE. On (b) (6) the patient died due to pneumonitis. The Investigator assessed the event as possibly related to blinded study drug. The Applicant assessed this event as having insufficient evidence to support a relationship between study therapy and pneumonitis as the patient had known pulmonary metastatic disease. No autopsy was performed.

Reviewer Comment: *Given the time course, the lack of history of radiation or chemotherapy, it is possible that this event could be related to study drug. However, there was no autopsy and the patient had known pulmonary metasteses and progressive pulmonary metasteses, including possible lymphangitic spread, could have explained this clinical picture as well. As noted previously, there does not appear to be an imbalance in pneumonitis events in the abemaciclib arm across the clinical development program at this point. Deaths due to pneumonitis are reported in the label and this will continue to be monitored as a possible safety signal.*

I3Y-MC-JPBL-382-01429 62-year-old patient with metastatic disease to the liver who had previously been treated with an aromatase inhibitor she initiated study treatment with abemaciclib and fulvestrant on April 3, 2015. Her death on (b) (6) was reported by the Investigator and Applicant as due to study disease.

Reviewer Comments: *Review of case report forms indicated that this patient died due to liver failure in the setting of known metastatic disease to the liver. Review of the adverse event database demonstrated no unresolved adverse events prior to death. Review of the laboratory database was consistent with worsening hepatic function and hyperbilirubinemia consistent with progressive hepatic metasteses.*

I3Y-MC-JPBL-496-01597 76-year-old with a past medical history of paroxysmal atrial fibrillation, venous thrombosis, and R breast cancer who received CMF and radiation after surgery who relapsed in 2013 with metasteses to the lung and bone and had received letrozole, left hip palliative radiation, and denosumab. She began taking study drug on 5/26/15 and on 6/9/15 developed diarrhea. On 6/18/15 she was febrile and had diarrhea. She was treated with levofloxacin. In July she had her last dose of study therapy on 7/22/15 and then developed altered mental status and had a fall with head trauma on (b) (6). She was admitted for confusion after the fall, non-febrile neutropenia, and then developed diarrhea on (b) (6) after being noted to be neutropenic on (b) (6). She then became hypotensive, received broad spectrum antibiotics, growth factor support, vasopressors, and a blood transfusion. Her hypotension was refractory to vasopressors, she developed oliguria, and respiratory failure. The cause of death was reported by the Investigator as septic shock and possibly related to

study therapy (abemaciclib). The Applicant indicates that both septic shock and neutropenia may be related to blinded study drug.

Reviewer Comments: *As diarrhea and neutropenia are both adverse effects of study therapy, these events, including the patient's development of sepsis and death may be related to study drug. Given this, information has been placed in the label in the Warnings and Precautions section that deaths due to sepsis in the setting of neutropenia have occurred.*

I3Y-MC-JPBL-802-01917 71-year-old female that initially started study therapy in September 2015. In November 2015, she developed neutropenia. Blinded study drug was discontinued on January 5, 2016. Patient was hospitalized due to dizziness and was found to have pneumonia. Her last dose of study drug was on January 5, 2016, and her dizziness and headache improved. She was treated for pneumonia with amoxicillin clavulanate and the patient received filgrastim for neutropenia. She resumed study drug at a lower dose and had resolution of her dizziness. In (b) (6), she fell in the street and was admitted for further evaluation. MRI of the spine demonstrated compression fractures. During her admission, work up for breathing difficulties and palpiations demonstrated a pericardial effusion and pleural effusion. Thoracentesis was performed and she was treated for possible pneumonia. The pleural effusion was found to be progressive disease. She was discontinued from study treatment on May 31, 2016, due to progressive disease. On (b) (6) the patient died at home. The Investigator and Applicant attributed the patient's death due to progressive disease.

Reviewer Comments: *The patient was no longer on study therapy at the time of death. While infection is a known risk associated with abemaciclib, pneumonia can also be seen in the setting of patients with worsening metastatic cancer. This death does not appear to be related to study therapy in this patient with known progressive metastatic disease.*

I3Y-MC-JPBL-804-01042 54-year-old with a history of anemia, AST increased, ALT increased, hepatic function abnormal who initiated study therapy on 10/14/14. She had study drug held due to neutropenia in October 2014, and then it was restarted at a reduced dose 11/25/14. It was held again in January 201 due to neutropenia, thrombocytopenia, and anemia. It was held in March 2015 for grade 4 thrombocytopenia without bleeding. Study drug was permanently discontinued on April 2, 2015, due to grade 4 thrombocytopenia and poor performance status. She developed worsening ascites and her paracentesis fluid was transudative but no definite malignant cells. Hepatitis serologies were negative. Her AST on 4/16/15 was 207. She was hospitalized on (b) (6) and MRI of the abdomen was performed demonstrating hepatic sinusoid injury. She had worsening hepatic function. PET/CT demonstrated progressive bony metastatic disease. Infiltrative liver metasteses were suspected by the investigator but were not proven by MRI or PET/CT. CT on (b) (6), demonstrated disease progression and pneumonia. On (b) (6) the patient expired. The Investigator assessed this event as related to progressive disease based on CT findings on (b) (6) with multiple new liver lesions. Biopsy was not obtained. The Applicant assessed there to be insufficient evidence to support a

relationship to the patient's worsening hepatic function in the setting of progressive metastatic disease.

Reviewer Comment: *While there was no biopsy performed, this event is most likely due to progressive study disease in the setting of new lesions on CT scan, development of worsening ascites, and diminishing performance status.This event does not appear to be associated with abemaciclib.*

I3Y-MC-JPBL-805-01869 54-year-old female with stage IV breast cancer who initiated therapy with study drug and fulvestrant on 9/11/15. Her last dose of study therapy was (b) (6) as it had been held due to hospitalization for Grade 3 diarrhea. On (b) (6), she had LUE weakness and was hospitalized. Brain MRI was performed and demonstrated a cerebral venous thrombosis. ECHO as performed and demonstrated normal LV function. On (b) (6), CT scans demonstrated progressive disease with multiple new liver nodules and bilateral pleural effusions. Treatment with study therapy was discontinued on this date. The patient was anticoagulated and on (b) (6) the patient developed altered consciousness, desaturated, and had emesis. She was transitioned to DNR status and expired on (b) (6) with cause of death noted as cerebral infarction. The Investigator did not think the cerebral infarction was related to study drug. The Applicant felt there was insufficient evidence to link this event to the study drug given that it is reasonably anticipated in this patient population.

Reviewer Comment: *The patient had a cerebral infarction in the setting of progressive metastatic disease. There was no apparent increase in arterial events in the abemaciclib clinical program, and given the patient's age and comorbidities this event is reasonably expected to occur and is not likely related to study therapy.*

I3Y-MC-JPBL-951-01687 69-year-old patient with metastatic breast cancer to the bone, L axilla, and with bilateral hilar lymphadenopathy. She had previously received chemotherapy with docetaxel and cyclophosphamide in the early stage setting, adjuvant radiation, and palliative radiation to the ribs and to T5-T7. She initiated blinded study therapy and fulvestrant on June 29, 2015, and the last dose of study drug was on an unknown date in July 2015. She developed grade 2 diarrhea treated with IV hydration and loperamide on 7/13/15. On (b) (6) the patient was admitted with bilateral pneumonia and septic shock with hypoxia. Her ANC at the time of admission was 1,000. She developed disseminated intravascular coagulation. BAL was CMV positive. On (b) (6) she was given high dose steroids for a clinical picture consistent with bronchiolitis obliterans with organizing pneumonia (BOOP) multiple organ dysfunction syndrome. The patient died in the ICU on (b) (6) after not responding to broad spectrum antibiotics. The Investigator assessed the event as possibly related to study drug given that the severity of pneumonia was greater than expected and as the patient was deconditioned from a recent episode of diarrhea, a known adverse reaction for abemaciclib. The Applicant assessed the relatedness to study drug as possibly related to study drug in the setting of sepsis associated with neutropenia.

Reviewer Comment: *The reviewer agrees that this event may be associated with abemaciclib therapy in the setting of severe infection associated with neutropenia and diarrhea. Information in the label discusses the risk of severe infection, sepsis and death in the Warnings and Precautions section.*

Table 50. FDA Analysis of Deaths On or Within 30 Days of Treatment Discontinuation in MONARCH 2

	Abemaciclib N=441 n (%)
All deaths	98 (22.2)
Deaths on therapy or within 30 days of treatment discontinuation	18 (4.1)
Reason for Death	
Adverse event	9 (2.0)
Sepsis	4 (0.9)
Cerebral infarction	1 (0.2)
Hepatic failure	1 (0.2)
Pneumonitis	2 (0.4)
Study Disease	8 (1.8)
Not reported	2 (0.5)

MONARCH 1 (I3Y-MC-JPBN)

In the MONARCH 1 study, as of October 30, 2016, a total of 47 deaths were reported with 9 deaths reported on therapy or within 30 days of treatment discontinuation including 2 deaths on study therapy. Of the 9 deaths, 6 were attributed to study disease and 3 were attributed to adverse events. Of those attributed to adverse events while on therapy, one patient died due to a TEAE of sepsis (400-01103) and one died due to a TEAE of pneumonitis (703-01083). The TEAE of sepsis was in the setting of a patient with a gram negative bacteremia after undergoing paracentesis for malignant ascites. While the investigator did not consider this death to be related to study drug, the Applicant could not rule out a minor contributory role of the study drug given its association with chronic neutropenia. The pneumonitis event was thought by the investigator to be related to study drug; however, review of the narrative indicates that the patient was found to have influenza and underwent CT scan which demonstrated multiple pulmonary nodules, lymphadenopathy, and new lesions consistent with hepatic metasteses. Prior to this event, she had been hospitalized for a newly diagnosed pulmonary embolism. Autopsy was performed and this patient was found to have lymphangitic spread of breast cancer at the time of death and thus this is not likely related to treatment toxicity. Additionally,

one patient (310-01215) died within 30 days of treatment discontinuation due to a lung infection. This patient had a past medical history significant for pneumonia, respiratory failure, and a hilar mass. She withdrew from study participation after approximately 2 months on study and nine days later was hospitalized with dehydration, diarrhea, and poor oral intake. She declined further therapy and was transferred to hospice care where she died due to atypical pneumonia and dehydration. This was not thought related to study therapy. A review of the narratives for the 9 patients who died on study treatment or within 30 days of treatment discontinuation was performed.

Table 51. Applicant Analysis of Deaths in MONARCH 1 Study

	Abemaciclib 200 mg N=132
All deaths	47 (35.6)
Death within 30 days of treatment discontinuation	9 (6.8)
Progressive Disease	6 (4.5)
Adverse Events	3 (2.3)
Pneumonitis	2 (1.5)
Sepsis	1 (0.8)
Deaths >30 days after treatment discontinuation	38 (28.8)

Source, adapted from MONARCH 1 CSR page 118

Table 52. FDA Analysis of Deaths within 30 days of Treatment Discontinuation in MONARCH 1

	Abemaciclib 200 mg N=132
Death within 30 days of treatment discontinuation	9 (6.8)
Progressive Disease	7 (5.3)
Neutropenic Sepsis	1 (0.8)
Pneumonia	1 (0.8)

The Applicant collected information concerning the cause of death in the case report forms as well in safety narrative summaries. Data from these sources provide similar information to the above, though indicate that the pneumonitis event in patient 703-01083 for one patient was later found to be associated with lymphangitic spread. The sepsis event in subject 400-01103 was thought to have a contributory role from study drug given that there was associated neutropenia. The patient who died from pneumonia, 310-01215, had self-discontinued therapy and decided to pursue hospice. It is unclear whether there was definitive disease progression, however there was no documented neutropenia associated with the event, so there is no clear relationship to study drug.

Reviewer Comment: *The majority of deaths in MONARCH 1 were due to disease progression.*

The investigator and Applicant considered that there may be a contribution of abemaciclib in the event of the death of subject 400-01103 as her ANC had fallen precipitously in the setting of recently initiated treatment with abemaciclib. The reviewer agrees with this assessment. Given this as well as the deaths observed in MONARCH 2, wording was added in section 5.2 in the Warnings and Precautions that deaths due to neutropenic sepsis have been observed. The pneumonitis event in patient 703-01083 was found at autopsy to be associated with lymphangitic spread of the patient's underlying disease. Thus, this was thought to be the driving factor and reason for her death. The third and final death was within 30 days of study treatment discontinuation in a patient who had a history of recurrent pneumonia. This patient had no documented neutropenia but had elected to discontinue therapy due to poor physical status. There is inadequate evidence to attribute this death to study therapy given the patient's existing comorbidities and clinical deterioration.

Deaths Across the Clinical Development Program

In JPBA part A, a patient with advanced CRC died during follow up due to a Grade 5 event of sepsis deemed not related to study drug. In part B, a NSCLC patient died due to Grade 5 sepsis thought not related to study drug. A second NSCLC patient died with the cause of death reported as disease progression, though just prior to death also had Grade 4 sepsis. In part E, a metastatic melanoma patient died due to a Grade 5 lung infection during Cycle 2 reported to not be related to study drug.

Serious Adverse Events

Table 53. MONARCH 2 Serious Adverse Events in >1 Patient By Descending Frequency in the Abemaciclib plus Fulvestrant Arm

	Abemaciclib N=441 n (%)	**Placebo N=223 n (%)**
Any	99 (22.4)	24 (10.8)
Pulmonary Embolism/Deep Vein Thrombosis/Cerebral Vein Thrombosis	8 (1.8)	1 (0.4)
Pneumonia/lower respiratory tract infection/pneumonia bacterial/lung infection	8 (1.8)	1 (0.4)
Diarrhea	7 (1.6)	0
Dyspnea/Cough	6 (1.4)	2 (0.9)
Sepsis	6 (1.4)	2 (0.9)[a]
Nausea	5 (1.1)	1 (0.4)
Acute kidney injury/Blood creatinine increased	5 (1.1)	0
Pneumonitis/Organizing Pneumonia	4 (0.9)	0
Abdominal Pain	4 (0.9)	1 (0.4)
Hepatic function abnormal/hepatic failure	4 (0.9)	0
Fracture/compression fracture/wrist fracture	4 (0.9)	2
Cholecystitis/Cholangitis	4 (0.9)	0
Anemia	3 (0.7)	0
Cellulitis	3 (0.7)	0
Entercolitis	3 (0.7)	0
Dehydration	3 (0.7)	1 (0.4)
Cerebral infarction	2 (0.5)	0
Drug induced liver injury	2 (0.5)	0
Noncardiac chest pain	2 (0.5)	0
Pyrexia	2 (0.5)	0
Volvulus	2 (0.5)	0
Pleural Effusion	2 (0.5)	4
Altered state of consciousness/confusional state	2 (0.5)	1 (0.4)[b]
Asthenia	2 (0.5)	0
Atrial fibrillation	2 (0.5)	0
Back pain	2 (0.5)	2 (0.9)
Dizziness	2 (0.5)	0
Fall	2 (0.5)	0
Febrile neutropenia	2 (0.5)	0
Headache	2 (0.5)	0
Vomiting	2 (0.5)	0
Wound complication	2 (0.5)	0

[a]Included in this for the placebo group is abdominal sepsis and salmonella bacteremia
[b] Included in this for the placebo group is coma
Source: FDA Reviewer Analysis using adae.xpt dataset and reviewing Table JPBL12.7 on page 153 of the MONARCH 2 CSR

Reviewer Comments: *The SAE table in the MONARCH 2 CSR was reviewed and was adapted slightly based on the reviewer's analysis. Of note, the greatest incidence of SAEs was found in venous thrombosis events including pulmonary embolism. While it is noted that patients with metastatic cancer have an increased risk for VTE events, it is noted that the number of events in the abemaciclib plus fulvestrant arm is markedly higher. Additionally, serious infections were seen including pneumonia, entercolitis, cholecystitis and cholangitis at a numerically higher rate in the abemaciclib plus fulvestrant arm as compared to the placebo plus fulvestrant arm. Sepsis was also a cause of death in the abemaciclib plus fulvestrant arm. Given these findings, additional wording in the Warnings and Precautions section regarding neutropenia was added. Acute kidney injury/blood creatinine increased was also noted as an SAE that occurred more frequently in the abemaciclib plus fulvestrant arm as compared to the placebo plus fulvestrant arm. While there are increases in serum creatinine that are thought due to direct action of abemaciclib on the renal tubules, this can also be seen in dehydration and increased diarrhea. Given this, a Warning and Precaution was added regarding changes in serum creatinine associated with this medication.*

Table 54. MONARCH 1 Serious Adverse Events in >1 Patient By Descending Frequency

	Abemaciclib 200 mg N=132 n (%)
Any	32 (24.2)
Infections/Infestations SOC term	6 (4.5)
Blood creatinine increased/acute kidney injury	4 (3.0)
Dehydration	3 (2.3)
Nausea	3 (2.3)
Abdominal pain	3 (2.3)
Dyspnea	2 (1.5)
Neutropenia/Neutrophil Count decreased/ WBC decreased	2 (1.5)
Pleural effusion	2 (1.5)
Febrile neutropenia/Sepsis	2 (1.5)

Source: Reviewer analysis using adae.xpt dataset. Additionally, data from the MONARCH 1 CSR pages 113-115 was reviewed.

Reviewer Comments*: While it is more difficult to interpret the incidence of SAEs in a single arm study, it is notable that there are similarities in the incidence of blood creatinine increased/acute kidney injury and dehydration. Given the small numbers, the SOC level term of infections and infestations was evaluated and there were 6 events that were considered to be SAEs. These data support the risk of infection associated with abemaciclib. Not included in this table is a single arterial thrombosis event. Given the increase in venous thromboembolic events, the reviewer requested the applicant evaluate this further. Based on their response on August 25, 2017, to an*

IR dated August 17, 2017, there did not appear to be an increase in arterial events in the abemaciclib clinical program safety database, but there was an imbalance in the incidence of venous thromboembolic events. This is discussed further below in Significant Adverse Events.

Hospitalizations
In MONARCH 2, the number of patients with one or more hospitalization was 93 (21.1%) in the abemaciclib plus fulvestrant arm and 24 (10.8%) in the placebo plus fulvestrant arm. Hospitalizations due to treatment related AEs based on Applicant and Investigator analysis were 31 (7.0%) in the abemaciclib plus fulvestrant arm and 3 (1.3%) in the placebo plus fulvestrant arm. The most common AE leading to hospitalization in MONARCH 2 was infection with 24 (5.4%) patients admitted for infection in the abemaciclib plus fulvestrant arm and 4 (1.8%) admitted in the placebo plus fulvestrant arm.

The incidence of hospitalizations due to AEs in the MONARCH 1 study was 22% with 29 patients experiencing at least one hospitalization due to an AE. Of these patients 8 patients had two hospitalizations and 2 patients had 3 hospitalizations due to AEs. The most common AE leading to hospitalization in MONARCH 1 was blood creatinine increased.

Dropouts and/or Discontinuations Due to Adverse Effects

MONARCH 2 I3Y-MC-JPBL

Patients were discontinued from study therapy and or study participation in the event of progressive disease as defined by RECIST 1.1, enrollment in any other clinical trial for an investigational product deemed incompatible with this study, investigator decision, patient decision, or sponsor decision. The reason for and date of discontinuation were collected for all patients. Study follow-up was to occur as per study protocol for those who discontinued therapy and permitted ongoing follow up. Treatment discontinuations due to adverse events were seen more frequently in the abemaciclib plus fulvestrant arm than in the placebo plus fulvestrant arm. Of note, patients in the abemaciclib plus fulvestrant arm could discontinue investigational therapy and continue on fulvestrant.

Table 55 below is a summary of TEAEs associated with Permanent Discontinuation from Treatment in patients receiving abemaciclib plus fulvestrant.

Table 55. Summary of TEAEs associated with Permanent Discontinuation from Treatment in Patients receiving Abemaciclib Plus Fulvestrant in MONARCH 2

	Abemaciclib plus Fulvestrant N=441
Any	38 (8.6)
Liver abnormalities including drug induced liver injury[a]	7 (1.6)
Diarrhea	6 (1.4)
Sepsis	5 (1.1)
Asthenia	2 (0.5)
Pneumonitis/Organizing Pneumonia	3 (0.7)
Venous thrombosis	1 (0.3)
Abdominal pain	1 (0.3)
Acute kidney injury	1 (0.3)
Enterocolitis	1 (0.3)
Fatigue	1 (0.3)
Gastritis	1 (0.3)
Hepatic lesion	1 (0.3)
Hydronephrosis	1 (0.3)
Limb injury	1 (0.3)
Myocardial infarction	1 (0.3)
Nausea	1 (0.3)
Pulmonary mycosis	1 (0.3)
Supraventricular tachycardia	1 (0.3)
Ventricular tachycardia	1 (0.3)
Weight decreased	1 (0.3)

[a]Terms pooled: blood alkaline phosphatase increased, blood bilirubin increased, hepatic failure, DILI, ALT increased, AST increased
Source: Reviewer Analysis using adae.xpt dataset.

As of February 14, 2017, 218 patients (49.4%) on the abemaciclib plus fulvestrant arm had a dose reduction of abemaciclib due to an adverse event. At that time, 132 patients (29.9%) had one dose reduction, 65 (14.7%) had 2 dose reductions, and 21 (4.8%) had three dose reductions. The most common reasons for dose reduction were adverse events with diarrhea being the most common with 18.8% of dose reductions due to this and neutropenia being the second most common. There were 46 (20.6%) dose reductions in the placebo plus fulvestrant

arm.

In the abemaciclib plus fulvestrant arm, 256 (58%) of patients had at least one dose omission with 93 (21.1%) of patients having 3 or more dose omissions. The most common reason for dose omissions was adverse events with diarrhea being the most common reason with 58 (18.8%) patients having dose omissions due to diarrhea and 732 (16.3%) of patients having dose omissions due to neutropenia. In the placebo plus fulvestrant arm, 49 (22.0%) patients had at least one dose omission due to an AE, no patients had a dose omission due to diarrhea and one patient (0.4%) had a dose omission due to neutropenia.

Significant Adverse Events
The incidence of Grade 3 or 4 adverse events in the abemaciclib plus fulvestrant arm was greater than that of the placebo plus fulvestrant arm with 62.6% of patients in the abemaciclib plus fulvestrant arm having a Grade 3 or 4 event while 40.2% of patients in the placebo plus fulvestrant arm had a Grade 3 or 4 event. The most common (≥10%) Grade 3 or 4 TEAEs associated with abemaciclib plus fulvestrant were neutropenia (26.8%, Grade 3 26.3%, Grade 4 2.9%) and diarrhea (13.4%, Grade 3 13.4%, Grade 4 0). The rate of Grade 3 or 4 neutropenia in the placebo plus fulvestrant arm was 3.0% with 1 (0.8%) grade 4 event at study follow up in the setting of new systemic therapy. One patient in the placebo plus fulvestrant arm (0.8%) had an episode of Grade 3 diarrhea.

In MONARCH 1, neutropenia and diarrhea were the most frequent Grade 3 or 4 adverse events with 24.2% of patients having Grade 3 neutropenia and 5.3% of patients having Grade 4 neutropenia. The incidence of Grade 3 diarrhea was 19.7% with no Grade 4 events.

Though less frequent, it was noted across the abemaciclib development program that there was an imbalance in venous thromboembolic events in the abemaciclib arms as compared to the placebo. Based on an information request dated August 17, 2017 with Applicant response provided on August 25, 2017, analysis of the abemaciclib clinical program safety database revealed 15 serious VTE events in the abemaciclib safety database of two studies in combination with endocrine based therapies and 2 events in the placebo arms of these studies. Additionally, there was at least one fatal event in the abemaciclib arm. In the entire safety database, it was noted that there were 35 non-fatal VTE events in those treated with abemaciclib (1.34%) and 4 fatal events (0.15%) as compared to 2 non-fatal events (0.4%) and no fatal events (0) in the non-abemaciclib treated patients in the safety database. Given this, as discussed above, a Warning and Precaution was added to the USPI labelling information to highlight these findings so that providers and patients are aware to monitor for the signs and symptoms of VTE events.

Treatment Emergent Adverse Events and Adverse Reactions
Table 56. TEAEs in MONARCH 2 ≥10% with ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

	Abemaciclib plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
	All Grades n (%)	**Grade 3 n (%)**	**Grade 4 n (%)**	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Diarrhea	381 (86.4)	59 (13.4)	0	55 (24.7)	1 (0.4)	0
Neutrophil count decreased	204 (46.3)	116 (26.3)	13 (2.9)	9 (4.0)	3 (1.3)	1 (0.4)
Fatigue[a]	207 (46.9)	14 (3.2)	0	75 (33.6)	2 (0.9)	0
Nausea	199 (45.1)	12 (2.7)	0	52 (23.3)	3 (1.3)	0
Infections and Infestations	193 (43.8)	24 (5.4)	6 (1.4)	59 (26.5)	8 (3.6)	1 (0.4)
Abdominal pain[b]	153 (34.7)	9 (2.0)	0	34 (15.2)	2 (0.9)	0
Anemia[c]	127 (28.8)	31 (7.0)	1 (0.2)	8 (3.6)	2 (0.9)	0
White blood cell count decreased/leukopenia	125 (28.3)	39 (8.8)	1 (0.2)	4 (1.8)	0	0
Decreased appetite	118 (26.8)	5 (1.1)	0	27 (12.1)	1 (0.4)	1 (0.4)
Vomiting	114 (25.9)	4 (0.9)	0	23 (10.3)	4 (1.8)	0
Headache	88 (20.0)	3 (0.7)	0	34 (15.2)	1 (0.4)	0
Rash[d]	81 (18.4)	7 (1.6)	0	19 (8.6)	0	0
Dysgeusia	79 (17.9)	0	0	6 (2.7)	0	0
Thrombocytopenia, platelet count decreased	70 (15.8)	12 (2.7)	6 (1.4)	6 (2.7)	0	1 (0.4)
Alopecia	68 (15.4)	0	0	4 (1.8)	0	0
Stomatitis[d]	61 (13.8)	2 (0.5)	0	20 (9.0)	0	0
Cough	59 (13.4)	1 (0.2)	0	25 (11.2)	0	0
ALT increased	58 (13.2)	18 (4.1)	1 (0.2)	11 (4.9)	3 (1.3)	0
Blood creatinine increased[f]	58 (13.2)	8 (1.8)	0	2 (0.9)	0	0
Pruritis[g]	56 (12.7)	0	0	12 (5.4)	0	0
AST increased	55 (12.5)	10 (2.3)	0	15 (6.7)	6 (2.7)	0
Dizziness[h]	58 (13.2)	4 (0.9)	0	13 (5.8)	0	0
Weight decreased	45 (10.2)	1 (0.2)	0	5 (2.2)	1 (0.4)	0
Pyrexia	46 (10.4)	1 (0.2)	1 (0.2)	13 (5.8)	1 (0.4)	0

[a] Terms pooled: fatigue, asthenia, malaise
[b]Terms pooled: abdominal discomfort, abdominal pain, abdominal pain upper, abdominal pain lower, abdominal tenderness
[c]Terms pooled: anemia, red blood cell count low
[d]Terms pooled: Dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, eczema, rash, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular
[e]Terms pooled: stomatitis, mucosal inflammation
[f]Terms pooled: blood creatinine increased, blood creatine increased (*sic),* acute kidney injury, renal failure, renal impairment, creatinine renal clearance abnormal, creatinine renal clearance decreased

[g]Terms pooled: pruritis, pruritis generalized
[h]Terms pooled: dizziness, vertigo
Source: Reviewer analysis using adae.xpt dataset and modification of table on page 142 in MONARCH 2 CSR.

Table 57. TEAEs with an Incidence of ≥10% in MONARCH 1

	Abemaciclib 200 mg N=132 n (%)		
	All Grades	**Grade 3**	**Grade 4**
Diarrhea	119 (90.2)	26 (19.7)	0 (0.0)
Fatigue, asthenia, malaise	87 (65.9)	18 (13.6)	0 (0.0)
Nausea	85 (64.4)	6 (4.5)	0 (0.0)
Decreased appetite	60 (45.5)	4 (3.0)	0 (0.0)
Abdominal Pain, AP upper, AP lower	50 (37.9)	3 (2.3)	0 (0.0)
Neutropenia, neutrophil count decreased	49 (37.1)	32 (24.2)	7 (5.3)
Vomiting	45 (34.1)	1 (0.8)	0 (0.0)
Infections and infestations	41 (31.1)	6 (4.5)	1 (0.8)
Anemia	33 (25.0)	6 (4.5)	0 (0.0)
Thromobcytopenia, platelet count decreased	27 (20.5)	5 (3.8)	0 (0.0)
Headache	25 (18.9)	0 (0.0)	0 (0.0)
Leukopenia, WBC decreased	23 (17.4)	8 (6.1)	1 (0.8)
Dry mouth	18 (13.6)	0 (0.0)	0 (0.0)
Creatinine increased, included AKI	18 (13.6)	1 (0.8)	1 (0.8)
Weight decreased	18 (13.6)	0 (0.0)	0 (0.0)
Dysgeusia	16 (12.1)	0 (0.0)	0 (0.0)
Alopecia	16 (12.1)	0 (0.0)	0 (0.0)
Dizziness	15 (11.4)	0 (0.0)	0 (0.0)
Pyrexia	14 (10.6)	0 (0.0)	0 (0.0)
Edema Peripheral, peripheral swelling	13 (9.8)	0 (0.0)	0 (0.0)
Rash	12 (9.1)	2 (1.5)	0 (0.0)
Stomatitis	11 (8.3)	0 (0.0)	0 (0.0)
Stomatitis	11 (8.3)	0 (0.0)	0 (0.0)
AST increased	11 (8.3)	3 (2.3)	0 (0.0)
Pruritis	10 (7.6)	1 (0.8)	0 (0.0)
ALT increased	9 (6.8)	1 (0.8)	0 (0.0)
Muscular weakness	5 (3.8)	1 (0.8)	0 (0.0)
Cough	25 (18.9)	0 (0.0)	0 (0.0)

Constipation	23 (17.4)	1 (0.8)	0 (0.0)
Arthralgia	20 (15.2)	0 (0.0)	0 (0.0)

Source: Reviewer analysis using adae.xpt dataset and modification of tables on page 115 of MONARCH 1 CSR.

Laboratory Findings
MONARCH 2

Abnormal hematological laboratory findings were more commonly observed in those patients who received abemaciclib plus fulvestrant as compared to those who received placebo plus fulvestrant. Almost all patients in the abemaciclib plus fulvestrant arm with laboratory tests for evaluation had an increase in creatinine from baseline (98.4%) and white blood cell decreased (90.1%). Eighty seven percent of patients had neutrophil count decreased in the abemaciclib plus fulvestrant arm as compared to 30.3% in the fulvestrant plus placebo arm. With the exception of white blood cell decreased, neutrophil count decreased, and lymphocyte count decreased, most events were Grade 1 or 2 in severity. Twenty-eight percent of patients on the abemaciclib plus fulvestrant arm had a Grade 3 decrease in neutrophil count while 3.5% had a Grade 4 decrease. Table 58 below is a Summary of Abnormal Clinical Laboratory studies by decreasing frequency in the MONARCH 2 study safety population.

Table 58. Summary of Laboratory Study Abnormalities in the MONARCH 2 Safety Population

	Abemaciclib N=441 n (%)				**Placebo N=223 n (%)**			
	N1	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**N1**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Patients with ≥1 CTCAE term	434	434 (100)	187 (43.1)	28 (6.5)	219	216 (98.6)	23 (10.5)	4 (1.8)
Creatinine Increased	434	427 (98.4)	5 (1.2)	0	219	154 (70.3)	7 (3.2)	0
WBC decreased	426	384 (90.1)	96 (22.5)	3 (0.7)	218	71 (32.6)	2 (0.9)	0
Neutrophil count decreased	426	371 (87.1)	122 (28.6)	15 (3.5)	218	66 (30.3)	8 (3.7)	1 (0.5)
Anemia	426	357 (83.8)	122 (28.6)	15 (3.5)	218	73 (33.5)	1 (0.5)	0
Lymphocyte count decreased	426	268 (62.9)	51 (12.0)	1 (0.2)	218	69 (31.7)	4 (1.8)	0
Platelet count	425	226	4 (0.9)	5 (1.2)	218	21	0	0

decreased		(53.2)				(14.7)		
ALT increased	434	178 (41.0)	17 (3.9)	3 (0.7)	219	71 (32.4)	3 (1.4)	0
AST increased	433	162 (37.4)	17 (3.9)	0	219	55 (25.1)	8 (3.7)	1 (0.5)
Hyponatremia	434	153 (35.3)	17 (3.9)	0	219	62 (28.3)	6 (2.7)	0
Hypokalemia	434	146 (33.6)	30 (6.9)	1 (0.2)	219	25 (11.4)	1 (0.5)	0
Hypercalcemia	434	132 (30.4)	1 (0.2)	1 (0.2)	219	70 (32.0)	1 (0.5)	1 (0.5)
Hypocalcemia	434	105 (24.2)	2 (0.5)	3 (0.7)	219	43 (19.6)	0	0
Alkaline phosphatase increased	434	78 (18.0)	4 (0.9)	0	219	38 (17.4)	3 (1.4)	0
Hypoalbuminemia	434	60 (13.8)	0	0	219	20 (9.1)	0	0
Hyperkalemia	434	31 (7.1)	3 (0.7)	1 (0.2)	219	26 (11.9)	1 (0.5)	0
Hypernatremia	434	15 (3.5)	0	0	219	5 (2.3)	0	0
Blood bilirubin increased	434	14 (3.2)	1 (0.2)	1 (0.2)	219	8 (3.7)	1 (0.5)	1 (0.5)
Lymphocyte count increased	426	4 (0.9)	0	0	218	3(1.4)	0	0
Hemoglobin increased	426	2 (0.5)	1 (0.2)	0	218	12 (5.5)	0	0

Source: MONARCH 2 CSR page 202

Table 59. Summary of MONARCH 1 Treatment Emergent Laboratory Abnormalities

CTCAE Term	N1	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Patients with ≥1 CTCAE term	130	7 (5.4)	55 (42.3)	60 (46.2)	7 (5.4)	129 (99.2)
Creatinine increased	130	61 (46.9)	66 (50.8)	1 (0.8)	0	128 (98.5)
White blood cell decreased	130	24 (18.5)	58 (44.6)	36 (27.7)	0	118 (90.8)
Neutrophil count decreased	130	23 (17.7)	56 (43.1)	29 (22.3)	6 (4.6)	114 (87.7)
Anemia	130	39 (30.0)	50 (38.5)	0	0	89 (68.5)
Lymphocyte count decreased	130	6 (4.6)	31 (23.8)	17 (13.1)	1 (0.8)	55 (42.3)
Platelet count decreased	130	37 (28.9)	13 (10.2)	3 (2.3)	0	53 (41.4)
ALT increased	130	30 (23.1)	6 (4.6)	4 (3.1)	0	40 (30.8)
AST increased	130	32 (24.6)	2 (1.5)	5 (3.8)	0	39 (30.0)
Alk phosphatase increased	130	22 (16.9)	10 (7.7)	2 (1.5)	0	34 (26.2)
Hypokalemia	130	0	27 (20.8)	7 (5.4)	0	34 (26.2)
Hyponatremia	130	23 (17.7)	0	4 (3.1)	0	27 (20.8)
Hypoalbuminemia	130	15 (11.5)	7 (5.4)	0	0	22 (16.9)
Hypocalcemia	130	7 (5.4)	7 (5.4)	1 (0.8)	0	15 (11.5)
Blood bilirubin increased	130	4 (3.1)	3 (2.3)	0	0	7 (5.4)
Hypercalcemia	130	4 (3.1)	0	0	0	4 (3.1)
Hyperkalemia	130	1 (0.8)	0	0	0	1 (0.8)

Source: MONARCH 1 CSR, page144

Vital Signs
MONARCH 2

Overall, the mean and median blood pressure, pulse rate and weight were well balanced at baseline between the abemaciclib plus fulvestrant arm and the placebo plus fulvestrant arm. The median treatment values for each cycle were comparable between the treatment arms. There was a numerically higher proportion of patients in the abemaciclib plus fulvestrant arm that developed a pulse rate ≥100 beats per minute. Otherwise, blood pressure, pulse and respiratory rate were similar over the course of treatment.

MONARCH 1

There were no clinically meaningful changes in temperature, blood pressure (systolic or diastolic), pulse rate, respiration rate, BMI or weight over the course of the study.

Electrocardiograms (ECGs)
MONARCH 2

In the MONARCH 2 study, ECGs were obtained at baseline, 2-4 hours after abemaciclib dosing on Cycle 1 Day 1, prior to fulvestrant dosing on Cycle 1 Day 15, 2-4 hours after abemacicilb dose on Cycle 4 Day 1 and at the short term follow up visit. Clinically relevant ECG findings observed in MONARCH 2 were reported as TEAEs are inTable 60 below.

Table 60. Clinically Relevant Cardiac Findings in MONARCH 2

	Abemaciclib plus Fulvestrant N=441			**Placebo plus Fulvestrant N=223**		
	All Grades n (%)	**Grade 3 n (%)**	**Grade 4 n (%)**	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
ECG QT prolonged	3 (0.7)	1 (0.2)	0	1 (0.1)	0	0
Sinus tachycardia/tachycardia	5 (1.1)	1 (0.2)	0	5 (2.2)	1 (0.1)	0
Atrial fibrillation	3 (0.7)	1 (0.2)	0	0	0	0
Bradycardia	0	0	0	2 (0.9)	0	0
Supraventricular tachycardia	3 (0.7)	1 (0.2)	0	0	0	0
Ventricular tachycardia	1 (0.2)	1 (0.2)	0	0	0	0

Source: *Reviewer analysis using adae.xpt*

MONARCH 1

In the MONARCH 1 study, central ECGs were collected as triplicates at baseline and during Cycle 1 (4-6 hours after abemaciclib on Day 1 and prior to evaluation on Day 15), Cycle 2 Day 1 and Day 1 of every cycle thereafter including the short term discontinuation follow up. Clinically relevant ECG findings observed in MONARCH 1 were reported as TEAEs in Table 61.

Table 61. Clinically Relevant Cardiac Findings in MONARCH 1

	Abemaciclib 200 mg N=132 n (%)		
	All Grades	**Grade 3**	**Grade 4**
ECG QT prolonged	1 (0.8)	0	0
Sinus tachycardia/tachycardia	5 (3.8)	1 (0.8)	0
Bradycardia	2 (1.5)	0	0

Source: *Reviewer analysis using adae.xpt*

QT

A QTc analysis was performed based on data submitted in both the healthy and cancer populations as part of the abemaciclib NDA submission. 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 2 study, there were five patients who developed QT prolongation while on study, 1 in the placebo group and 4 in the abemaciclib group. One patient had a grade 3 QT prolongation that was deemed not related to study therapy as this patient developed prolonged QT in the setting of a history of hypokalemia in the setting of diuretic therapy and this worsened in the setting of nausea and vomiting which was later found due to leptomeningeal metasteses. A second patient developed grade 2 QT prolongation on cycle 1 day 5 thought related to study treatment. She discontinued therapy at the end of cycle 1 at which time she discontinued treatment due to diarrhea.

In the MONARCH 1 study, there was one patient on abemaciclib 200 mg twice daily who developed prolonged QT interval initially at the first cycle in the setting of diarrhea. Laboratory studies including serum potassium and sodium were within normal limits at the cycle 1 visit. She had mild hyponatremia at cycle 5 however she had no other laboratory abnormalities. The patient discontinued study therapy at cycle 7 due to this adverse event. The maximal severity of this event was grade 2.

Immunogenicity

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Not applicable.

7.4.5. Analysis of Submission-Specific Safety Issues

Diarrhea

The incidence of diarrhea in MONARCH 2 and MONARCH 1 was greater than 80% in each. There were no Grade 4 diarrhea events, however there were grade 3 events that resulted in hospitalizations in the abemaciclib plus fulvestrant arm (4, 0.9%) with no similar events in the placebo plus fulvestrant arm. Given the incidence of this adverse event and incidence of hospitalization associated with this event, a Warning and Precaution was added to notify providers about this adverse event and its management to mitigate risk. Given that there were relatively few Grade 3 events and that prophylactic antidiarrheal treatment has its own set of adverse events associated with this, there is no indication at this time for an active prophylaxis regimen, but rather need for active clinical monitoring to intervene should this adverse effect occur.

Neutropenia

While the incidence of neutropenia in the abemaciclib plus fulvestrant arm was lower than that of other available CDK 4/6 inhibitors, there continues to be an elevated incidence of neutropenia, including grade 3 and 4 events. The incidence of febrile neutropenia was 0.9% (n=4) and resulted in one hospitalization. Additionally infections and sepsis were noted to be higher in the abemaciclib plus fulvestrant arm than in the placebo plus fulvestrant arm. Given this, a Warning and Precaution was recommended by the Applicant with the Agency modifying the wording to add in information about the risk of febrile neutropenia, infection, sepsis and death.

Blood Creatinine Increased

Per studies performed by the Applicant, abemaciclib is known to increase serum creatinine by inhibiting renal tubular secretion of creatinine without affecting glomerular function. This was determined by measuring cystatin c levels as an alternative to serum creatinine to determine creatinine clearance. Four hundred thirty four patients (98.9%) of patients had a normal creatinine at baseline. At cycle 1, this decreased to 4.9% of patients having a Grade 0 laboratory value for serum creatinine with 78.6% of patients having Grade 1 laboratory values, 16.2% of patients having Grade 2 laboratory values, and 1 patient having a Grade 3 laboratory value. Increases in serum creatinine were also seen in the setting of dehydration due to diarrhea and/or vomiting. Most events were reversible as demonstrated in the Applicant's analysis in their response to and Information Request on August 4, 2017, demonstrating that the median change from baseline creatinine on treatment was approximately 0.16 to 0.2 mg/dL and at the follow up visit was 0.03 mg/dL. It is notable that patients discontinued therapy in both MONARCH 2 and MONARCH 1 due to this adverse event. Given that there is alternative

laboratory study that can assess glomerular function in this setting as well as confounding events which can lead to acute kidney injury such as diarrhea and vomiting, a Warning and Precaution was recommended to inform providers of this alternate testing as well as to evaluate multiple causes of changes in a patient's baseline renal function after initiation of abemaciclib.

Hepatotoxicity and Drug Induced Liver Injury (DILI)

Abnormal liver function tests including ALT and AST were more common in the abemaciclib plus fulvestrant arm of the study as compared to the placebo plus fulvestrant arm. Additionally, in the abemaciclib plus fulvestrant arm, two patients discontinued therapy due to drug induced liver injury. Both patients who developed DILI were Asian and discontinued therapy after this. In both instances, the Applicant considered the fulvestrant to be the greater contributor to the DILI event and felt that these events were unlikely due to abemaciclib therapy. As noted in Table 58, the incidence of ALT increased based on laboratory findings was 41.0% in the abemaciclib plus fulvestrant arm and 32.4% in the placebo plus fulvestrant arm. Similarly, ALT was increased in 37.4% of patients in the abemaciclib plus fulvestrant arm and 25.1% of patients in the placebo plus fulvestrant arm. In the MONARCH 1 study, 30.8% of patients had an ALT increase and 30.0% of patients had an AST increase. A total of 68 patients had abnormal treatment emergent liver function tests over the course of the study. There was one possible Hy's law case in the abemaciclib plus fulvestrant arm and one possible case in the placebo plus fulvestrant arm. In the MONARCH 1 study, there was one possible Hy's law case and this patient discontinued study treatment due to progressive disease.

Given the increased incidence in ALT/AST abnormalities and the concern for DILI seen in two patients in the abemaciclib plus fulvestrant arm and in no patients in the abemaciclib plus fulvestrant arm, the Warnings and Precautions were modified (b) (4) with recommendations that providers assess LFTs twice monthly for the first month, monthly for the following two months and subsequently as clinically indicated.

Thromboembolic events

There were a numerically greater number of thromboembolic SAEs in the abemaciclib plus fulvestrant arm (8, 1.8%) as compared to the placebo plus fulvestrant arm (1, 0.4%). It appeared that there may be an increased incidence of arterial events as well. Based on these findings, an information request was sent to the sponsor to query the entire safety database to evaluate the incidence of thromboembolic events. As discussed previously the Applicant response on August 25, 2017, revealed 15 serious VTE events in the abemaciclib safety database of two studies in combination with endocrine based therapies and 2 events in the placebo arms of these studies. Additionally, there was at least one fatal event in the abemaciclib arm. In the entire safety database, it was noted that there were 35 non-fatal VTE events in those treated with abemaciclib (1.34%) and 4 fatal events (0.15%) as compared to 2 non-fatal events (0.4%)

and no fatal events (0) in the non-abemaciclib treated patients in the safety database. Given this, as discussed previously, a Warning and Precaution was added to the USPI labelling information to highlight these findings so that providers and patients are aware to monitor for the signs and symptoms of VTE events.

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 parynchemal lung metasteses, 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.

7.4.6. Safety Analyses by Demographic Subgroups

Age

In the MONARCH 2 study, 34.8% of patients (155/446) in the abemaciclib plus fulvestrant arm were age 65 or greater and 40.4% of patients (90/223) were age 65 or older in the placebo plus fulvestrant arm.

The overall incidence of SAEs was numerically greater patients ≥65 years (48/155, 31.0%) than in patients <65 years (75/286, 26.2%) in the abemaciclib plus fulvestrant arm. The most frequently reported (≥10%) TEAEs in patients ≥65 years are in Table 62 below.

Table 62. TEAEs ≥10% in Patients 65 or greater in MONARCH 2

	Abemaciclib plus fulvestrant, n=155			Placebo plus fulvestrant, n=90		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Diarrhea	132 (85.2)	26 (16.8)	0	28 (31.1)	1 (1.1)	0
Fatigue, asthenia, malaise	93 (60.0%)	7 (4.5)	--	31 (34.4)	1 (1.1)	0

Abdominal Pain, AP upper, AP lower	85 (54.8)	5 (3.2)	0	10 (11.1)	1 (1.1)	0
Nausea	82 (52.9)	5 (3.2)	0	22 (24.4)	1 (1.1)	0
Neutropenia, neutrophil count decreased	64 (41.3)	34 (21.9)	3 (1.9)	2 (2.2)	0	1 (1.1)
Decreased appetite	58 (37.4)	1 (0.6)	0	12 (13.3)	0	1 (1.1)
Infections and infestations	58 (37.4)	4 (2.6)	3 (1.9)	22 (24.4)	3	0
Anemia	43 (27.7)	9 (5.8)	0	4 (4.4)	1 (1.1)	0
Leukopenia, WBC decreased	43 (27.7)	14 (9.0)	1 (0.6)	1 (1.1)	0	0
Dysgeusia	39 (25.2)	0	0	3 (3.3)	0	0
Vomiting	36 (23.2)	2 (1.3)	0	9 (10.0)	1 (1.1)	0
Creatinine increased, included AKI	35 (22.6)	6 (3.9)	0	1 (1.1)	0	0
Dizziness	28 (18.1)	1 (0.6)	0	5 (5.6)	0	0
Rash	28 (18.1)	4 (2.6)	0	7 (7.8)	0	0
Cough	28 (18.1)	1 (0.6)	0	9 (10.0)	0	0
Thromobcytopenia, platelet count decreased	26 (16.8)	4 (2.6)	2 (1.3)	3 (3.3)	0	0
Constipation	23 (14.8)	1 (0.6)	0	13 (14.4)	1 (1.1)	0
Edema Peripheral, peripheral swelling	22 (14.2)	0	0	9 (10.0)	0	0
Weight decreased	22 (14.2)	1 (0.6)	0	3 (3.3)	0	0
Alopecia	21 (13.5)	0	0	3 (3.3)	0	0
Pruritis	17 (11.0)	0	0	8 (8.9)	0	0
Headache	17 (11.0)	1 (0.6)	0	3 (3.3)	0	0

Source: FDA Analysis using adsl.xpt

In the MONARCH 1 study, 31.8% of patients (42/132) treated with abemaciclib were age 65 or greater.

The overall incidence of SAEs was 26.2% (11/42) in patients ≥65 years as compared to 23.3% (21/90) patients <65 years treated with abemaciclib. Treatment emergent adverse events reported in ≥10% of patients over 65 in the MONARCH 1 study are in Table 63 below.

Table 63. TEAEs in Patients 65 or greater in MONARCH 1

	Abemaciclib N=42		
	All Grades	**Grade 3**	**Grade 4**
Diarrhea	37 (88.1)	9 (21.4)	0
Fatigue, asthenia, malaise	28 (66.7)	6 (14.3)	0
Nausea	28 (66.7)	3 (7.1)	0
Decreased appetite	25 (59.5)	2 (4.8)	0
Neutropenia, neutrophil count decreased	16 (38.1)	11 (26.2)	2 (4.8)
Abdominal Pain, AP upper, AP lower	15 (35.7)	0	0
Vomiting	15 (35.7)	0	0
Infections and infestations	13 (31.0)	1 (2.4)	1 (2.4)
Anemia	12 (28.6)	1 (2.4)	0
Cough	10 (23.8)	0	0
Constipation	10 (23.8)	0	0
Thromobcytopenia, platelet count decreased	9 (21.4)	0	0
Creatinine increased, included AKI	8 (19.0)	1 (2.4)	0
Rash	8 (19.0)	1 (2.4)	0
Leukopenia, WBC decreased	7 (16.7)	2 (4.8)	0
Weight decreased	7 (16.7)	0	0
Edema Peripheral, peripheral swelling	6 (14.3)	0	0
Dysgeusia	5 (11.9)	0	0
Dizziness	5 (11.9)	0	0
Headache	5 (11.9)	0	0
Pruritis	4 (9.5)	1 (2.4)	0
Alopecia	2 (4.8)	0	0

Source: FDA Analysis using adsl.xpt

Race

In the MONARCH 2 study, the 53.1% (237/446) of patients treated with abemaciclib and fulvestrant were Caucasian while 33.4% (149/446) were Asian. Two percent of patients (9/446) were black or African-American and 4.0% (18/446) were American Indian or Alaska Native.

The overall incidence of SAEs was similar in Asian patients compared to the Causcasian population in the abemaciclib plus fulvestrant arm. The most frequently reported TEAEs in Asian patients were similar to those in the patient population overall with the most commonly reported adverse event being diarrhea. There was an increased incidence of Grade 3 or greater neutropenia with 44.6% of Asian patients and 17.6% of non-Asian patients having a reported TEAE of neutropenia and 50.4% of Asian patients and 23.3% of non-Asian patients had a TEAE report of neutrophil count decreased. The incidence of Grade 3 or greater abnormal LFTs was higher in Asian patients as well with ALT laboratory toxicity 6.9% in Asian patients and 2.7% in non-Asian patients and AST laboratory toxicity 6.9% in Asian patients and 1.9% in non-Asian patients. There were no major differences in the rate of blood creatinine increased or laboratory toxicity of creatinine increased, and no major differences in the rate of infections.

In the MONARCH 1 study, 84.8% of patients were Caucasian with 4.5% of patients reported as Black or African-American and 1.5% of patients reported as Asian.

Gender

All patients in the MONARCH 2 and MONARCH 1 studies were female.

Reviewer Comment: *Patients aged 65 and older who were treated with abemaciclib account for 36.6% of the study population. As can be seen above, there was a numerical increase in TEAEs seen in the older population in both studies, with a larger difference seen in the MONARCH 2 study. Asian patients were the largest non-white group represented in the MONARCH 2 study. There were differences in the rate of neutropenia and LFT abnormalities with a slightly increased incidence of each in Asian patients. The other subgroups are too small to be able to make meaningful comparisons.*

7.4.7. Specific Safety Studies/Clinical Trials

Based on responses received on September 8 to an information request regarding ongoing studies evaluating safety concerns, 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).

7.4.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
See Pharmacology/Toxicology Review.

Pediatrics and Assessment of Effects on Growth
Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Overdose
No accidental overdoses were reported in MONARCH 2 or MONARCH 1.

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.

7.4.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
Not applicable.

Expectations on Safety in the Postmarket Setting
In the postmarketing setting, it is anticipated that there may be reduced incidence of diarrhea given provider and patient awareness based on labelling recommendations and earlier active management. It is thought that the incidence of neutropenia and risk of infection will be similar. There may be increased risks associated with thromboembolic events given this phenomenon was seen across two randomized clinical trials in the development program. The

relative risk is not sufficient to merit thromboprophylaxis or recommendations to discontinue treatment after an event, however providers and patients should be vigilant about the signs and symptoms of VTE events to ensure they are diagnosed and treated promptly.

7.4.10. Integrated Assessment of Safety

The safety profile of abemaciclib plus fulvestrant or abemaciclib as a single agent for the treatment of patients with advanced or metastatic HR-positive, HER2-negative breast cancer is acceptable with adverse reactions typically manageable through the use of abemaciclib dose reduction, temporary treatment discontinuation, and/or standard medical care. There is increased risk of diarrhea associated with this drug as compared to other agents in the same class.

Like other agents in this class, there was an increased risk of neutropenia and infection. This was highlighted in the Warnings and Precautions section with recommendations regarding white blood cell count and differential monitoring and appropriate dose reductions and management.

Additionally, there was an increased risk for VTE events seen in multiple studies within the clinical program with deaths associated with these events. Labelling has reflected these increased risks so that providers and patients are aware of the signs and symptoms of these events and promptly address them to mitigate potential harm.

SUMMARY AND CONCLUSIONS

7.5. Statistical Issues

There are no major statistical issues with this application.

7.6. Conclusions and Recommendations

Based on the favorable risk:benefit profile, the clinical and statistical reviewers recommend approval for abemaciclib in combination with fulvestrant for women with HR-positive, HER2-negative MBC who have progressed on endocrine therapy and as monotherapy for adult patients with HR-positive, HER2-negative MBC who have progressed on endocrine therapy and chemotherapy in the metastatic setting. The risks identified are addressed in product labelling 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

8 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held for this NDA.

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9 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.

APPEARS THIS WAY ON ORIGINAL

10 Labeling Recommendations

10.1. Prescribing Information

The table below summarizes changes to the proposed prescribing information made by FDA. See the final approved prescribing information for VERZENIO (abemaciclib) accompanying the approval letter for more information.

Summary of Significant Labeling Changes		
Section	**Proposed Labeling**	**Approved Labeling**
Highlights		
Indications and Usage	…	*See revisions to Full Prescribing Information, Indications and Usage*
Warnings and Precautions	Diarrhea (5.1)	*See revisions to Full Prescribing Information, Warnings and Precautions (5.1).*
Warnings and Precautions	Hepatotoxicity (5.3)	*See revisions to Full Prescribing Information, Warnings and Precautions (5.3).*
Warnings and Precautions	Venous Thromboembolism (5.4)	FDA added this Warning and Precaution. *See revisions to Full Prescribing Information, Warnings and Precautions (5.4).*
Warnings and Precautions	Embryo-Fetal Toxicity (5.5)	FDA added this Warning and Precaution. To Highlights, *FDA added:* "Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. (5.5, 8.1, 8.3)". *See revisions to Full Prescribing Information, Warnings and Precautions (5.5).*
Adverse Reactions	…	FDA revised the most common ARs from incidence ≥

		(b) (4) % to ≥ 20% and revised the listed Adverse Reactions (ARs) reflect FDA safety review findings (i.e., added abdominal pain and revised order of listed ARs).
Drug Interactions	…	FDA revised this section to add "avoid concomitant use of ketoconazole and removed the (b) (4)
Full Prescribing Information (FPI)		
1. Indications and Usage	(b) (4)	FDA revised to the following: VERZENIO™ (abemaciclib) is indicated: • 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. • 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 See *Conclusions on the Substantial Evidence of Effectiveness* for more information.
2. Dosage and	2.1 Recommended Dose and	FDA added the following

Administration	Schedule …	information to better clarify the indicated dose and schedule: "When given with VERZENIO, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, and 29; and once monthly thereafter. Refer to the Full Prescribing Information for fulvestrant. Pre/perimenopausal women treated with the combination of VERZENIO plus fulvestrant should be treated with a gonadotropin-releasing hormone agonist according to current clinical practice standards."
	2.2 Dose Modification …	FDA removed non-actionable statements describing general dose modification considerations and removed redundant information from text also listed in the dose modification tables for adverse reactions. FDA added "and increase intake of fluids" to the dose modification and management of diarrhea table (Table 3). FDA added "Avoid concomitant (b) (4) use of the strong CYP 3A4 inhibitor ketoconazole." to the Dose Modifications for Use with Strong CYP3A Inhibitors subsection. *See the FDA Clinical Pharmacology review for more*

		information.
5. Warnings and Precautions	5.1 Diarrhea … 5.3 Hepatotoxicity …	FDA added this Warning and Precaution due to the high incidence of diarrhea, occurrence of severe cases of diarrhea that are sometimes dose limiting, and because the diarrhea adverse reactions associated with Verzenio often require dose modification and management to avoid serious outcomes. *[see FDA Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling, Section II.A. 1 and 2]* FDA revised (b) (4) to "Hepatotoxicity" to accurately characterize the risk to patients (b) (4) This is consistent with current best labeling practices within OHOP and FDA Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling, [Section II.D.1].
	5.4 Venous Thromboembolism …	FDA added this Warning and Precaution based on FDA safety review and analysis. See "Thromboembolic events" for more information.
	(b) (4) Embryo-Fetal Toxicity	FDA added this Warning and Precaution based on animal studies and Verzenio's mechanism of action to communicate the risk of fetal harm to a pregnant woman and to provide information for contraception.

6. Adverse Reactions	6.1 Clinical Studies Experience	FDA revised the summary of the safety information to clarify the number of patients exposed to Verzenio in the MONARCH 2 trial (n=441 patients) with HR-positive, HER2-negative advanced breast cancer; the safety database used to safety analyses for the indicated patient population. FDA added and revised the adverse reactions that led to dose modification and permanent discontinuation of Verzenio. FDA added deaths due to adverse events that occurred on treatment or within 30 days of discontinuation of Verzenio (regardless of causality) (i.e., underlying disease, sepsis, pneumonitis, hepatic failure, and cerebral infarction). FDA revised the most common ARs (≥ 20%) to add neutropenia, abdominal pain, and headache. Consistent with the revisions made for the MONARCH 2 trial, FDA made revisions to the summary of safety information for the MONARCH 1 trial. FDA added a section to describe creatinine elevations without changes in renal function due to Verzenio and to provide alternate test

		methodologies.
7. Drug Interactions	7.1 Effect of Other Drugs on VERZENIO …	FDA revised this subsection to add a heading for ketoconazole and advice to avoid concomitant use of (b) (4) ketoconazole and a statement that cross references to dose reductions required for use with strong CYP3A inhibitors. FDA removed non-actionable information related to drug interactions that lacked clinical relevance or that were theoretical (b) (4) (b) (4). Some of this information was retained in Section 12 Clinical Pharmacology.
8. Use in Specific Populations	8.1 Pregnancy Risk Summary …	FDA revised the risk summary and fetal harm information to include mechanism of action concerns for Verzenio. FDA added additional data to clarify the nonclinical findings in the embryo-fetal development study as follows: "These findings included absent innominate artery and aortic arch, malpositioned subclavian artery, unossified sternebra, bipartite ossification of thoracic centrum, and rudimentary or nodulated ribs."
	8.6 Renal Impairment …	FDA clarified that the pharmacokinetics of abemaciclib in patients with severe renal impairment, end

		stage renal disease, or in patients on dialysis is unknown.
	8.7 Hepatic Impairment …	FDA added the following: "Reduce the dosing frequency when administering VERZENIO to patients with severe hepatic impairment (Child-Pugh C) [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]."
12. Clinical Pharmacology	12.1 Mechanism of Action …	FDA revised this section to remove vague undefined terms to avoid unsupported suggestions of therapeutic advantages based on MOA that could be false or misleading (b) (4) (b) (4)
	12.2 Pharmacodynamics …	FDA removed (b) (4) that did not well established or clearly related to the drug's clinical effects and lacking clinical relevance consistent with the advice in the FDA's Guidance for the Clinical Pharmacology Section of Labeling (Section IV.B.).
	<u>Specific Populations</u> <u>…</u>	FDA removed redundant pharmacokinetic figures for (b) (4) (b) (4) findings already described in detailed text descriptions.
	<u>Drug Interaction Studies</u> <u>…</u>	FDA revised the information related to Strong CYP3A inhibitors (including

		ketoconazole and itraconazole) based on FDA clinical pharmacology review findings. FDA also made similar revisions to the findings related to moderation CYP3A inhibitors, and strong and moderate CYP3A inducers.
13. Nonclinical Toxicology	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility …	FDA revised the nonclinical findings to clarify the effects of abemaciclib on male reproductive organs in animals and the exposure levels at which these toxicities were observed respective to the human maximum recommended dose.
14. Clinical Studies	<u>VERZENIO in Combination with Fulvestrant (MONARCH 2)</u> …	In accordance with best labeling practice, FDA added the clinical trial names (throughout labeling) and the NCT number of the trials listed in the Clinical Studies section. FDA clarified that patients enrolled in the MONARCH2 trial had not received chemotherapy in the metastatic setting and added the definition for primary endocrine therapy resistance. FDA removed (b) (4) and described the key baseline disease in text. FDA added Eastern Cooperative Oncology Group (ECOG) performance status. FDA also clarified and revised clinically relevant information related to patient

		characteristics for *de novo* metastatic disease, bone-only disease, visceral disease, and primary endocrine therapy resistance. FDA removed redundant efficacy results in the text that were also presented in the efficacy results table (Table 11) and removed (b) (4) analyses (b) (4) (b) (4) (b) (4) according to OHOP best labeling practices. The revisions above were applied for the MONARCH 1 study characteristics, patient characteristics, and efficacy results. FDA also clarified and revised clinically relevant patient characteristics related to median duration of metastatic disease, visceral metastases, lines (one) of chemotherapy in the metastatic setting, taxane-based regimen in the metastatic setting, and capecitabine in the metastatic setting. FDA also removed efficacy results (b) (4) (b) (4)
	<u>VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)</u> …	

		(b) (4) according to OHOP best labeling practices and lack of multiplicity adjustment.
15. References	…	FDA removed (b) (4) due to existing information in labeling for healthcare providers.
16. How Supplied / Storage and Handling	…	FDA removed (b) (4) to improve comprehension, readability, and to better conform to the labeling requirements for Section 16.
17. Patient Counseling Information	…	FDA reorganized the counseling topics to reflect the order and add new topics consistent with the Warnings and Precautions sections.

10.2. Patient Labeling

The Patient Information for Verzenio was reviewed and revised by the FDA's Patient Labeling Team (PLT) and FDA Review Team. In summary, the following revisions were made to the Patient Information:

"What is the most important information I should know about VERZENIO?"

- To be consistent with the Warnings and Precautions the following revisions were made to this subsection:
  - Diarrhea information was added
  - A list of signs and symptoms for "liver problems" was added.
  - A subsection for "blood clots" was added.

"Before taking VERZENIO, tell your healthcare provider about all of your medical conditions, including if you:"

- Information was added for signs of an infection, liver, and kidney problems
- Pregnancy and breastfeeding information was revised
- A statement for patients to inform healthcare providers when taking ketoconazole was added.

"What should I avoid during treatment with (b) (4) VERZENIO?"

- Information not found in the prescribing information was removed for consistency.

Other revisions were made throughout the Patient Information for consistency with the prescribing information and to improve readability and formatting. *See the FDA PLT review filed with NDA 208716 for complete details.*

11 Risk Evaluation and Mitigation Strategies (REMS)

None.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

None.

11.2. Conditions of Use to Address Safety Issue(s)

None.

11.3. Recommendations on REMS

None.

11.4. Patient Reported Outcomes

Patient reported outcomes (PRO) data were collected as part of both the MONARCH 2 and MONARCH 1 studies. For the MONARCH 2 study, the Applicant chose to use the Modified Brief Pain Inventory, Short Form (mBPI-sf) as the primary health outcome research goal was to determine whether abemaciclib in combination with fulvestrant was able to palliate pain. Additionally, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and Breast Cancer (EORTC QLQ-BR23) questionnaires were used to assess symptom specific data, the impact of therapy on health related quality of life (HRQoL), and other disease specific data. The EQ-5D-5L was used to allow for assessment of health status for comparison with other disease and tumor types. These assessments were collected at baseline, cycle 2 day 1, and then beginning with cycle 3 at every second cycle through cycle 13 and then every third cycle after cycle 13. Data were also collected at the short term follow up visit.

In the MONARCH 1 study, the primary health outcome research goal was the assessment of whether abemaciclib was able to palliate pain as measured by the mBPI-sf. Addtionally, the EORTC QLQ-C30 was used to evaluate the impact of abemaciclib on treatment related symptoms and broader HRQoL. These assessments were collected at days 1 and 15 of cycle 1 and then with each visit when the patient was at the clinic for other study assessments. Data were also collected at the short term follow up visit.

At this time, when there are no prespecified hypotheses to test, no claims for treatment benefit that are associated with clear PRO endpoint definition, formal statistical testing, or adjustment for multiplicity, the Agency evaluates PRO data to describe symptomatic adverse events and the experience of patients on therapy including the impact on patient physical function and other aspects of HRQoL.

The choice of tools for assessment of patient reported outcome measures, the EORTC QLQ-C30 and the EORTC-QLQ BR23 can aid in assessments of the tolerability of therapy. The Agency considers the EORTC-QLQ BR23 to have a number of limitations in the metastatic setting given the disease module contains many questions related to body image, sexual function, and localized symptoms that are not likely to be responsive to the effects of systemic therapy in the metastatic setting. The EORTC QLQ-C30 does have multiple items that are able to assess various domains of HRQoL. However, within these instruments, there are few questions that are able to specifically assess treatment-related symptoms and their interference.

<u>Statistical Analysis Plan</u>

Key patient reported outcomes in MONARCH 2 were pain deterioration and quality of life.

Completion rates for each instrument were calculated for each planned assessment for each instrument. The completion rate for each PRO assessment was defined as the number of

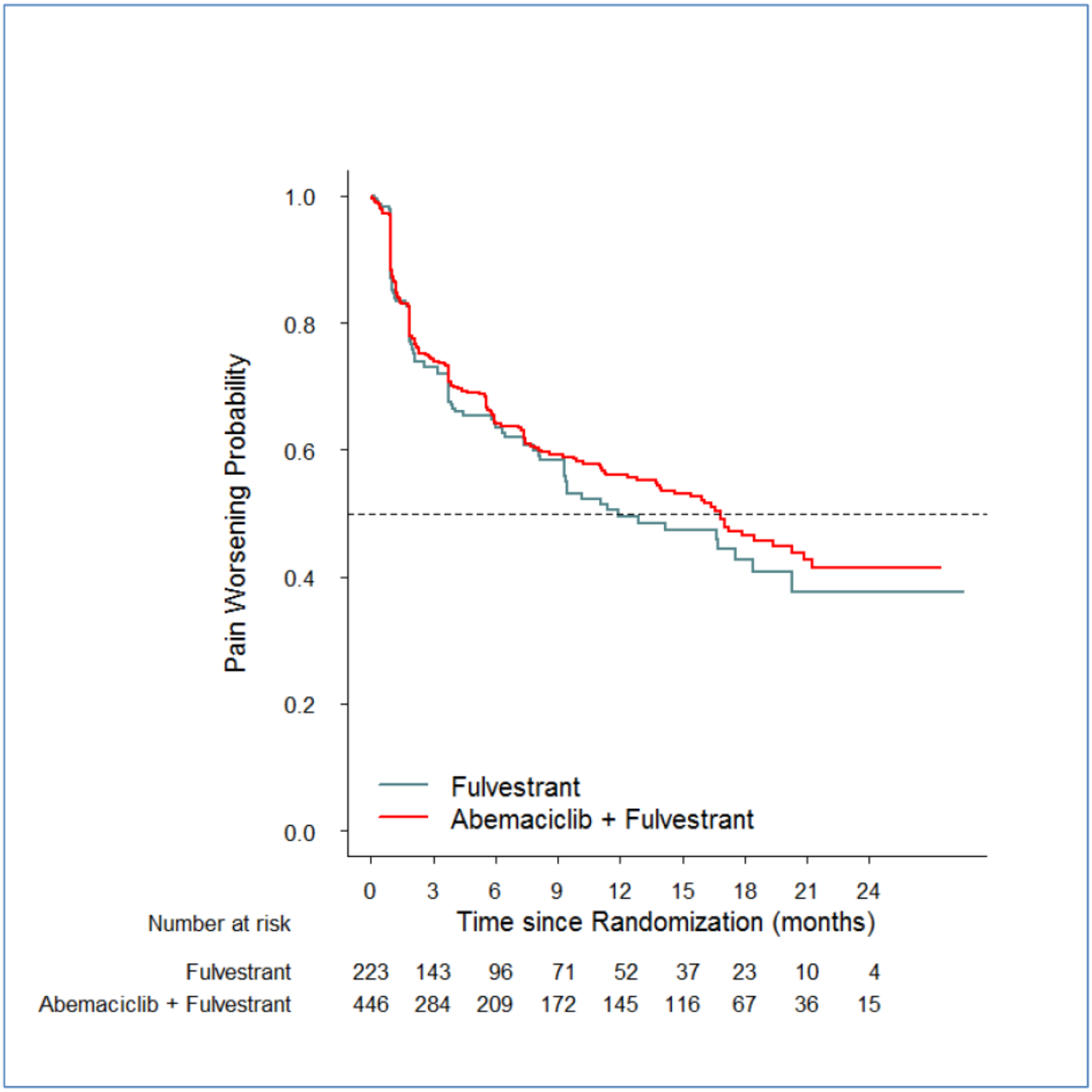
patients eligible to be assessed for that study visit. Changes from baseline in continuous scores were analyzed descriptively by treatment in each cohort in the MONARCH 2 and descriptively for those in MONARCH 1.

Patient Reported Outcome Results

PRO Completion Rates
As shown in Table 64, the completion rates for the EORTC QLQ-C30, EORTC QLQ-BR23, EQ 5D-5L and mBPI-sf were good with rates above 90% at most cycles. A similar completion rate was seen in MONARCH 1 (see Table 65).

Pain (MONARCH 2)
The primary health reported outcome was time-to-progression of pain as measured by the mBPI-sf. Time-to-progression was defined as a two-point increase in “worst-pain” or a one-point increase in analgesic drug use. Analgesic drug use was coded into three categories: non-opioid, weak opioid, and strong opioid, so a one-point increase would be moving to a stronger category. The result was not statistically significant (HR=0.90, 95% CI = 0.70, 1.15). A Kaplan-Meier plot of time-to-progression is shown in Figure 10 below.

Figure 10. Kaplan-Meier Plot of Pain Worsening (MONARCH 2)

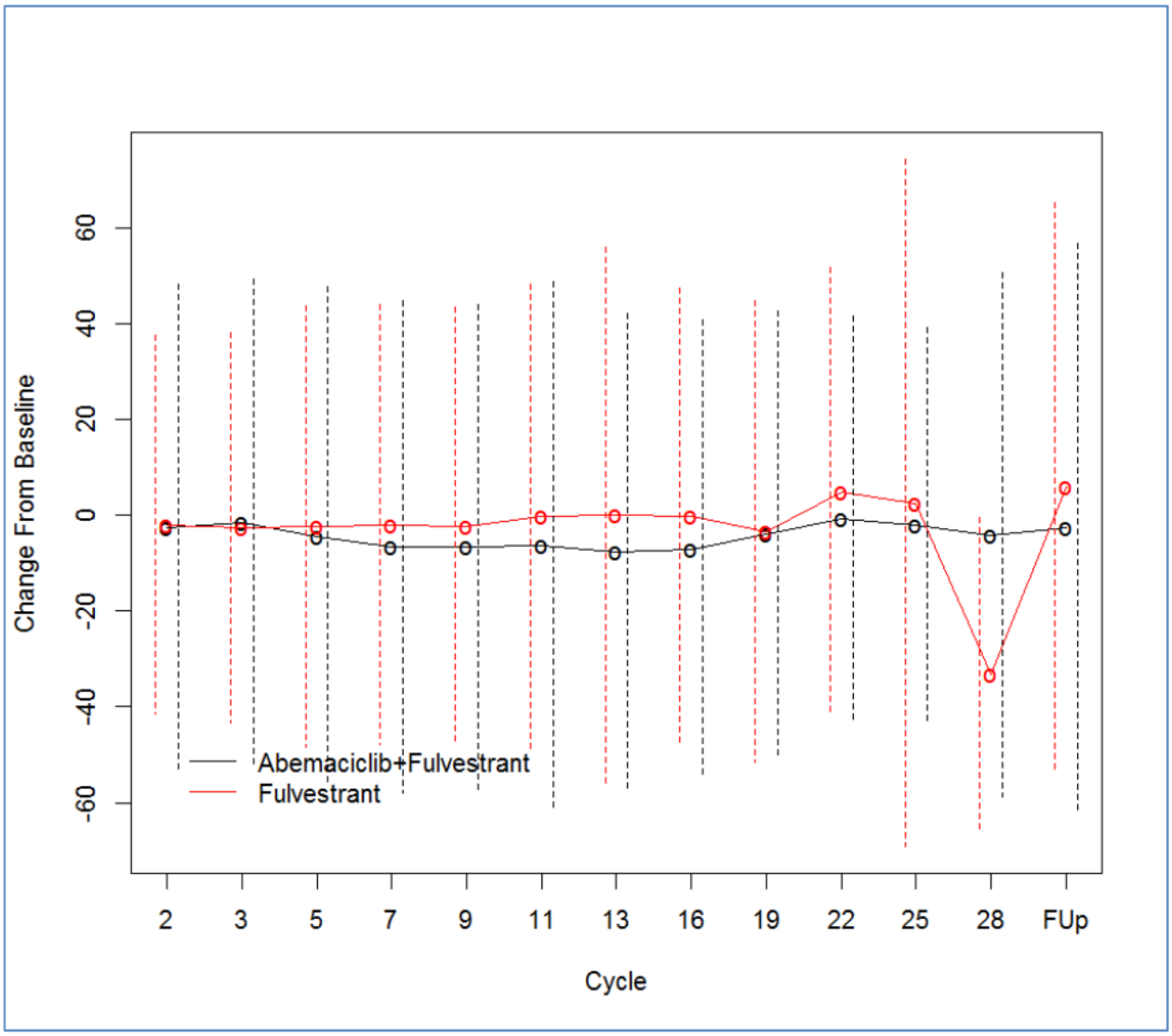


Source: Reviewer's Analysis (dataset: adtteqs.xpt)

To further examine how pain changed over time, we looked at change from baseline for the pain scale in the EORTC QLQ-C30 instrument. As shown in

Figure 11, the abemaciclib + fulvestrant arm had a slightly lower change from baseline for the pain score, but the results are not significant due to the large variability in the data.

Figure 11. Change From Baseline EORTC QLQ-C30 Pain Scale (MONARCH 2)



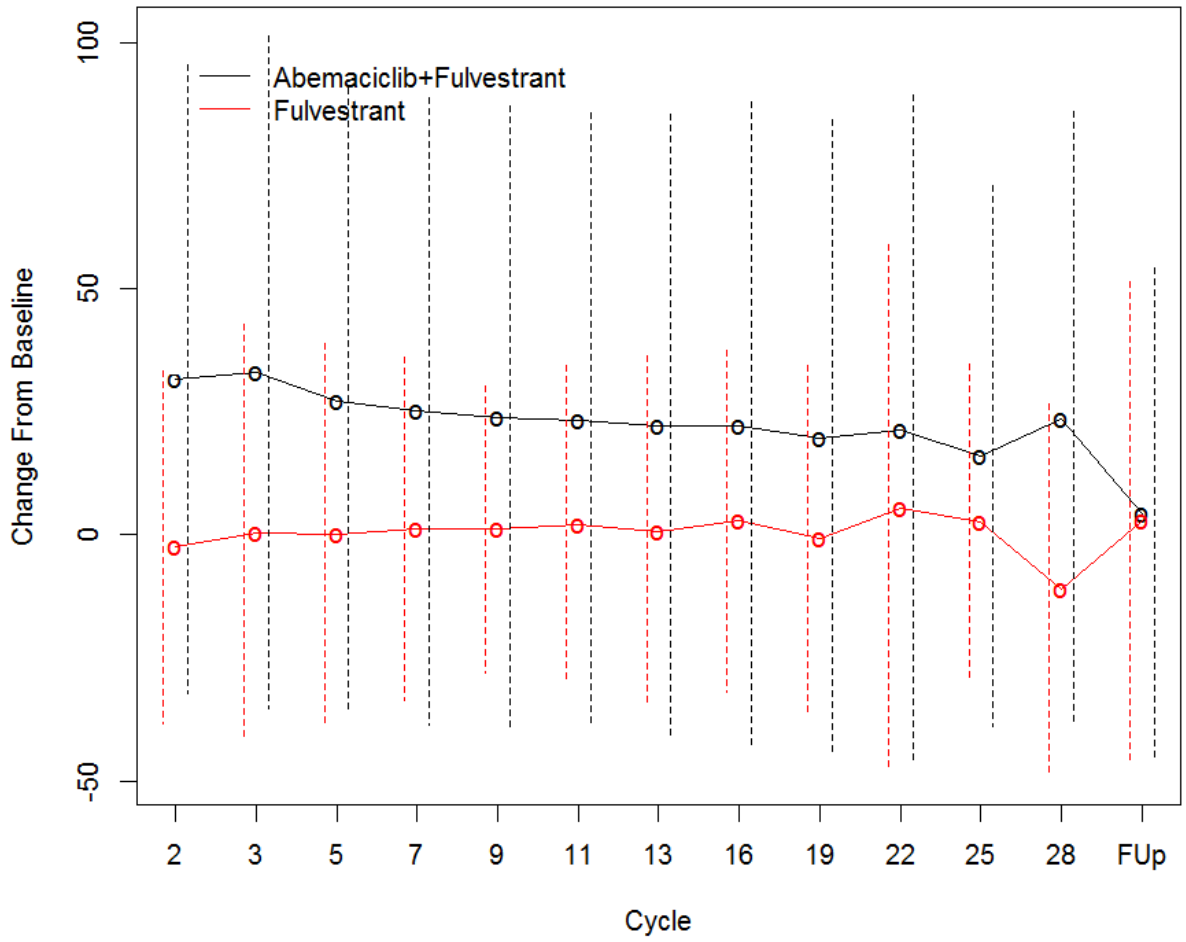
Source: Reviewer's Analysis (dataset: adqlq.xpt). The error bars represent two standard deviations from the mean.

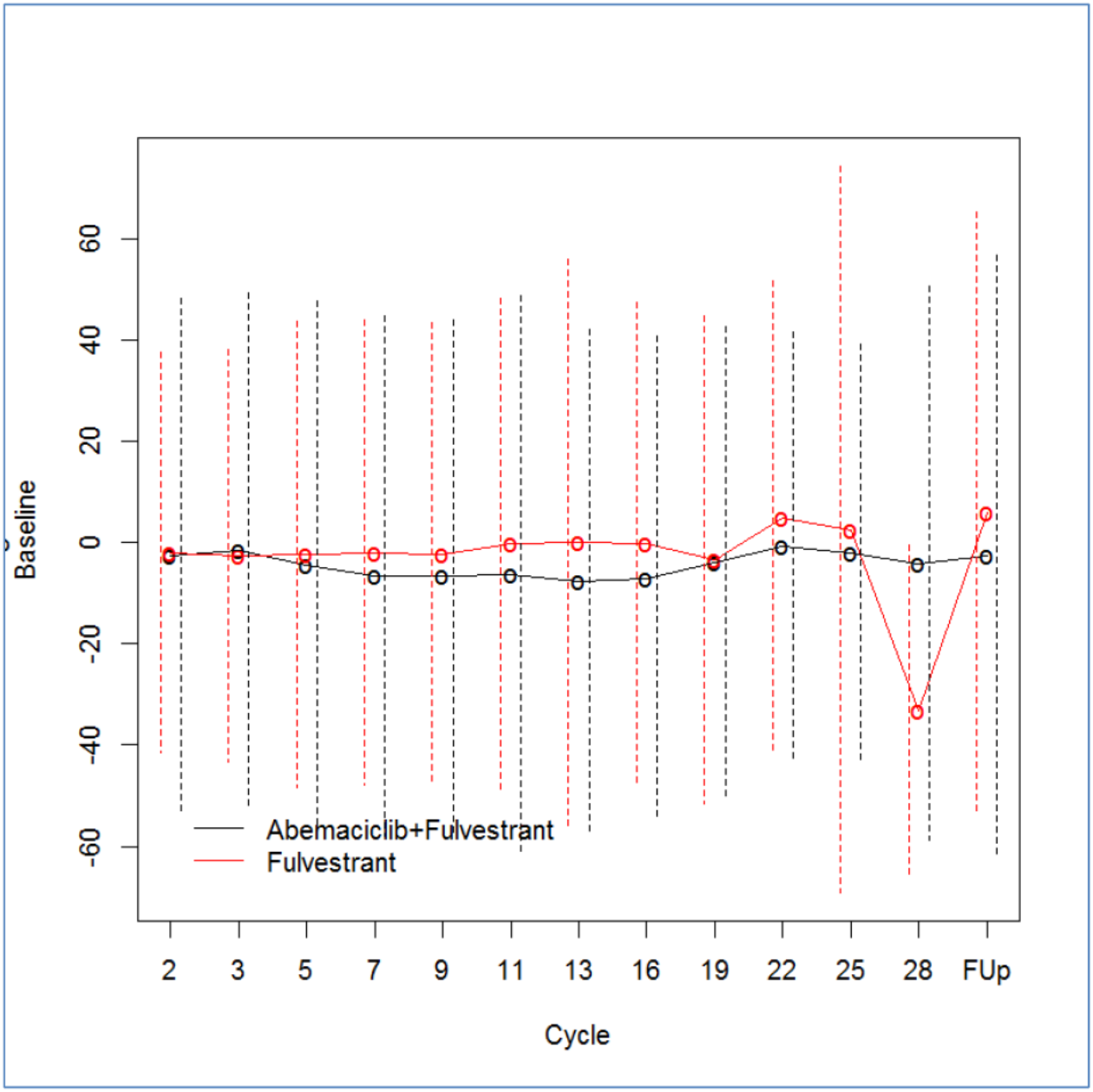
Additional PRO Analyses (MONARCH 2)

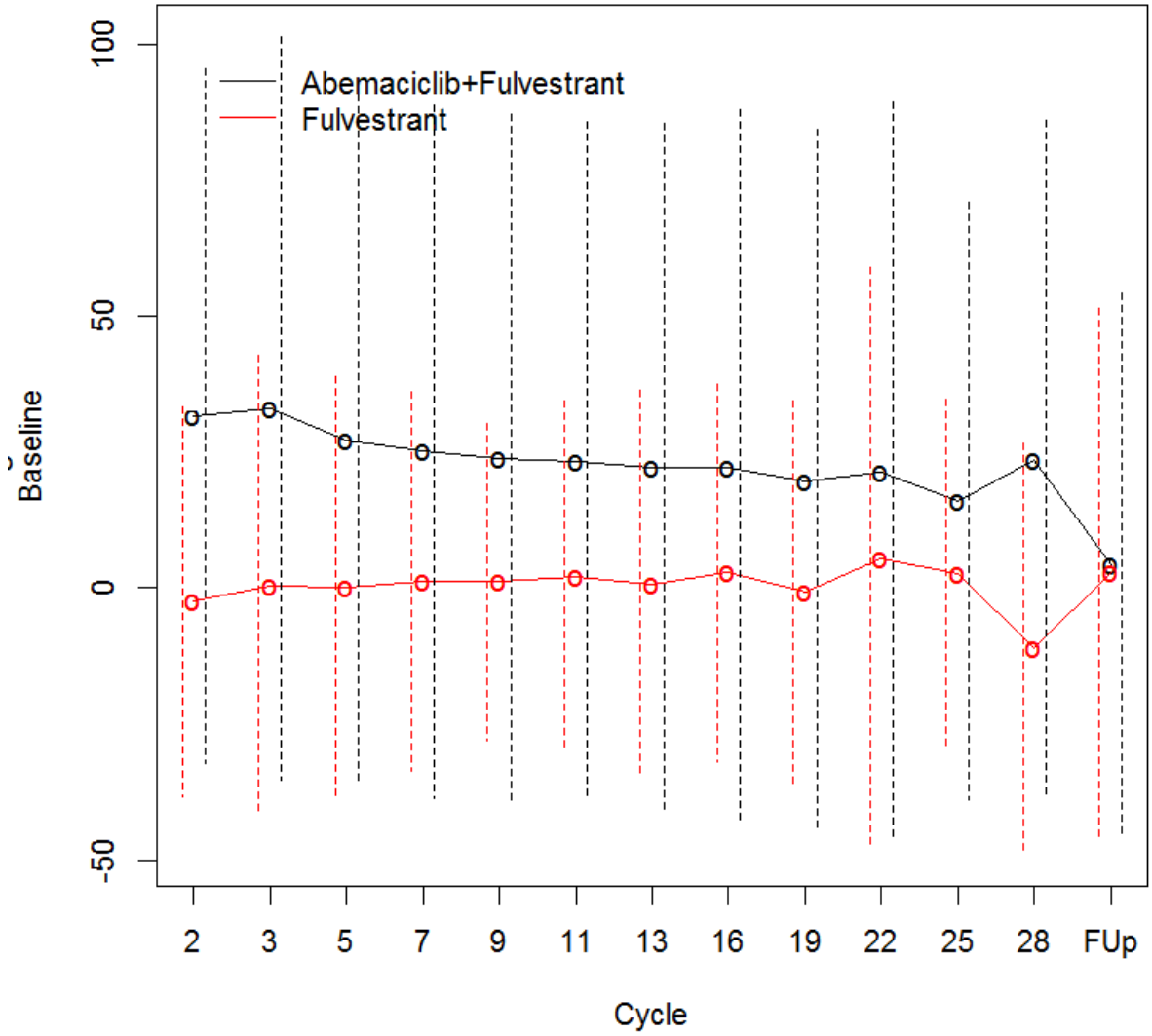
The last two aspects of PRO examined data was the change from baseline for the diarrhea scale and the change from baseline for the global health scale (EORTC QLQC-30). Figure 12 shows the

change from baseline for the diarrhea scale and Figure 12 shows the change from baseline for the global health. As expected, patients taking abemaciclib and fulvestrant reported consistently worse scores for diarrhea than those on the fulvestrant arm. Importantly, the difference disappeared during the follow-up period. Note that on the global health scale, there was little difference between the two arms over time.

Figure 12. Change from baseline EORTC QLQ-C30 Diarrhea Scale (MONARCH 2)

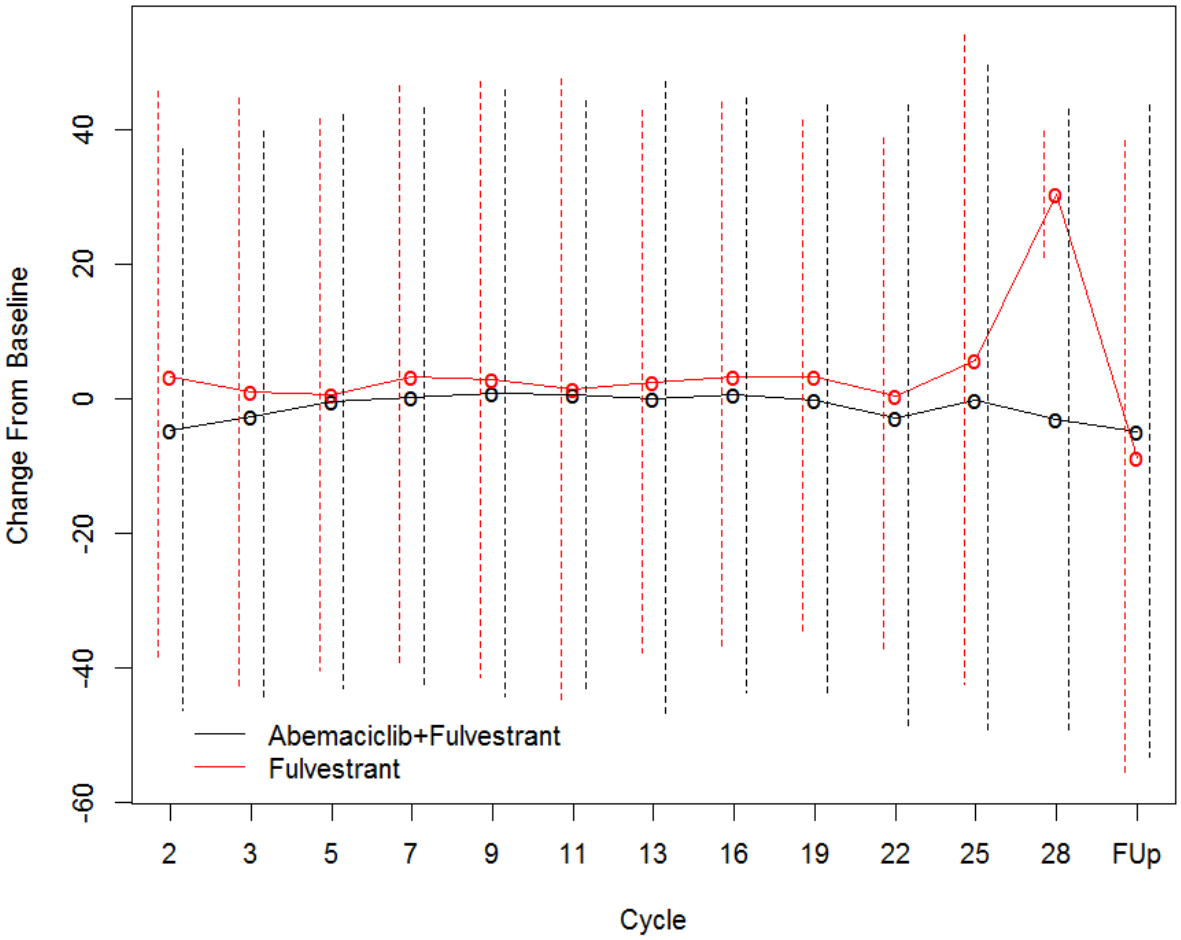



Baseline
60
40
20
0
-20
-40
-60
Abemaciclib+Fulvestrant
Fulvestrant
2
3
5
7
9
11
13
16
19
22
25
28
FUp
Cycle



Source: Reviewer's Analysis (dataset: adqlq.xpt). The error bars represent two standard deviations from the mean.

Figure 13. Change from baseline EORTC QLQ-C30 Global Health Scale (MONARCH 2)



Source: Reviewer's Analysis (dataset: adqlq.xpt).
The error bars represent two standard deviations from the mean.

PRO Analyses (MONARCH 1)

In Monarch 1, PRO data collected on individuals taking single agent abemaciclib. Using the EORTC QLQ C-30, similar results were seen for quality of life and diarrhea scales.

Table 64. PRO Completion Rates by Visit in MONARCH 2

	# of expected patients		EORTC QLQ-C30		EORTC QLQ-BR23		mBPIsf		EQ 5D-5L	
	Abemaciclib + Fulvestrant	Placebo + Fulvestrant	Abemaciclib + Fulvestrant	Placebo + Fulvestrant	Abemaciclib + Fulvestrant	Placebo + Fulvestrant	Abemaciclib + Fulvestrant	Placebo + Fulvestrant	Abemaciclib + Fulvestrant	Placebo + Fulvestrant
Baseline	441	223	97.7%	98.2%	97.7%	98.7%	95.5%	97.8%	97.5%	98.2%
Cycle 2	411	216	96.4%	94.4%	95.4%	94.0%	94.6%	92.6%	95.9%	95.4%
Cycle 3	382	196	96.9%	96.9%	96.1%	95.9%	95.3%	93.9%	96.6%	96.4%
Cycle 5	334	159	96.7%	96.9%	96.4%	98.1%	95.8%	95.0%	96.1%	98.1%
Cycle 7	307	134	94.5%	97.8%	94.1%	97.0%	93.5%	97.0%	94.8%	97.8%
Cycle 9	282	114	95.0%	97.4%	95.7%	96.5%	95.0%	95.6%	94.7%	97.4%
Cycle 11	262	101	95.8%	97.0%	95.4%	97.0%	95.8%	97.0%	96.2%	97.0%
Cycle 13	242	90	97.1%	97.8%	96.7%	97.8%	96.3%	97.8%	96.3%	98.9%
Cycle 16	210	74	92.4%	94.6%	91.9%	94.6%	91.4%	94.6%	92.4%	94.6%
Cycle 19	148	53	95.3%	100.0%	95.3%	100.0%	94.6%	100.0%	95.3%	100.0%
Cycle 22	91	28	96.7%	85.7%	97.8%	85.7%	96.7%	85.7%	97.8%	85.7%
Cycle 25	52	13	98.1%	100.0%	98.1%	100.0%	98.1%	100.0%	98.1%	100.0%
Cycle 28	25	3	96.0%	100.0%	96.0%	100.0%	96.0%	100.0%	96.0%	100.0%
Follow-up	236	138	77.1%	94.2%	78.4%	94.2%	77.5%	89.9%	78.4%	93.5%

Source: CSR Addendum Tables JPBL 7.1, 7.2, 7.3, 7.4

Table 65. PRO Completion Rates by Visit in MONARCH 1

	Abemaciclib Arm		
	# of expected patients	EORTC QLQ-C30	mBPIsf
Baseline	132	99.2%	99.2%
Cycle 1	130	93.8%	93.1%
Cycle 2	119	99.2%	99.2%
Cycle 3	94	95.7%	94.7%
Cycle 4	80	93.8%	93.8%
Cycle 5	69	94.2%	94.2%

Cycle 6	62	95.2%	95.2%
Cycle 7	50	94.0%	94.0%
Cycle 8	47	91.5%	89.4%
Cycle 9	40	97.5%	97.5%
Cycle 10	36	97.2%	94.4%
Cycle 11	36	97.2%	97.2%
Cycle 12	32	96.9%	96.9%
Cycle 13	24	95.8%	91.7%
Cycle 14	21	95.2%	95.2%
Cycle 15	15	100.0%	100.0%
Cycle 16	12	100.0%	100.0%
Cycle 17	8	100.0%	100.0%
Cycle 18	7	100.0%	100.0%
Cycle 19	5	100.0%	100.0%
Cycle 20	3	100.0%	100.0%
Cycle 21	2	100.0%	100.0%
Cycle 22	1	100.0%	100.0%
Cycle 23	1	100.0%	100.0%
Follow-up	107	67.3%	68.2%

Source JPBN Table 14.6, 14.12

Reviewer Comments: *As can be seen in the analyses above, there was a high completion rate of PRO data demonstrating that collection of these data were feasible. The time to pain progression was slightly better in the abemaciclib plus fulvestrant group, however it is hard to know what magnitude in change of TTP would be considered clinically significant. Given the lack of prespecified objectives and that treatment related symptom data do not add significantly to the existing adverse event data, there are no recommendations to include these data in labelling.*

12 Postmarketing Requirements and Commitments

The following Postmarketing Requirements (PMR) were recommended and agreed upon with the Applicant:

- Submit a final report and data sets from a new clinical trial to evaluate the incidence of dose reductions and dose interruptions due to severe diarrhea when abemacicib is administered with a meal, compared to abemaciclib taken in the modified fasted condition, and when it is administered without regard to food in patients.

  Timelines: Final Protocol Submission: 06/30/2018
  Trial Completion: 06/30/2021
  Final Report Submission: 12/31/2021

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

- Conduct PBPK analysis to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of abemaciclib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. If the results from the PBPK analysis are inconclusive, conduct a pharmacokinetic trial to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinectics of abemaciclib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations." Submit final report and data sets.

  Timelines: Final Report Submission: 02/2018

- Submit the overall survival (OS) data and final report from clinical trial MONARCH 2: Entitled "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer"

  Timelines: Final Protocol Submission: 04/01/2014
  Trial Completion: 12/31/2021
  Final Report Submission: 06/30/2022

13 Appendices

13.1. References

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13.2. Financial Disclosure

APPEARS THIS WAY ON ORIGINAL

Covered Clinical Study (Name and/or Number): MONARCH 2 I3Y-MC-JPBN and MONARCH 1 I3Y-MC-JPBL

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2167		
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 S 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) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

None.

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

13.4.1. Pharmacometrics Review

13.4.1.1. Summary of Findings

Based on data submitted in this application, the proposed 200 mg BID dosing regimen for monotherapy and 150 mg BID dose regimen for use with fulvestrant are acceptable from a pharmacometrics (PM) perspective. Dose adjustment based on age, body weight, gender, race, mild or moderate renal impairment, or the presence of hepatic metastases is not necessary.

13.4.1.1.1. Key Review Questions

The purpose of this review is to address the following key questions:

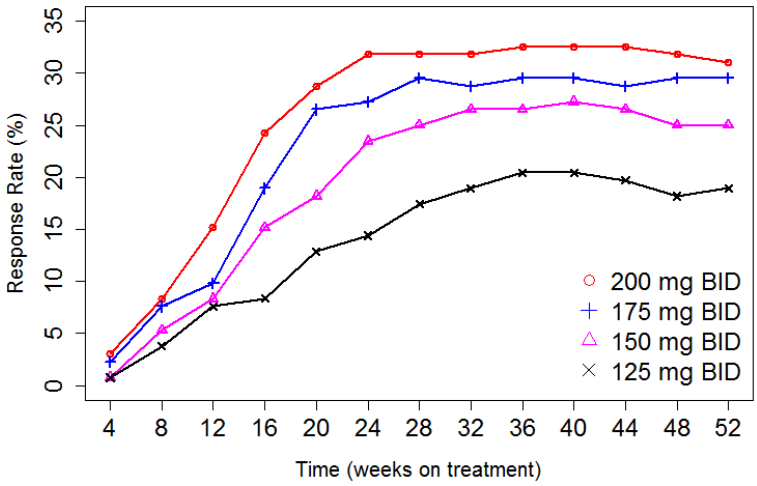
1. **Does clinical data and exposure-response (E-R) analysis support the proposed regimen of abemaciclib as a (b) (4) and in combination with fulvestrant?**

Yes.

<u>The dose regimen of 200 mg BID as monotherapy in late line setting (MONARCH 1 study)</u>

E-R analysis suggests a trend of higher response rate being associated with a higher dose level in the MONARCH 1 study. Based on PK/PD simulations, the response rate based on target lesion at 52 weeks after the start of treatment, is predicted to be 31.1% with 200 mg BID doses vs 25.0% with 150 mg BID doses (Figure 14). Therefore, it is more beneficial from an efficacy perspective to start patients with the proposed 200 mg BID dose rather than with a 150 mg BID dose. In the MONARCH1 study nearly 50% patients who started with 200 mg BID experienced dose reduction and the median duration of 200 mg BID dose was 39 days. Most incidences of Grade 3 or above diarrhea and neutropenia occurred within the first month on the 200 mg BID regimen and were manageable. Therefore, the proposed starting dose of 200 mg BID as monotherapy in the late line setting is acceptable given the favorable risk/benefit profile in MONARCH 1.

Figure 14. Simulated Response Rate (Target Lesion) in MONARCH 1.

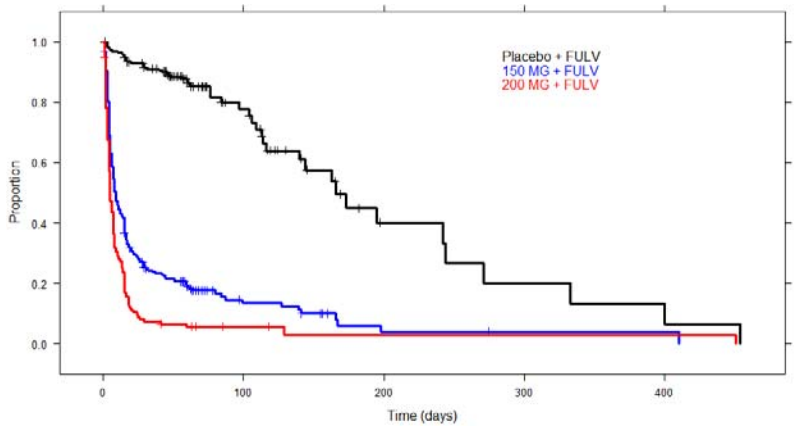


Sources: FDA's reviewer's analysis

<u>The dose regimen of 150 mg BID in combination with fulvestrant in early line setting (MONARCH 2 study)</u>

E-R relationship for tumor size is positive in patients (n=477) with measurable disease in the MONARCH 2 study. Therefore, a higher starting dose (e.g., 200 mg BID) may result in better efficacy than the proposed 150 mg BID. On the other hand, a higher starting dose could lead to a higher risk of diarrhea and a shorter time to first diarrhea based on the dose-response analysis for safety (Figure 15). Therefore, the risk/benefit profile of a higher starting dose in the early line setting is unclear. Overall, the proposed dosing regimen of 150 mg BID in combination with fulvestrant is acceptable based on the clinical and efficacy data from the MORNARCH 2 study.

Figure 15. Kaplan–Meier Plot of Time to First Diarrhea Event in MONARCH 2 Study.

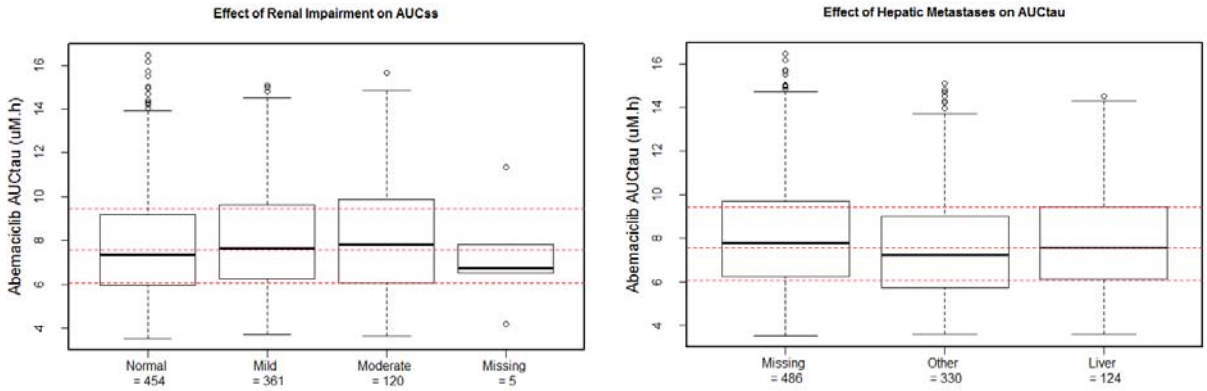


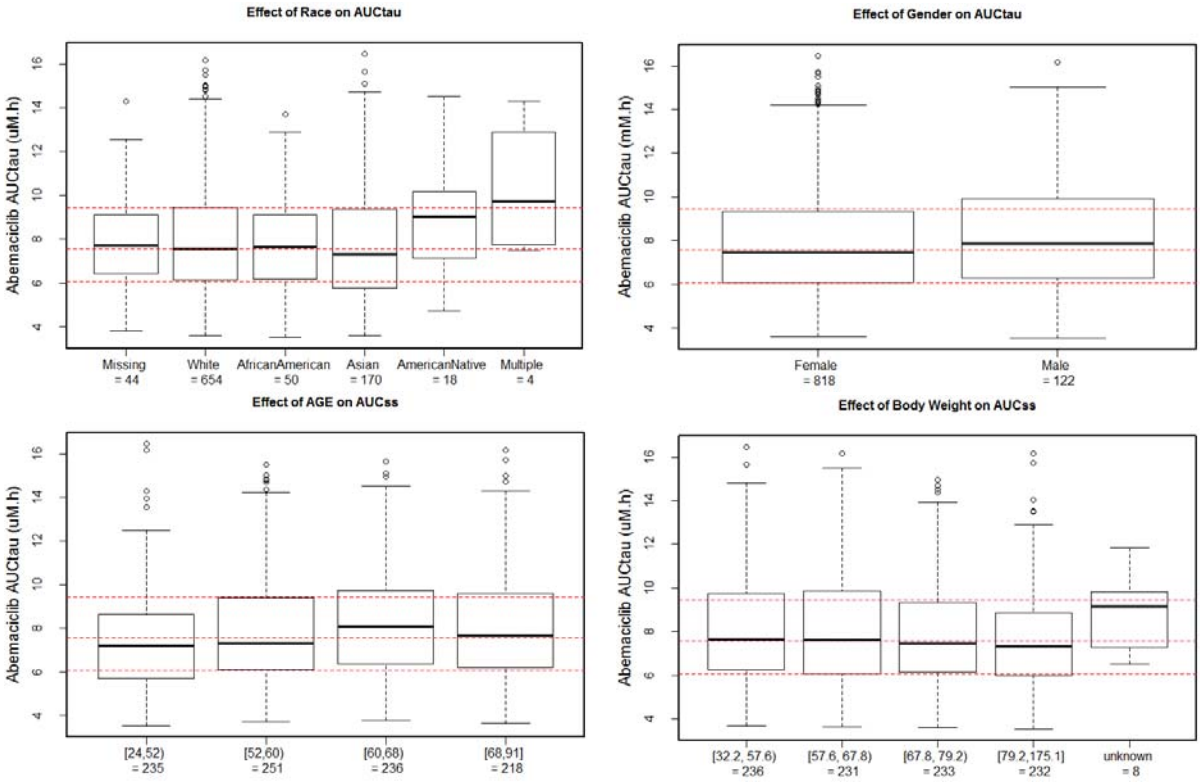
Sources: FDA's reviewer's analysis

2. **Does population pharmacokinetics (popPK) analysis support a lack of covariate effect on abemaciclib PK?**

Yes, the popPK analysis suggests that dose adjustment based on age, weight, gender, race, presence of hepatic metastases, and mild or moderate renal impairment, is not necessary (Figure 16).

Figure 16. The Effect of Selected Covariates on Steady State Abemaciclib AUC. Red dashed lines represent the 125%, 100% and 80% of geometric mean AUCtau in the analysis population.





Sources: FDA's reviewer's analysis

3. Does abemaciclib demonstrate dose proportional PK in the therapeutic range (50-200 mg)?

Even though the final popPK model implies a less than dose proportional increase in abemaciclib exposure, there is a high chance of concluding PK linearity in the range of 50-200 mg, single dose or BID, based on a dose proportionality evaluation using simulated dose escalation studies.

13.4.1.1.2. Recommendations

The Applicant's proposed dosing regimen and labeling claims regarding covariate effects on abemaciclib PK are acceptable from a PM perspective.

13.4.1.2. Sponsor's Population Pharmacokinetics and E-R Analysis

13.4.1.2.1. PPK Analysis

Objectives

- Describe abemaciclib PK in a meta-analysis population including healthy subjects and patients with metastatic breast cancer
- Identify patient factors and laboratory parameters that may influence abemaciclib PK.

Data, Software, Methods

The analysis dataset contained data from nine Phase 1 studies (Studies JPBA, JPBC, JPBD, JPBE, JPBF, JPBG, JPBS, JPBU, JPBV), two Phase 2 studies (Study JPBB and Study JPBN [MONARCH 1]), and one Phase 3 study (Study JPBL, MONARCH 2) (Table 66). The analysis covered abemaciclib doses ranging from 50 mg to 275 mg. Five formulations were evaluated, including three formulations of oral capsules (C3 is the only formulation that was tested in a bioequivalence study and the PK profile closely matches that of the commercial formulation (T1)), one oral solution formulation, and one IV solution formulation. Patient data without correct dosing records, below the lower limit of quantitation, with implausible concentrations, with concomitant drug use in drug-drug interaction studies, or in patients with hepatic impairment were excluded from the analysis.

A PopPK analyses were performed with NONMEM 7.3. Model development consisted of three stages: (1) an empiric model for abemaciclib alone; (2) covariate screening based on the empiric model; (3) a final mechanistic model for abemaciclib and two active metabolites, M2, and M20.

The empiric model was developed without data from Studies JPBL, JPBU, and JPBV. Various PK models of abemaciclib disposition and the effect of diarrhea on abemaciclib bioavailability were tested using the Laplacian method with Stochastic Approximation Expectation-Maximization (SAEM) and Monte Carlo importance sampling (IMP) estimation methods.

Covariates were screened for significance based on parameter precision, plausibility, magnitude, and >10% relative decrease in the inter-individual variance (IIV) estimates. Continuous covariates were tested in a sequential manner: if a covariate is significant in a linear model, a power model would be tested; if a covariate is significant in a power model, an exponential model would be tested; if covariates were not significant using a linear model, further models were not evaluated. Categorical covariates were tested using a categorical model.

The final mechanistic model was developed based on the observed secondary peaks following oral dosing and the expectation of both gut metabolism and hepatic metabolism in first pass effect. Significant covariates identified on the empiric model were included on the parameters in the full mechanistic model that most closely related to the parameters in the empiric model. As a result of numerical difficulties with FOCE and LAPLACE, SAEM and IMP were used to obtain standard errors and objective function value. IIV was assumed to be log-normally distributed. Where IIV was not required or could not be identified, a fixed OMEGA value of 0.005 was used to avoid adding unnecessary variability into the model. Correlations between the random effects of relevant parameters were assessed using off-diagonal elements of an omega block. Proportional and combined (additive + proportional) residual error models were evaluated. Correlations between the residual errors for abemaciclib, M2, and M20 were tested using the L2 data item. IIV in the residual error was tested, which eases the assumption that magnitude of the residual error is the same in all patients.

Selection of the most appropriate final mechanistic model was determined with data without Studies JPBL, JPBU, and JPBV, based on agreement between predicted and observed plasma concentrations, lack of pattern in the weighted residuals versus the predicted values, changes in IIV, and significant decreases in the minimum objective function. After confirming that the mechanistic model adequately described the new abemaciclib and metabolite data from Studies, JPBL, JPBU, and JPBV, all model parameters were re-estimated with data from the 12 studies.

Bootstrap analysis was performed to assess the precision of parameter estimates. A total of 200 bootstrap datasets were created and the 95% confidence intervals (CIs) for each parameter were reported. Visual predictive check (VPC) was performed to investigate the agreement between the observed and predicted concentrations. Prediction-correction of VPC was applied where appropriate to allow comparison of model performance across dosing regimens.

Table 66. Study Design and Sampling Schedules for Data Used in popPK Analysis

Trial Alias (Formulation)	Objectives	N (N_{PK})	Design	Treatment	PK Sampling Times
JPBA (C1)	Safety, tolerability, and PK in patients with cancer	225 (224)	Phase 1, multi-center, dose escalation study	Part A (dose escalation): LY 50-, 100-, 150-, and 225-mg po Q24H, or 75-, 100-, 150-, 200-, and 275-mg po Q12H Parts B – G (tumor-specific expansion): LY no greater than the MTD (200 mg po Q12H)	Cycle 1 Day -3 to -1: Pre, and 1, 2, 4, 6, 8, 10, 24, and 48 h Cycle 1 Day 1: Pre Cycle 1 Day 15: Pre, and 1, 2, and 4 h Cycle 1 Day 22: Pre Cycle 1 Day 28 to 29: Pre, and 1, 2, 4, 6, 8, 10, and 24 h
JPBB (C1)	Efficacy, safety, and PK, in patients with MCL	28 (27)	Phase 2, multi-center, nonrandomized, open-label study	LY 200 mg Q12H	Pre and 1, 2, 4, 6, 8, and 10 h on Days 1 and 15.

JPBC (C1)	Safety and tolerability of LY in patients in Japan with advanced cancer	12 (12)	Phase 1, nonrandomized, open-label, dose-escalation study	LY 100-, 150-, or 200-mg Q12H	Cycle 1 Day -3 to Day -1: Pre, and 1, 2, 4, 6, 8, 10, 24, and 48 h Cycle 1 Day 1: Pre Cycle 1 Day 15: Pre, and 1, 2, and 4 h post Cycle 1 Day 22: Pre Cycle 1 Day 28-29: Pre, and 1, 2, 4, 6, 8, 10, and 24 h
JPBD (Oral solution)	Disposition of radioactivity and LY in healthy subjects	6 (6)	Phase 1, nonrandomized, open-label, single dose study	LY 150 mg (approximately 5 µCi) [^{14}C]-LY2835219	Pre and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, and 336 h
JPBE (C1)	Effect of clarithromycin (CYP3A inhibitor) on the PK of LY and its metabolites in patients with cancer	26 (26)	Phase 1, open-label, 2-period, fixed-sequence study	Period 1: single oral dose of 50 mg LY Period 2: single oral dose of 50 mg LY on Day 5 of clarithromycin dosing. Clarithromycin 500 mg po Q12H for 12 days	Period 1: Pre, 1, 2, 4, 6, 8, 10, 24, 48, 72, 96, 120, 144, 168 h Period 2: Pre, 1, 2, 4, 6, 8, 10, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240 h
JPBF (C3)	Effect of rifampin (CYP3A inducer) on the PK of LY and its metabolites in healthy subjects	24 (24)	Phase 1, open-label, 2-period, fixed-sequence study	Period 1: single oral dose of 200 mg LY Period 2: Rifampin 500 mg po QD for 14 days, single oral dose of 200 mg LY on Day 7 of rifampin dosing	Periods 1 and 2: Pre, 1, 2, 4, 6, 8, 10, 24, 48, 72, 96, 120, 144, 168, 192 h
JPBG (C2)	Effect of food on the PK of LY in healthy subjects	24 (24)	Phase 1, open-label, randomized, single-dose, 3-period crossover study	LY 200 mg fasted, standard meal, or high fat meal	Pre, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, 192 h each period
JPBN (C3)	Efficacy, safety, and PK in patients with HR+, HER2- metastatic breast cancer	132 (128)	Phase 2, multi-center, non-randomized, open label study	LY 200 mg Q12H	C1D1 predose; C1D15 ~ 4 hours post dose and 7 hours postdose; C2D1 predose and ~3 h postdose; C3D1 predose
JPBS (C3 and IV solution)	Estimate the absolute bioavailability of LY using an IV tracer method in healthy subjects	11 (11)	Phase 1, single-center, open-label, single-period study	Single oral 200-mg dose of LY followed by a single IV 0.4-mg dose of [$^{13}C_8$]-LY infused over 15 minutes	Pre, 2, 4, 6 (immediately before the start of infusion), 6.25 (immediately at the end of infusion), 6.5, 6.75, 7.25, 8.25, 10, 12, 14, 24, 48, 72, 96, 120, 144, 168, and 192 h
JPBL (C3)	Efficacy, safety, and PK in patients with HR+, HER2- metastatic breast cancer	713 (465)	Phase 3, blinded, randomized, multi-center study	LY or placebo 200 mg Q12H plus fulvestrant 500 mg IM C1D1 and C1D15, then on D1 of C2 and beyond, Amendment a changed the LY starting dose to LY 150 mg Q12H	C1D1 2 to 4 h post dose; C1D15 ~ 4h and 7 h postdose; C2D1 pre dose and 3h post dose; C3D1 pre dose
JPBU (C3)	Effect of food on the PK of LY in healthy subjects	30 (30)	Phase 1, open-label, randomized, single-dose, 2-period crossover study	LY200 mg fasted or high fat meal	Pre, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, and 192 h each period
JPBV (C3)	Effect of hepatic impairment on LY PK	35 (10)	Phase 1, open-label, single period study	Single oral 200 mg dose of LY	Pre, 1, 2, 3, 4, 6, 8, 10, 24, 48, 72, 96, 120, 144, 168, and 192 h

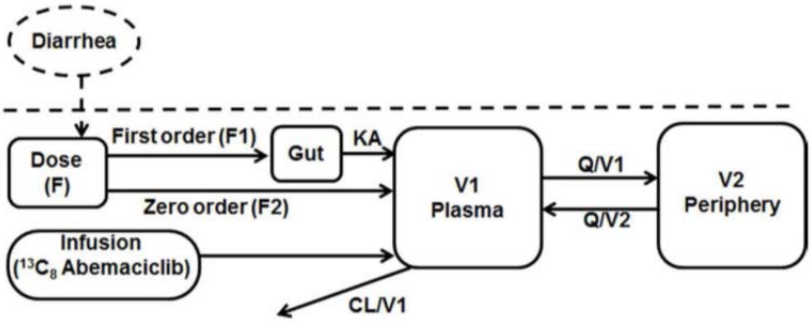
Source: Pop PK 02 report (update), Table 7.1

Results

29925 PK data for abemaciclib and its major metabolites (M2 and M20) from 990 individuals were used in the popPK analysis. Baseline characteristics for subjects in the popPK analysis were summarized in an Appendix.

In base model development, a 2-compartment structural model with parallel first and zero order absorption in terms of absorption lag time (ALAG1), absorption rate constant (KA), central volume of distribution (V1), peripheral volume of distribution (V2), clearance (CL), and inter-compartmental clearance (Q) best described abemaciclib PK. Absolute bioavailability is 32% lower in subjects with diarrhea than in subjects without diarrhea (0.19 vs. 0.28). VPC suggested that the empiric model over-predicted the IV exposure and therefore under-predicted absolute bioavailability of the oral formulations (Appendix).

Figure 17. Base Empirical Model Structure.



Source: Pop PK 02 report, Figure 8.5

Covariates were screened for significance based on criteria of accounting for at least a 10% relative decrease in variability in the empiric model. Weight was included in base model development; hence it was not tested as an additional covariate. Covariates that appeared significant (formulation on lag time and KA) were tested in the mechanistic model (Table 67).

Table 67. Covariates Tested in the Empirical Model.

Parameter	Covariate Tested																	
ALAG1	FOOD	FORM													LOPE	OPIO		
F	FOOD	FORM	ALBM	ALKP	ALT	AST	TBI	TPRO		AGE	WTE	GEN	RACE	POPU	LOPE	OPIO	IND	INH
KA	FOOD	FORM							CGCL	AGE	WTE	GEN	RACE	POPU	LOPE	OPIO		
CL			ALBM	ALKP	ALT	AST	TBI	TPRO	CGCL	AGE	WTE	GEN	RACE	POPU			IND	INH
V1										AGE	WTE	GEN	RACE					
D2	FOOD	FORM													LOPE	OPIO		

Abbreviations: AGE = baseline age; ALAG1 = lag time; ALBM = albumin; ALKP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; CGCL = baseline creatinine clearance; CL = clearance; D2 = duration of zero order absorption; F = absolute bioavailability; FORM = formulation; GEN = gender; IND = CYP3A-inducers, concomitant medications; INH = CYP3A-inhibitors, concomitant medications; KA = absorption rate constant; LOPE = loperamide, concomitant medications; OPIO = opioids, concomitant medications; POPU = population; RACE = race; TBI = total bilirubin; TPRO = total protein; V1 = central volume of distribution; WTE = baseline weight.

Red: Covariates had > 10 % relative decrease in ETA values and parameter values were precisely estimated (relative standard errors <30%). These covariates were considered for inclusion in the mechanistic model except for CGCL on KA (lack of clinical relevance) and WTE on KA (since weight was already on various parameters in the mechanistic model).

Orange: Covariates had > 10 % relative decrease in ETA values, but parameter values were not precisely estimated and/or small magnitude of effect. These covariates were not included in mechanistic model.

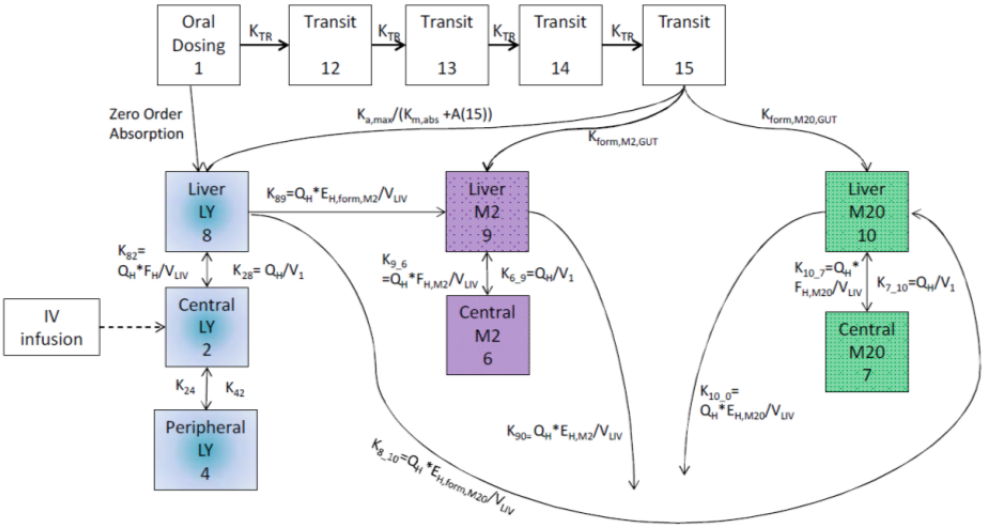
Yellow: Covariates had < 10 % relative decrease in ETA values and were not included in mechanistic model.

Source: Pop PK 02 report, Table 8.5

The final mechanistic model structure was shown in Figure 18. Parameter estimates and nonparametric bootstrap medians are reported in Table 68. Goodness-of-fit plots for the final model were shown in Figure 19. VPC suggested general concordance of model predictions with the observed abemaciclib, M2, and M20 concentration-time profiles (Figure 20). In general, there was a random distribution of residual values suggesting no consistent bias in the predicted concentrations. The absorption of abemaciclib was slow and highly variable. The C3 formulation had a longer zero order absorption lag time and a slightly lower maximum absorption rate than the early phase formulations. Post hoc analysis suggested comparable abemaciclib exposure across different capsule formulations. Due to a lack of diarrhea records in the large part of dataset, the estimated effect of diarrhea on the fraction entering gut (Fa) should be interpreted with caution. Between-subject variability in intrinsic clearance of

abemaciclib (CLint) was comparable in healthy subjects and in patients. The inter-occasional variability (IOV) in CLint was estimated to be 105% in patients. IOV could not be estimated in healthy subjects as there was no repeated dosing in the population. Given the low η-shrinkage, covariate-η plots were used to evaluate potential covariate relationships. No trends were observed for the covariates of interest such as hepatic metastases, age, race, sex, and renal function.

Figure 18. Mechanistic Model Structure.



Source: Pop PK 02 report (Update),Figure 7.2

Table 68. Pharmacokinetic and Covariate Parameters in Final Population Model.

Parameter	Estimate (%SEE)	Variability[a] (%SEE)	Shrinkage (%)	Bootstrap Median (95% CI)	Variability[a] (95% CI)
Fraction of dose entering gut compartment, Fa	0.92 (0.00)	7.1 (fixed)[b]	48.4	0.89 (0.88, 0.89)	7.1 (fixed)[b]
Fraction of Fa absorbed via transit compartments	0.493 (0.2)	7.1 (fixed)	40.6	0.487 (0.473,0.504)	7.1 (fixed)
Maximum rate of absorption, Ka,max (µmol/h)	94.1 (3)	61.0 (7.4)	9.5	93.8 (86.3, 104.8)	61.8 (56.5, 70.1)
Km for saturable absorption (µmol)	53.6 (0.3)	7.1 (fixed)	48.0	52.0 (50.0, 53.6)	7.1 (fixed)
Mean transit time, MTT (h)	1.54 (2.4)	76.9 (5.7)	17.2	1.55 (1.45, 1.67)	76.4 (68.4, 87.7)
Central volume (L)	549 (2.1)	70.3 (10.9)	9.8	535 (511, 560)	69.6 (64.4, 74.8)
Q (L/h)	4.37 (0.3)	7.1 (fixed)	46.5	4.54 (4.30, 4.76)	7.1 (fixed)
Peripheral volume (L)	174 (0.3)	7.1 (fixed)	47.1	176 (166, 186)	7.1 (fixed)
Zero order abs. duration (h)	2.84 (6.1)	390.9 (2.0)	26.4	3.14 (2.63, 3.65)	485 (369, 622)
Absorption lag time (h)	1.71 (0.5)	7.1 (fixed)	31.9	1.72 (1.64, 1.78)	7.1 (fixed)
Rate constant for formation of M2 from gut (h^{-1})	0.347 (0.3)	7.1 (fixed)	34.2	0.363 (0.350, 0.376)	7.1 (fixed)
Rate constant for formation of M20 from gut (h^{-1})	0.259 (0.3)	7.1 (fixed)	36.9	0.276 (0.264, 0.290)	7.1 (fixed)
CLint to form M2 in liver (L/h)[c]	285 (0.3)	BSV: H: 41.2 (5.6) P: 44.5 (5.0)	BSV: H: 4.1 P: 13.0	280 (264, 302)	BSV: H: 40.2 (34.4, 46.0) P: 47.3 (41.7, 55.6)
CLint to form M20 in liver (L/h)[c]	819 (0.3)	WSV: P:104.9 (1.8)		774 (745, 810)	WSV: P: 100.6 (90.0, 110.3)
CLint of M2 in liver (L/h)	259 (1.1)	31.5 (12.3)	23.5	256 (245, 271)	31.9 (27.5, 38.3)
CLint of M20 in liver (L/h)	452 (1.1)	31.3 (3.2)	22.0	438 (424, 453)	31.6 (27.1, 38.8)
Box-cox shape for random effects of	0.292 (6.1)	-		0.220 (0.187, 0.251)	-

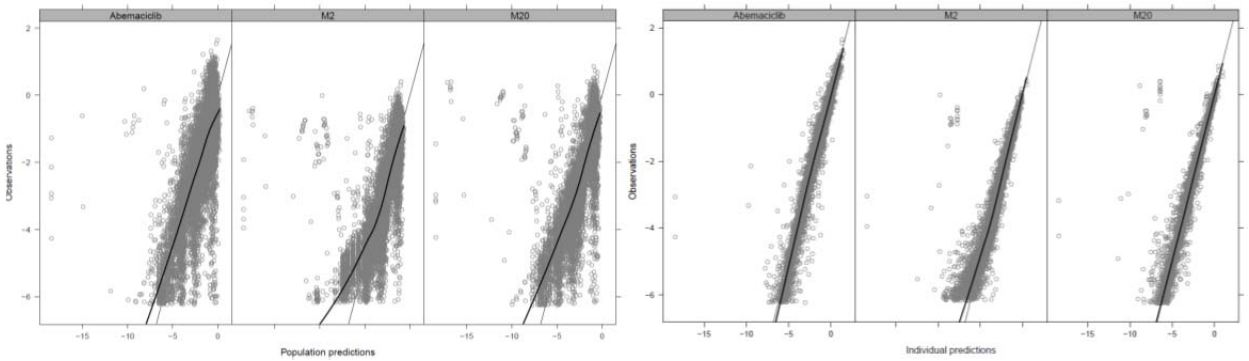
Parameter	Estimate (%SEE)	Variability[a] (%SEE)	Shrinkage (%)	Bootstrap Median (95% CI)	Variability[a] (95% CI)
zero order duration					
Diarrhea effect on Fa[d]	-1.28 (1.4)	-		-0.563 (-1.146, 2.42×10^{-8})	-
C2 on absorption lag[e]	0.822 (3.1)	-		0.809 (0.617,1.109)	-
C3 on absorption lag[e]	1.06 (1.2)	-		1.0 (0.83, 1.13)	-
Formulation on $K_{a\ max}$[f]	-0.16 (19.6)	-		-0.166 (-0.249,-0.069)	-
Correlation between variability for MTT and zero order duration		0.335 (28.9)			0.329 (0.216, 0.420)
Correlation between variability in CLint of M2 and M20		0.88 (17.4)			0.885 (0.844, 0.919)
IIV for residual error		65.6 (3.7)	10.6		61.5 (57.8,65.5)
Prop. error parent - oral (%)	17.0 (1.5)		9.6	18.4 (17.3,19.8)	
Prop. error M2 (%)	15.7 (1.3)		5.8	17.1 (16.3,18.1)	
Prop. error M20 (%)	10.4 (1.8)		5.4	11.5 (10.8,12.4)	
Prop. error parent - IV (%)	61.6 (fixed)			61.6 (fixed)	
Additive error parent (oral)	0.000001 (fixed)			0.000001 (fixed)	
Additive error M2 (µmol/L)	0.000001 (fixed)			0.000001 (fixed)	
Additive error M20 (µmol/L)	0.000001 (fixed)			0.000001 (fixed)	

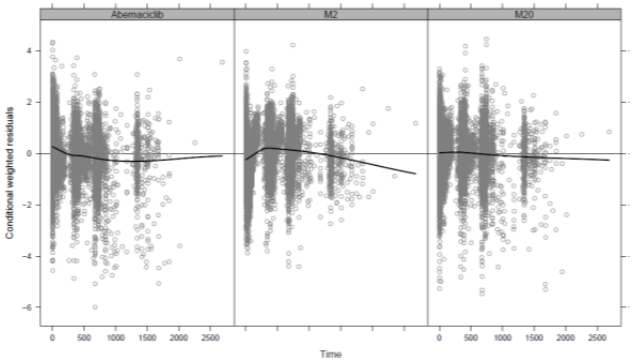
Abbreviations: BSV = between subject variability; CI = confidence interval; CV = coefficient of variation; SEE = standard error of the estimate; WSV = within-subject variability (no WSV for healthy individuals); H = healthy subjects; P = patients.

a. Reported as %CV, calculated as: 100 · sqrt(exp(ω^2)-1), where ω^2 is the NONMEM output for the inter-subject variability of the parameter.
b. Fixed OMEGA to 0.005 to facilitate efficiency of SAEM algorithm.
c. Variability incorporated in model on total CLint which was sum of the typical values of CLint to form M2 and CLint to form M20. CLint = $(TVCL_{int,form,m2} + TVCL_{int,form,m20})$*exp(BSV+WSV).
d. Estimate is on the logit parameter for Fa. This translates to a 8% decrease in Fa when there is diarrhea.
e. ALAG8 = TVALAG8*(1+0.822*FORM1)*(1+1.06*FORM2). Where FORM1 has a value of zero except for individuals with C2 formulation, and FORM2 has a value of zero except for individuals with the C3 formulation where the values are then set to 1.
f. Ka,max = TVKa,max *(1-0.16*FORM2). Where FORM2=0 except for individuals with the C3 formulation where it is set to 1.

Source: Adapted from Pop PK 02 report (Update), Table 8.4

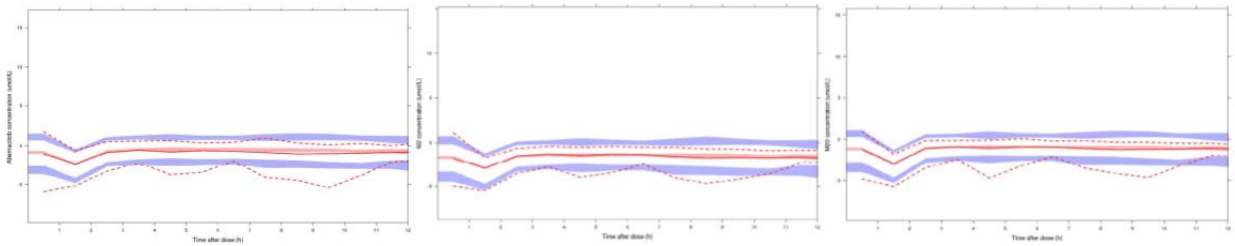
Figure 19. Goodness-of-Fit Plot for the Final Mechanistic Model. (Upper Left) Observation vs. population prediction; (Upper Right) Observation vs. individual prediction. (Lower) Conditional weighted residuals vs. Time.





Source: Pop PK 02 report (Update), Attachment 3

Figure 20. Prediction-Corrected Visual Predictive for Log Abemaciclib vs Time after Dose in Study JPBL. (Left) Abemaciclib. (Middle) M2. (Right) M20.



Source: Pop PK 02 report (Update), Figure 8.4, 8.5, and 8.6.

<u>Reviewer's Comments:</u>

1. *The final mechanistic model is not optimized for describing abemaciclib PK after oral administration of the C3 formulation. While Study JPCA suggests dose proportional PK after a single dose of 200-600 mg abemaciclib, the model predicts a less than dose proportional increase in abemaciclib exposure over the same range. Non-linearity is introduced by the saturable absorption from the last transit compartment to systemic circulation and the parallel process of metabolism into M2 and M20 in the last transit compartment. When absorption rate is saturated, more parent drug becomes available for metabolism and absorption as M2 and M20, and hence the reduced bioavailability of the parent drug. It should be noted that Study JPCA was not included in popPK analysis to inform model development.*

   Despite of inconsistent conclusions on PK linearity in the wider range, model prediction supports the labeling claim of close to dose proportionality exposure increase between 50-200 mg with the C3 formulation (which is bioequivalent to the commercial formulation with closely matched PK profiles). Because of the extensive computational burden and acceptable model performance in describing abemaciclib PK in the registration studies, further optimization of the PK model is not pursued. The sequential approach in exposure-response analysis, which relies on individual estimates of PK parameters from the final model, is found acceptable.
2. *The effect of diarrhea on bioavailability should be interpreted with caution. Due to a lack of end time of diarrhea AE in multiple studies, diarrhea effect on bioavailability was evaluated as a static covariate in the final model. That is, if a patient expereinced diarrhea anytime during the study treatment, diarrhea effect was added on bioavailabily throughout the course of PK sampling. Diarrhea effect on bioavailability would be systemically underestimated if modeled as a static covariate. In an subset of popPK dataset where the end time of diarrhea AE was available and diarrhea effect on bioavailability was modeled as a time-varying covariate (per Response to Information Request), diarrhea was estimated to reduce Fa by 16% and absolute bioavailabiliyt by 10%. Considering that the estimate in the subset remains small (10% decreasein absolute bioavailability), the change of bioavailability due to diarrhea could be concluded as not clinically meaningful.*
3. *Monte Carlo noise in the objective function value obtained from the SAEM/IMP estimation meant that reliance on the OFV would not be ideal. Other measures of model improvement such as goodness-of-fit plots and*

parameter estimates and precision were considered in covariate search. The reviewer conducted posthoc analysis to confirm a lack of covariate effect on abemaciclib exposure in patients.

13.4.1.2.2. Exposure-Response (E-R) Analysis

Objectives

- Evaluate any relationship between abemaciclib exposure and efficacy (e.g. tumor size, PFS) in patients with metastatic breast cancer.
- Characterize any relationship between abemaciclib exposure and adverse events of interest (e.g., neutropenia, diarrhea, nausea, and vomiting) in patients.

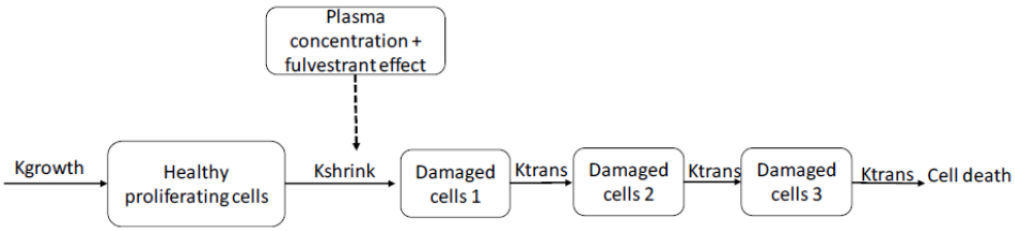
Reviewer's Comments: With data from Study MONARCH 1 or MONARCH 2, the applicant conducted static E-R analyses, including time-to-event analysis for PFS and logistic regression analysese for best objective response, neutropenia, diarrhea, nausea, fatigue, and vomiting, with the steady state exposure metrics estimated from the average daily dose on treatment or the maximun concentration, minimum concentration, or $AUC_{0\text{-}12hr}$ *after the first dose as covaraites. These exposure metrics have known limitations in light of the high dose modifcation rate in the registration studies. The applicant also conducted time-to-event analysis for the first diarrhea incidence to evaluate dose-response relationship and dynamic PK/PD modeling for tumor size change and neutrophil count. These analyses are less biased than the static E-R analysis in the presence of high dose modification rate. This review will focus on the time-to-event analysis on diarrhea and PK/PD modeling for tumor size change and neutrophil count.*

Data, Software, and Methods

1. Dynamic PK/PD model for tumor size change

A sequential approach was undertaken for the PK/PD modeling for tumor size change in MONARCH 1 and MONARCH 2, separately. The individual post hoc PK parameters from the final mechanistic model were used to obtain abemaciclib plasma concentrations in patients who had measurable disease. Tumor size was defined as the sum of longest diameters of the target lesions. A series of 3 transit compartments was used in a model structure similar to that of Simeoni and colleagues (*Cancer Res. 2004 Feb 1;64(3):1094-101*). The baseline tumor size was estimated and used as the initial value in the tumor size compartment. A zero order growth rate for the tumor cells in this compartment was estimated. As shown in Figure 21, the action of abemaciclib was to damage these "healthy proliferating" cells through a first order decline in the amount of cells, that would then go through a series of 3 transit compartments until cell death. The SAEM estimation algorithm was used along with a full covariance block. Goodness of fit plots, VPC, and bootstrapping were used for model evaluation.

Figure 21. Model Diagram for Change in Tumor Size.



Source: Pop PK 02 report (Update), Figure 7.4

2. Diarrhea time-to-event analysis

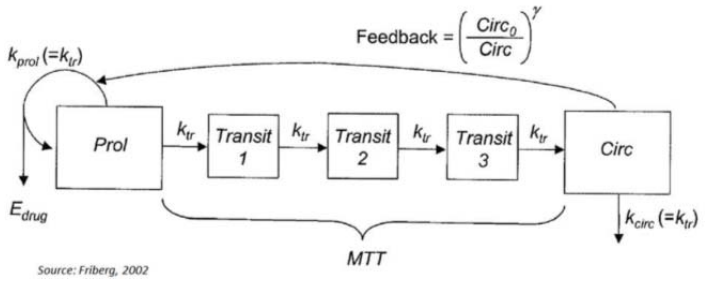
The occurrence of the first diarrhea AE was described using a time-to-event approach in Study MONARCH 2 and pooled dataset from MONARCH 1, Studies JPBA, JPBB, and JPBC. Various parametric hazard models were tested including exponential, Weibull, and Gompertz. The probability of not having diarrhea was calculated as the inverse of the exponent of the cumulative hazard from time=0 to time=j. The censoring time for those who did not have an event was the time of the last dose that the patient received. Continuous and categorical covariates, including

assigned dose, predicted exposure metrics after the first dose, demographics and certain baseline disease characteristics, were tested in the time-to-event model.

3. Dynamic PK/PD model for neutrophil count

The model by Friberg (*J Clin Oncol. 2002 Dec 15;20(24):4713-21)* was used to analyze the effect of abemaciclib and fulvestrant on the time-course of neutrophils in Study MONARCH 2 (Figure 22). The model featured a proliferation pool representing the progenitor cells. The baseline growth of this pool was dependent on the number of cells present. Maturation of progenitor cells was represented by 3 transit compartments, which eventually transition into a circulation pool that represent the neutrophils in systemic circulation. The effect of abemaciclib and fulvestrant was assumed to inhibit the production rate of proliferating progenitors. A feedback mechanism based on the current circulating levels of neutrophils was used to capture the physiological mechanism that compensates for the suppression. Given the timing and sparse sampling for neutrophils, the proliferation rate and the removal rate of circulating neutrophils were made to equal transit rate for identifiability concerns. The effect of abemaciclib was considered to be additive to the effect of fulvestrant. Given that the maximum decrease was observed during the first 3 cycles when samples for abemaciclib, M2, and M20 were collected, the E-R analysis was limited to the first 3 cycles. Due to the computational burden, only the single dose and steady-state individual exposure, estimated from the assigned dose, were tested as a covariate for the effect of abemaciclib on the progenitor pool. The predictive performance and robustness of the final exposure-response model was evaluated using VPC and nonparametric bootstrapping.

Figure 22. The Structure of the PK/PD Model for Chemotherapy-Induced Myelosupression.



Source: Pop PK 02 report (Update), Figure 7.3

Results

1. Dynamic PK/PD model for tumor size change

A total of 477 patients with measurable disease were included in the tumor size model analysis for MONARCH 2 and 132 patients contributed to tumor size change model for MONARCH 1. Model parameters are summarized in Table 69 and Table 70. In both studies, a positive relationship was observed between abemaciclib plasma concentration and tumor shrinkage. In MONARCH 2, the drug effect on tumor shrinkage start decreasing after 1.7 months, however, there was high variability (473%) in the start time of decrease. The 'half-life' of this decrease in drug effect was estimated to be 2.51 weeks and 8.44 weeks for patients in the control arm and abemaciclib arm respectively with high variability. The negative correlations between the random effects of abemaciclib drug effect and the half-life of developing resistance or between the abemaciclib drug effect and the delay in the onset of resistance implied that patients who are more susceptible to drug effect in the beginning have a greater chance of experiencing a decrease in drug effect than those in whom the drug had a lesser effect at the start of treatment. The positive correlation between half-life of resistance to abemaciclib and delay in onset of resistance suggested that some patients were less likely to develop resistance in general than others. In MONARCH 1, no significant correlations were identified between the random effects at p=0.001 level. Diagnostic plots and VPCs showed that the models described the data reasonable well (Appendix).

Table 69. Parameter Estimates of the PK-Change in Tumor Size Model for MONARCH 2

Parameter	Estimate (%SEE)	BSV[a] (%CV) (%SEE)	Bootstrap median (95% CI) for parameter estimate	Bootstrap median (95% CI) for BSV[a] (%CV)
Baseline tumor size (mm)	36.7 (3.21)	79.0 (6.64)	36.9 (34.7, 39.6)	79.6 (73.5, 85.5)
Transit rate constant (week^{-1})	0.934 (129)	15.1 (fixed)[b]	1.14 (0.867, 1.43)	15.1 (fixed)[b]
Tumor growth rate (mm/week)	0.00715 (8.02)	11400[c] (16.8)	0.0138 (0.00486, 0.0350)	4580 (1710, 23400)
Correlation between the random effects of baseline tumor size and growth rate		0.265 (31.2)		0.312 (0.115, 0.452)
Tumor shrinkage due to fulvestrant (week^{-1})	0.00647 (3.65)	268 (22.5)	0.00782 (0.00464, 0.0116)	202 (124, 438)
Abemaciclib drug effect per unit plasma concentration (week $^{-1}$)	0.0399 (29.3)	293 (21.6)	0.0398 (0.0259, 0.0661)	334 (184, 717)
Correlation between the random effects of fulvestrant and abemaciclib drug effects		-0.140 (128)		-0.273 (-0.626, 0.0732)
Time to get half of initial drug effect for control arm (weeks)[d]	2.51 (8.21)	19.7 (42.9)	2.44 (2.24, 2.61)	23.0 (17.1, 31.3)
Time to get half of initial drug effect for abemaciclib arm (weeks)[d]	8.44 (14.3)	203 (19.3)	10.0 (6.70, 16.0)	246 (154, 517)
Delay of onset of waning of drug effect (weeks)	7.11 (15.5)	473 (22.0)	4.09 (1.61, 8.22)	971 (313, 8200)
Correlation between the fulvestrant drug effect and half-life of resistance to fulvestrant		-0.380 (70.9)		-0.286 (-0.647, 0.130)
Correlation between the abemaciclib drug effect and half-life of resistance to fulvestrant		-0.636 (45.7)		-0.599 (-0.820, -0.320)
Correlation between the fulvestrant drug effect and half-life of resistance to abemaciclib		0.213 (89.9)		0.253 (-0.126, 0.704)
Correlation between the abemaciclib drug effect and half-life of resistance to abemaciclib		-0.880 (15.6)		-0.862 (-0.942, -0.735)
Correlation between half-life of resistance to fulvestrant and half-life of resistance to abemaciclib		0.235 (141)		0.190 (-0.197, 0.555)
Correlation between fulvestrant drug effect and delay in onset of resistance		0.412 (30.0)		0.440 (0.103, 0.661)
Correlation between abemaciclib drug effect and delay in onset of resistance		-0.507 (33.9)		-0.424 (-0.692, -0.0332)
Correlation between half-life of fulvestrant resistance and delay in onset of resistance		-0.0862 (229)		-0.120 (-0.543, 0.287)
Correlation between half-life of resistance to abemaciclib and delay in onset of resistance		0.632 (28.3)		0.441 (0.0410, 0.719)
Additive error (mm)	1.39 (4.40)		1.41 (1.05, 1.76)	
Proportional error (%)	9.04 (5.89)		8.76 (6.45, 11.1)	

Source: Pop PK 02 report (Update), Table 8.16

Table 70. Parameter Estimates of the PK-Change in Tumor Size Model for MONARCH 1

Parameter	Estimate (%SEE)	BSV (%CV) (%SEE)
Baseline tumor size (mm)	38.4 (6)	75 (13)
Transit rate constant (week-1)	0.796 (138)	169 (42)
Tumor growth rate (mm/week)	0.0880 (17)	1658 (28)
Abemaciclib drug effect per unit plasma concentration (week -1)	0.0418 (21)	142 (36)
Time to get half of initial drug effect for abemaciclib arm (weeks)	5.62 (59)	2451(83)
Delay of onset of waning of drug effect (weeks)	11.3 (9)	5(355)
Additive error (mm)	1.49 (12)	
Proportional error (%)	25 (19)	

Abbreviations: BSV = between subject variability; CV = coefficient of variation; SEE = standard error of the estimate.
Source: Response to Information Request, Table 1

2. Diarrhea time-to-event analysis

Data from 676 patients in MONARCH 2 were included in the analysis. The median times to first diarrhea event are 120 days, 7.29 days, and 3.96 days, for control (fulvestrant + placebo arm), 150 mg, and 200 mg starting dose,

respectively. The instantaneous risk of diarrhea at an earlier time is higher with a higher abemaciclib dose compared to placebo, and the risk of diarrhea decreases with time, which may be due to individualized interventions to manage diarrhea such as dose reduction or the use of anti-diarrheal medication such as loperamide.

Table 71. Parameter Estimates for Time to First Diarrhea Event Model (MONARCH 2)

Parameter	Estimate (%SEE)
Baseline hazard	0.0134 (12.1%)
Weibull Shape	-0.315 (8.3%)
Placebo on baseline hazard	-0.993 (0.8%)
200 mg abemaciclib on baseline hazard	0.452 (44.9%)
Absence of Opioids on the baseline hazard	-0.705 (6.3%)
Placebo on shape	-1.42 (31.9%)
Baseline weight on the baseline hazard	-0.00869 (37.6%)
dHaz/dt = 0.0134 $*$ (1+ θ_{1drug}) * (1+ θ_{Opioid}) * (1 + θ_{Wt} * (baseline weight – 64.5)) * exp(-0.315*(1+ θ_{2drug}))*log(t)). Where Haz is hazard of getting the first event of diarrhea and θ_{1drug} is -0.993 for Placebo, 0 for 150 mg and 0.452 for 200 mg; θ_{2drug} is 0 for 150 mg or 200 mg and -1.42 for Placebo; θ_{Opioid} is 0 for using opioids and -0.705 for not using opioids; θ_{Wt} is -0.00869.	

Source: adapted from Pop PK 02 report (Update), Table 8.8

Out of 397 patients from MONARCH 1, Studies JPBA, JPBB, and JPBC, 312 patients had diarrhea records. A hazard function, which includes a Gompertz function that describes the change in hazard over time, best described the occurrence of diarrhea. The shape parameter was negative, indicating that the risk of getting diarrhea was greatest at early times and the risk decreased with time in the study. The hazard was greater when patients received a starting dose greater than or equal to 200 mg (N=242) (median time to first event: 9 days), than when patients had a dose of 150 mg or less (N=118) (median time to first event: 42 days).

Table 72. Parameter Estimates for Time to First Diarrhea Event Model (Pooled Dataset)

Parameter	Estimate (%SEE)
Baseline hazard <= 150 mg dose	0.0134 (12.1%)
Gompertz Shape Parameter for ≤150 mg dose	-0.315 (8.3%)
Baseline Hazard >150 mg dose	-0.993 (0.8%)
Gompertz Shape Parameter for>150 mg dose	0.452 (44.9%)
* The baseline hazard is a constant representing the instantaneous risk of diarrhea at the beginning of the study.	

Source: adapted from Pop PK 02 report, Table 8.4

3. Dynamic PK/PD model for neutrophil count

A total of 535 patients from the MONARCH 2 study contributed 2793 neutrophil data records for the dynamic PK/PD model. Outliers identified during the exploratory model development, data prior to the first dose of study medication, and missing data were excluded. In general, the model by Friberg and colleagues described the neutrophil data in the control and abemaciclib treatment arms well. After stepwise covariate model building, the final model included the relationship between total $C_{max,ss}$ and the effect of abemaciclib on the neutrophil progenitor pool (Table 73). The model estimated a median decrease in neutrophil production rate of 5.41% (range: 3.37%-27.7%) and 20.10% (range: 8.92%-67.6%), in the fulvestrant + placebo and fulvestrant + abemaciclib treatment arms, respectively. The model predicted that a maximum of 23% (95% CI: 16%-30%) of MONARCH 2 patients would experience Grade 3 or Grade 4 neutropenia occurring between 20 to 35 days following the start of treatment. The predictive performance and robustness of the final model was confirmed by VPC and nonparametric bootstrap evaluation (data not shown).

Table 73. Pharmacokinetic and Covariate Parameters in the Final Neutropenia Model

Parameter	Estimate	BSV (%CV)	Bootstrap median (95% CI)	Bootstrap BSV (CV%) (95% CI)
Baseline neutrophil (10^9 cells/L)	3.25	40.4	3.27 (3.23, 3.47)	40.3 (38.0,42.1)
Mean transit time, MTT (h)	190	21.7	190 (186, 195)	21.9 (21.5,24.0)
Gamma	0.369	41.4	0.368 (0.348, 0.376)	41.4 (40.0, 48.5)
Effect of fulvestrant on progenitor pool (%)	5.53	70.6	5.53 (5.34, 6.11)	70.6 (67.1, 80.1)
Effect of abemaciclib on progenitor pool (%)	17.0	0.245	17.0 (16.6, 18.6)	0.245 (0.245, 0.245)
$C_{max\ ss\ total}$ relationship for abemaciclib effect [a]	1.09		1.07 (0.901, 1.13)	
Proportional residual variability	0.0285		0.0282 (0.0208, 0.305)	

[a] Relationship = θ_6 * log(1+$C_{max,ss,total}$), where $C_{max,ss,total}$ is predicted from the assigned dose.

Source: Pop PK 02 report (Update), Table 8.12

Reviewer's Comments:

1. *The applicant's exploratory analysis of the exposure-response or dose-response relationships ontumor size change, diarrhea AE, and neutrophil change from baseline are acceptable. The reviewers agree with applicant's conclusions on the negative relationship between starting dose and the time to first diarrhea event and the positive relationship between abemaciclib exposure and neutrophil decrease. The reviewers agree that there is a positive E-R relationship for tumor size in both the MONARCH 1 and MONARCH 2 studies.*
2. *After obtaining the dynamic tumor size model, the applicant conducted a time-to-event analysis to evaluate the risk of disease progression in MONARCH 2. Post hoc tumor size model parameters, simulated tumor size change from baseline, hepatic metastases, and ECOG status were tested as a predictor of hazard. An interval censoring approach was employed in the analysis. Study result is not presented in this review. However, it is noted that patients without measurable disease appear to have a lower baseline hazard of disease progression than patients with measurable disease. The difference is reflected in a separation in the K-M curves for PFS in patients with or without measurable disease, in both the control and abemaciclib arms.*

13.4.1.3. Reviewer's Analysis

Objectives

- Evaluate covariate effect on abemaciclib steady state exposure by graphical analysis.
- Evaluate dose proportionality of oral abemaciclib formulations.
- Simulate tumor response rate with 200 mg BID or 150 mg BID dosing regimen in the monotherapy indication.

Data, Software, Methods

Name	Description	Link to EDR
run10-lst.txt; patab10.txt	final mechanistic model output and post hoc PK parameters	nda208716\0003\m5\datasets\population-pk\analysis\programs\pk-base-final-mechanistic
jpbn-tumor-size-survival-cat-psn-csv.txt; run4-lst.txt; patab4.txt	MONARCH 1 tumor size change model input, output, and post hoc model parameters	nda208716\0013\m5\datasets\population-pk\analysis\programs\base

Individual post hoc PK parameters in 990 subjects were used to predict steady state exposure metrics after 50-600 mg single dose or 50-200 BID doses without dose modification. Boxplots were used to identify potential covariate relationships between abemaciclib steady state exposure at 200 mg BID vs. renal function category, age, body weight, gender, race, and the presence of hepatic metastases. Dose proportionality was evaluated by simulating dose escalation studies in which predicted abemaciclib exposures from a given number of patients on C3 were randomly selected for analysis.

Individual post hoc PK parameters and tumor size change parameters in 132 patients in MONARCH 1 were used to predict tumor size over time profiles, assuming that patients were on 200 mg BID, 175 mg BID, 150 mg BID, or 125 mg BID dosing regimen without dose modification. The average daily dose in the MONARCH 1 study is 175 mg BID,

representing the actual exposure with a starting dose of 200 mg BID and and with similar diarrhea management measures as used in MONARCH 1. The average daily dose after first dose reduction in the MONARCH 1 study is 125 mg BID, representing the actual exposure with a starting dose of 150 mg BID. Response rate were calculated at 4-week intervals, representing the percentage of patients with a greater than 30% tumor size reduction from baseline.

The Reviewer's simulation of abemaciclib exposure is based on the assumption that no new diarrhea events occurred during the course of treatment. In addition, the tumor size model alone does not take into account of disease progression in the non-target lesion and new lesion. The reviewer's analysis on efficacy outcome solely relies on tumor size modeling. Therefore, the simulated response rate is expected to be higher than that was observed in a clinical study at the corresponding dose level.

NONMEM (v7.3), Pirana (2.9.0), and R (v3.2.2) were used for the FDA reviewer's analysis.

Results and Discussion

There were no relationships between covariates of interest and $C_{max,ss}$, $C_{min,ss}$, or AUC_{tau}. Figure 16 shows the boxplot of AUCtau distribution across covariate range after excluding extreme predictions in steady state metrics (i.e. AUCtau between the 2.5% or 97.5% quantiles of the population were included). Conclusions are the same with all data included.

The final mechanistic model implies less than dose proportional PK of oral abemaciclib formulations due to saturable absorption and the competing gut metabolism. However, the degree of non-linearity is not significant. Of the 644 subjects who were treated with the C3 formulation, the slope between log transformed AUC vs. log transformed dose level was 0.96 between 50-200 mg single dose or BID doses. In simulated dose escalation studies with different sample sizes, there is high a chance of concluding linear PK within the dose range of 50-200 mg. It should be noted that the commercial formulation (T1) was not included in the popPK analysis to inform PK linearity evaluation. However, the C3 formulation was demonstrated to be bioequivalent to the commercial formulation, with closely matched PK profiles. Therefore, the estimates of PK parameters and linearity conclusions based on simulated dose escalation studies should be similar between the two formulations.

Table 74. Summary of linearity evaluations in simulated dose escalation studies (50-200 mg BID). Slope, the lower bound and upper bound of 95%CI of slope are reported as the median from 1000 simulated studies.

Sample Size	Slope	Lower Bound	Upper Bound	Chances of Failure to Conclude Linearity
20	0.9616	0.8703	1.0530	0
40	0.9619	0.8957	1.0282	0
60	0.9616	0.9063	1.0169	0.006
80	0.9616	0.9136	1.0097	0.029
100	0.9617	0.9191	1.0044	0.140

Sources: FDA's reviewer's analysis

Simulation suggests a trend of higher response rate being associated with a higher dose level in the MONARCH 1 population. Response rate, based on target lesion at 52 weeks after the start of treatment, is predicted to be 31.1% with the 200 mg BID dose vs. 25.0% with the 150 mg BID dose, and 29.5% with the 175 mg BID dose vs. 18.9% with the 125 mg BID dose. It is more beneficial, from an efficacy perspective, to start patients on the proposed 200 mg BID dose than on the 150 mg BID dose.

The major AE events leading to dose reduction in MONARCH 1 are diarrhea and neutropenia. In the nearly 50% of patients who experienced dose reduction, the median duration of the 200 mg BID dose was 39 days (25-67 days). Most incidences of Grade 3 or above diarrhea and neutropenia occurred within the first month on treatment and are considered manageable with anti-diarrhea treatment or dose reduction. As the overall safety and tolerability profile in MONARCH 1, with a 200 mg BID dose, is considered acceptable, starting patients with a 150 mg BID dose does not bring additional benefit from a safety perspective.

Simulation of tumor size change in MONARCH 2 also suggests a higher target lesion response rate with a 200 mg BID dosing regimen compared to a 150 mg BID dosing regimen (66.1% vs. 55.9% in patients with measurable

disease after 56 weeks on treatment). However, only two thirds of the intent-to-treat population in MONARCH 2 had measurable disease and there appeared to be differences in disease progression dynamics in patients with or without measurable disease. On the other hand, even though the reviewers agree that there is a positive E-R relationship for tumor size in MONARCH 2, the predicted difference in response rate between two dose regimens in the early line setting (combination with fulvestrant) should be interpreted with caution. In addition, dose response analysis for safety suggested that patients with a 200 mg starting dose had a higher risk of diarrhea and shorter time to first diarrhea compared to patients with a 150 mg dose in the MONARCH 2 study (Figure 15). Therefore, the risk/benefit profile of a higher starting dose in the early line setting is unclear.

13.4.1.4. Appendix

1. Summary of Baseline Demographic Information (Categorical) in the popPK Dataset.

	Age (year)	Weight (kg)	CGCL (mL/min)	ALBM (g/L)	ALKP (U/L)	ALT (U/L)	AST (U/L)	TBI (μmol/L)	TPRO (g/L)
All 12 Studies JPB A/B/C/D/E/F/G/L/N/S/U/V									
N	994	994	989	865	865	865	861	859	992
N_{miss}	0	0	5	129	129	129	133	135	2
Minimum	24	36.0	32.6	24	30	4	8	1.5	48
Median	59	67.2	89.1	41	79	18	23	6	66
Maximum	91	175.1	315.2	49	1331	155	231	32	88
Geo Mean	58.2	68.1	88.0	40.1	86.5	19.8	24.3	5.95	68.3
Geo CV%	20	23	34	10	57	60	49	54	7
JPBL*									
N	468	468	466	466	466	466	463	466	466
N_{miss}	0	0	2	2	2	2	5	2	2
Minimum	33	36.0	32.6	25	30	6	10	1.5	57
Median	60	64.5	87.8	41	79	18	23	6	71
Maximum	91	128.3	225.7	49	715	155	173	32	88
Geo Mean	58.8	65.2	86.6	40.8	82.9	20.0	24.8	6.00	70.8
Geo CV%	19	22	33	8	52	59	44	54	7

Abbreviations: ALBM = albumin; ALKP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CGCL = Cockcroft-Gault creatinine clearance; N = number of patients in the enrolled population; N_{miss} =number missing ; TBI = total bilirubin; TPRO = total protein.

*Patients who received abemaciclib.

Source: Pop PK 02 report (update), Table 8.1

2. Summary of Baseline Demographic Information (Continous) in the popPK Dataset.

	All 12 Studies* (Active) N (%)	JPBL* (Active) N (%)	JPBL (Control) N (%)	JPBL (All)[c] N (%)
Sex				
Female	859 (86.4%)	468 (100%)	239 (100%)	707 (100%)
Male	135 (13.6%)	0 (0%)	0 (0%)	0 (0%)
Race				
American Indian or Alaska Native	19 (1.9%)	17 (3.6%)	9 (3.8%)	26 (3.7%)
Asian	180 (18.1%)	156 (33.3%)	71 (29.7%)	227 (32.1%)
Black or African American	56 (5.6%)	9 (1.9%)	5 (2.1%)	14 (2.0%)
Missing	44 (4.4%)	31 (6.6%)	10 (4.2%)	41 (5.8%)
Multiple	4 (0.4%)	1 (0.2%)	0 (0%)	1 (0.1%)
White	691 (69.5%)	254 54.3%)	144 (60.3%)	398 (56.3%)

Oral Formulation				
25% (w/w) 100 mg (C3)	30 (3.0%)	0 (0%)	NA	0 (0%)
25% (w/w) 50 mg (C3)	644 (64.8%)	468 (100%)	NA	468 (66.2%)[a]
50% (w/w) 50 mg (C2)	50 (5.0%)	0 (0%)	NA	0 (0%)
DIC (25 mg or 150 mg) (C1)	264 (26.6%)	0 (0%)	NA	0 (0%)
Solution	6 (0.6%)	0 (0%)	NA	0 (0%)
Population				
Healthy Subjects	104 (10.5%)	0 (0%)	0 (0%)	0 (0%)
Cancer Patients	890 (89.5%)	468 (100%)	239 (100%)	707 (100%)
Subrace[b]				
Japanese		65 (13.9%)		
Non-Japanese		403 (86.1%)		
Liver metastasis[b]				
Present		118 (25.2%)		
Absent		350 (74.8%)		

Abbreviations: C1 = drug in capsule; C2 = 50% w/w formulated capsule; C3 = 25% w/w formulated capsule; DIC = drug in capsule; N = number of individuals in the PK dataset.

* Patients who received abemaciclib.

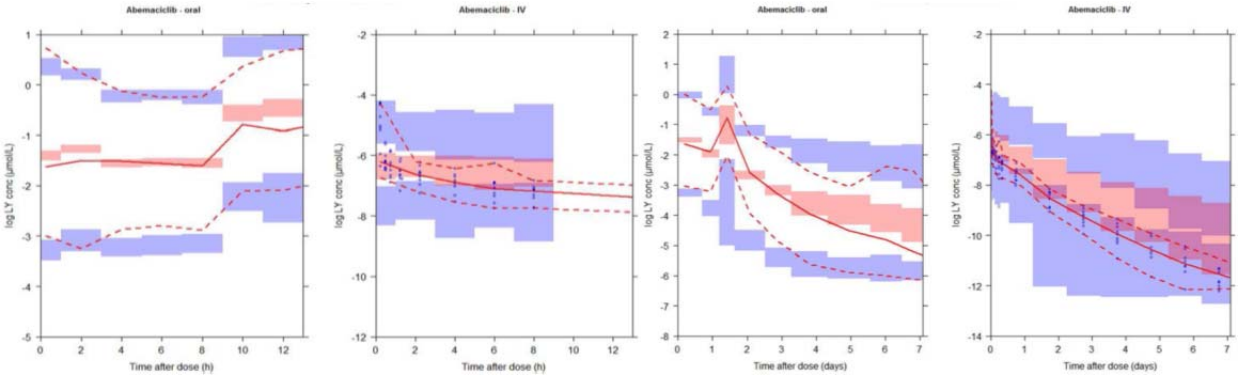
[a] 239 (33.8%) patients received placebo

[b] Subrace and liver metastasis information is presented for Study JPBL active treatment only as this was used in the mechanistic population pharmacokinetic graphical analysis of Study JPBL data.

[c] This population comprises the PK/PD population.

Source: Pop PK 02 report (update), Table 8.2

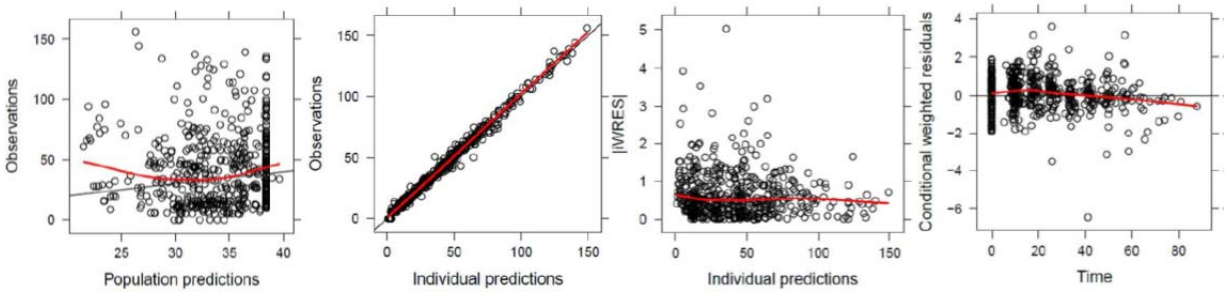
3. Prediction-Corrected VPC of the Base Empirical PK Model.



Source: Pop PK 02 report, Figure 8.6

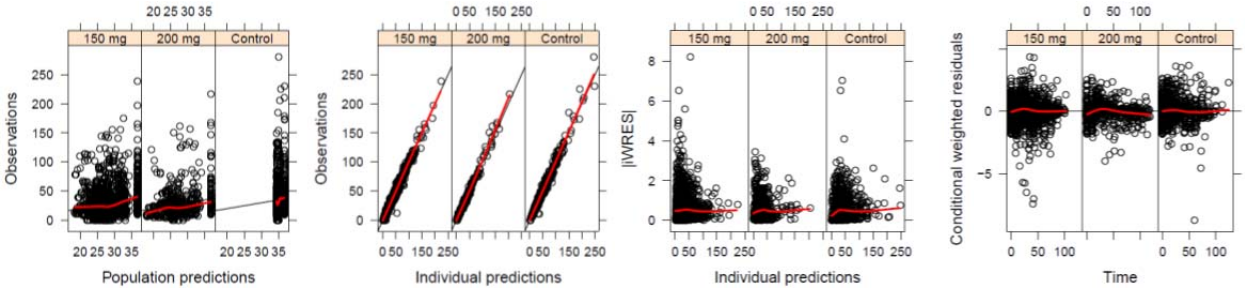
4. Diagnostic Plots and VPC of the Tumor Size PKPD Model.

Figure 23. Basic goodness-of-fit plots of Final Tumor Size Model in MONARCH 1.



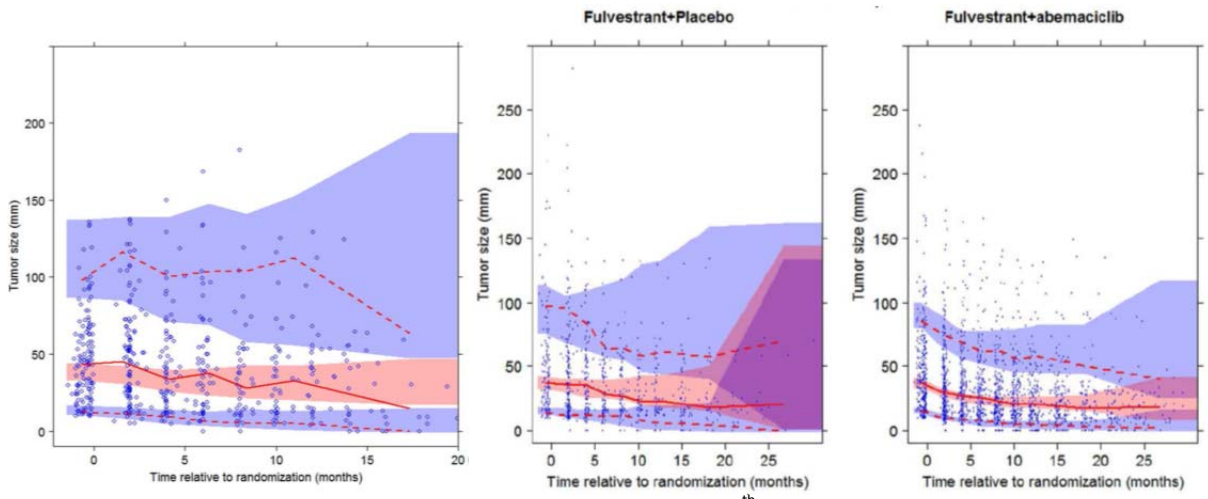
Source: Response to Information Request, Page 18

Figure 24. Basic goodness-of-fit plots of Final Tumor Size Model in MONARCH 2.



Source: Pop PK 02 report (Update), Page 607

Figure 25. Visual Predictive Check of Final Tumor Size Models in MONARCH 1 (Left) and MONARCH 2 (Middle and Right).



* The blue points are the observed data. The dotted lines are the 10th and 90th percentiles of the observed data, with the red continuous lines being the median of the observed data. The shaded areas are the 95% confidence intervals for the corresponding percentiles from the simulated data.

[#] Simulations was performed with dropout. In MONARCH 1 VPC, dropout was identified by predicted tumor size change from baseline. In MONARCH 2 VPC, dropout was identified by predicted disease progression event based on the PK-change in tumor size-PFS model.

Source: Response to Information Request, Figure 2; Pop PK 02 report (Update), Figure 8.2

13.4.2. What bioanalytical methods are used to assess concentrations?

The concentration of abemaciclib and its metabolites were quantified in human plasma, cerebral spinal fluid and urine using liquid chromatography with tandem mass spectrometry (LC-MS/MS) detection methods. Similar methodology was used to quantify the serum concentration of concomitant drugs such as fulvestrant, clarithromycin, rifampin, and loperamide. Refer to Table 75 for a complete list of the methods used in the clinical development of abemaciclib and their respective standard curve range.

The validated LC-MS/MS assay (method 141609) was initially used in the first in human trial JPBA to quantify the concentration of abemaciclib, M2 and M1 based on preclinical metabolism data. Assay 142981 was subsequently developed and validated to quantify metabolites M20 and M18, in addition to abemaciclib, M1, and M2 based on the preliminary observed PK data in trial JPBA. Upon transfer to [redacted] (b) (4) from [redacted] (b) (4), the applicant noted that the method 142981 was successfully cross-validated, and modified ([redacted] (b) (4); LY2835219 Cross Val-[redacted] (b) (4)) to exclude metabolite M1 based on low observed M1 plasma concentrations (near LLOQ of 1 ng/mL) in the late phase trial. As per the applicant, [redacted] (b) (4) developed method [redacted] (b) (4) to measure the concentration of [$^{13}C_8$]-abemaciclib in the absolute bioavailability study JPBS. Overall the precision, accuracy, selectivity, and performance of the assays were acceptable and within FDA guidance recommended criteria. Incurred sample reanalysis met the acceptance criteria for most studies which require that at least two thirds of reanalyzed samples fall within 20% of the original measurement. The % of failed samples during incurred sample reanalysis are reported inTable 76.

Table 75 List of bioanalytical methods used in the clinical development of abemaciclib

Study Identifier	Matrix/ Method Type	Analytical Laboratory (Method)	Sensitivity of Method/Range	Analytes
I3Y-MC-JPBA Additional study-specific plasma bioanalytical data	Plasma/ LC-MS/MS	[redacted] (b) (4)	1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2), LSN2878851 (M1)[b], LSN3106726 (M20), and LSN3106729 (M18)
	CSF/ LC-MS/MS		1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2) and LSN3106726 (M20)
	Plasma/ LC-MS/MS		0.5 ng/mL to 250 ng/mL	Fulvestrant
I3Y-MC-JPBB	Plasma/ LC-MS/MS		1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2), LSN3106726 (M20), and LSN3106729 (M18)
I3Y-JE-JPBC Additional study-specific bioanalytical data	Plasma/ LC-MS/MS		1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2), LSN2878851 (M1), LSN3106726 (M20), and LSN3106729 (M18)
I3Y-MC-JPBD Additional study-specific bioanalytical data	Plasma/ LC-MS/MS		1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2), LSN2878851 (M1), LSN3106726 (M20), and LSN3106729 (M18)
I3Y-MC-JPBE	Plasma/ LC-MS/MS		1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2), LSN2878851 (M1), LSN3106726 (M20), and LSN3106729 (M18)
	Plasma/ LC-MS/MS		5 ng/mL to 5000 ng/mL	Clarithromycin
I3Y-MC-JPBF	Plasma/ LC-MS/MS		1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2), LSN2878851 (M1), LSN3106726 (M20), and LSN3106729 (M18)

Study Identifier	Matrix/ Method Type	Analytical Laboratory (Method)	Sensitivity of Method/Range	Analytes
I3Y-MC-JPBG Additional study-specific bioanalytical data	Plasma/ LC-MS/MS	(b) (4)	1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2), LSN3106726 (M20), and LSN3106729 (M18)
MONARCH 1 (I3Y-MC-JPBN)	Plasma/ LC-MS/MS		1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2), LSN3106726 (M20), and LSN3106729 (M18)
I3Y-MC-JPBS	Plasma/ LC-MS/MS		1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2), LSN3106726 (M20), and LSN3106729 (M18)
	Plasma/ LC-MS/MS		0.002 ng/mL to 2 ng/mL	[$^{13}C_8$]-abemaciclib
I3Y-MC-JPBU	Plasma/ LC-MS/MS		1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2) and LSN3106726 (M20)
I3Y-MC-JPBV	Plasma/ LC-MS/MS		1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2), LSN3106726 (M20), and LSN3106729 (M18)
I3Y-MC-JPCA	Plasma/ LC-MS/MS		1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2) and LSN3106726 (M20)
	Plasma/ LC-MS/MS		0.05 ng/mL to 50 ng/mL	Loperamide and N-desmethyl loperamide
I3Y-MC-JPCC	Plasma/ LC-MS/MS		1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2) and LSN3106726 (M20)
MONARCH 2 (I3Y-MC-JPBL)	Plasma/ LC-MS/MS		1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2), LSN3106726 (M20), and LSN3106729 (M18)
	Plasma/ LC-MS/MS		0.5 ng/mL to 250 ng/mL	Fulvestrant

Study Identifier	Matrix/ Method Type	Analytical Laboratory (Method)	Sensitivity of Method/Range	Analytes
I3Y-MC-JPCK	Plasma/ LC-MS/MS	(b) (4)	1 ng/mL to 500 ng/mL	Abemaciclib and Metabolites LSN2839567 (M2) and LSN3106726 (M20)
	Plasma/ LC-MS/MS		1000 ng/mL to 500,000 ng/mL	Iohexol
	Plasma/ LC-MS/MS		2 ng/mL to 2000 ng/mL	Metformin
	Urine/ LC-MS/MS		1000 ng/mL to 200,000 ng/mL	Metformin

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Table 76 Percentage of samples that failed Incurred Sample Reanalyses

Study Identifier	Abemaciclib	LSN2839567	LSN3106726	LSN3106729	LSN2878851
I3Y-MC-JPBA[a]	0.56%	1.09%	3.33%	4.68%	NA
I3Y-MC-JPBA[b]	0.00%	0.00%	0.00%	0.00%	NA
I3Y-MC-JPBB	5.36%	5.36%	14.3%	8.93%	NA
I3Y-JE-JPBC	0.00%	6.12%	2.04%	2.04%	NA
I3Y-MC-JPBD	ND	ND	ND	ND	NA
I3Y-MC-JPBE	5.33%	5.33%	4.00%	4.00%	NA
I3Y-MC-JPBF	17.3%	12.0%	13.3%	13.3%	26.7%
I3Y-MC-JPBG	0.00%	0.00%	0.00%	0.75%	NA
I3Y-MC-JPBL	1.00%	4.50%	1.50%	2.00%	NA
I3Y-MC-JPBN	0.00%	5.88%	0.00%	0.00%	0.00%
I3Y-MC-JPBS	0.00%	2.22%	0.00%	2.22%	NA
I3Y-MC-JPBS	2.22%[c]	NA	NA	NA	NA
I3Y-MC-JPBU	0.00%	0.85%	0.00%	NA	NA
I3Y-MC-JPBV	0.00%	3.33%	1.67%	1.67%	NA
I3Y-MC-JPCA	0.63%	0.00%	0.63%	NA	NA
I3Y-MC-JPCC	2.38%	2.38%	3.24%	NA	NA

Abbreviations: NA = not applicable due to the compound not analyzed in this study, ND = not determined due to no ISR run in this study.

a Samples from patients who were dosed with abemaciclib only.

b Samples from patients who were dosed with abemaciclib along with fulvestrant.

c Results from [$^{13}C_8$]-LY2835219.

Sources: Applicant response to FDA's information request SDN008

Failed samples accounted for less than 20% of total samples during ISR for all studies except study JPBF which involved the evaluation of CYP3A induction on the PK of abemaciclib. Although failed ISR samples were above 20% for analyte M1 in study JPBF, this finding is inconsequential to the overall conclusion from the study.

Dose proportionality assessment

The applicant evaluated the dose proportionality properties of abemaciclib in trials JPBA (formulation C1, multiple doses in patients) and JPCA (formulation C3, single dose in healthy subjects). In trial JPBA, the dose proportionality assessment was evaluated over single and repeated Q12H doses of abemaciclib ranging from 50 mg to 275 mg and 75 to 200 mg, respectively. In general the exposure of abemaciclib increased in an approximately dose proportional manner after single and repeated doses. After a single administration, the mean dose normalized ratio (90%CI) for C_{max} and $AUC_{0\text{-}INF}$ of abemaciclib was respectively 1.11 (0.64, 1.91) and 1.61 (0.85, 3.05). For repeated doses, the dose normalized ratio (90% CI) for Cmax and $AUC_{0\text{-}tau}$ were 0.84 (0.38, 1.83) and 0.96 (0.43, 2.13). The reviewers concur with the applicant's conclusion that the study was not powered to statistically assess dose proportionality given the high inter-subject variability in C_{max} (117% CV) and $AUC_{0\text{-}last}$ (96% CV). On the other hand, the results of trial JPCA, established statistical evidence of dose proportionality for abemaciclib after a single dose for doses ranging from 200 mg to 600 mg. There is no evidence of marked time-dependent changes in the PK of abemaciclib based on the results of trial JPBA and popPK simulations (see the PM review in section Pharmacometrics Review). Thus, it is acceptable to conclude that abemaciclib exhibit approximately linear PK properties.

13.4.3. Physiologically-Based Pharmacokinetic Modeling Review

13.4.3.1. Objectives

The main objectives of this review are to 1) evaluate the adequacy of the Applicant's conclusions regarding the ability of a physiologically-based pharmacokinetic (PBPK) model to predict the drug-drug interaction (DDI) potential of VERZENIO (abemaciclib) as a victim of the CYP3A metabolic pathway; 2) provide dosing recommendations based on the predicted DDI potential. To support its conclusions, the applicant provided the following PBPK modeling and simulation reports and response to information requests:

- In the study report entitled "Prediction of the Effect of CYP3A4 Inhibitors on the Systemic Exposure of Abemaciclib (LY2835219) and its Active Metabolites LSN2839567, LSN3106726 and LSN3106729 in Humans After a 200 mg Oral Dose of Abemaciclib (LY2835219) Using Physiologically-Based Pharmacokinetic (PBPK) Modeling" [1].
- In the study report entitled "Prediction of the Effect of CYP3A4 Inhibitors on the Systemic Exposure of Abemaciclib (LY2835219) and its Active Metabolites LSN2839567, LSN3106726, and LSN3106729 after a 50-mg Oral Dose of LY2835219 in Cancer Patients Using Physiologically-Based Pharmacokinetic (PBPK) Modeling" [2].

- In the study report entitled "Prediction of the Effect of CYP3A Inducers on the Systemic Exposure of Abemaciclib (LY2835219) and its Active Metabolites LSN2839567, LSN3106726 and LSN3106729 in Humans using Physiologically-based Pharmacokinetic (PBPK) Modeling" [3].
- In the study report entitled "Mechanistic Absorption Modeling of Abemaciclib (LY2835219) and particle size sensitivity analysis" [4].
- Response to FDA Information Request received on July 5, 2017 [5].
- Response to FDA Information Request received on July 10, 2017 [6].

13.4.3.2. Background

Abemaciclib is an inhibitor of cyclin D-dependent kinases 4 and 6 (CDK4 and CDK6) for the [redacted] (b) (4) . The proposed dosing regimen of abemaciclib is 200 mg orally twice daily (BID) as a [redacted] (b) (4) or 150 mg BID in combination with fulvestrant. Abemaciclib (LY2835219) is metabolized by CYP3A to form 3 major circulating active metabolites, M2 (N-desethylabemaciclib; LSN2839567), M20 (hydroxyabemaciclib; LSN3106726), and M18 (hydroxy-N-desethylabemaciclib; LSN3106729), which respectively account for 13%, 26%, and 5% of the total analytes AUC in plasma following a single oral dose of 150 mg abemaciclib in healthy subjects. Abemaciclib and its metabolites (M2, M20, M18) are generally equipotent for binding to the CDK4/6 target for efficacy and safety. The IC_{50} for inhibition of CDK4 by abemaciclib was 1.57 nM versus 1.24, 1.46, and 1.54 nM for metabolites M2, M18, and M20, respectively. Similarly, the IC_{50} for inhibition of CDK6 was 2.0, 1.33, 2.65, and 1.86 nM for abemaciclib, M2, M18, and M20, respectively [7]. Neutropenia is a known on-target effect of binding to CDK4/6 and exposure-response relationships for safety (i.e., neutropenia) with abemaciclib and metabolites have been observed.

PBPK models for abemaciclib have been developed by the Applicant to predict the effect of CYP3A modulators on the pharmacokinetics (PK) of abemaciclib. In this submission, the Applicant used PBPK models to predict the effect of ketoconazole, itraconazole, diltiazem, verapamil, and carbamazepine on abemaciclib PK. Clinical DDI studies were conducted to evaluate the effects of clarithromycin, a strong CYP3A inhibitor (Study JPBE) and rifampin, a strong CYP3A inducer (Study JPBF), on abemaciclib PK. These data were used to verify the abemaciclib PBPK model. Table 77 summarizes the observed AUC and C_{max} ratios of abemaciclib coadministered with clarithromycin and rifampin following a single dose of abemaciclib 50 mg or 200 mg, with abemaciclib alone as reference. Potency-adjusted unbound exposure (relative potency adjusted unbound AUC of abemaciclib plus its active metabolites) was calculated by converting the analyte concentrations to molar units (nmol·h/mL) and accounting for the fraction unbound and CDK4/6 IC_{50}s of abemaciclib, M2, M20, and M18.

Table 77. Observed DDI Effects of Clarithromycin and Rifampin on Abemaciclib PK

	Abemaciclib 50 mg + clarithromycin 500 mg BID[a]		Abemaciclib 200 mg + rifampin 600 mg QD[b]	
	AUC Ratio[1] Geometric Mean (90% CI)	C_{max} Ratio[1] Geometric Mean (90% CI)	AUC Ratio[1] Geometric Mean (90% CI)	C_{max} Ratio[1] Geometric Mean (90% CI)
Abemaciclib	3.37 (2.85, 3.99)	1.30 (1.10, 1.52)	0.05 (0.04, 0.06)	0.08 (0.07, 0.09)
M2	1.32 (1.14, 1.53)	0.33 (0.27, 0.40)	0.35 (0.32, 0.38)	0.96 (0.81, 1.13)
M20	0.94 (0.84, 1.06)	0.27 (0.21, 0.34)	0.20 (0.19, 0.22)	0.64 (0.56, 0.73)
M18	- [2]	- [2]	1.31 (1.18, 1.44)	4.26 (3.42, 5.31)
Total Analytes	2.19 (1.87, 2.56)	0.93 (0.79, 1.09)	0.23 (0.21, 0.25)	0.55 (0.50, 0.61)

[1]Ratios expressed as abemaciclib + perpetrator/abemaciclib alone.

[2]M18 concentrations were below limit of quantification following coadministration of abemaciclib and clarithromycin.

Source: [a]JPBE Final Study Report, Tables 7.2, 7.9, Pages 23, 35; [b]JPBF Final Study Report, Tables 7.2, 7.10, Pages 23, 36.

Based on the observed data from the clinical DDI studies and PBPK analyses, the Applicant proposed the following dosing recommendations in the USPI:

- Avoid concomitant use of CYP3A inducers.
- (b) (4)
-
-

Table 78. Applicant's Labeling Dosing Recommendations

(b) (4)

(b) (4)

This review evaluates the adequacy of PBPK modeling to support dosing recommendations in the abemaciclib labeling.

13.4.3.3. Methods

The population based PBPK software package Simcyp® (b) (4) version 14.1 was used by the Applicant to develop the PBPK models for abemaciclib and metabolites assessed in this review. The Applicant's PBPK modeling of abemaciclib can be summarized in three parts: model building, model verification, and model applications. Table 79 summarizes the design of clinical studies and simulations for the development, verification, and application of the abemaciclib PBPK model using Simcyp®. PBPK model parameters for abemaciclib and its metabolites were summarized in Appendix Table 82, Table 83, Table 84 and Table 85.

Table 79. Summary of the Clinical Studies and Simulations for the Development, Verification, and Application of the Abemaciclib PBPK Model

Interacting Drugs (purposes)	Simulation Design	Clinical Study Design
None (model development)	Simulations were done using 10 trials with 10 subjects per trial (n=100). Healthy Volunteers. Age 40-65 years, 80% females. Abemaciclib oral single doses of 50 and 200 mg under fasted conditions.	Clinical studies JPBD, JPBS, JPBE: • JPBD: Human mass balance study in 6 healthy subjects administered an oral 150 mg single dose of radiolabeled abemaciclib • JPBS: Human absolute bioavailability study in 8 healthy subjects administered an oral 200 mg single dose of abemaciclib • JPBE: Clarithromycin DDI study (see below)
Clarithromycin (model verification)	Simulations were done using 10 trials with 10 subjects per trial (n=100). Healthy Volunteers. Age 40-65 years, 80% females. Clarithromycin oral 500 mg BID for 12 days, abemaciclib 50 mg or 200 mg single doses on day 7 together with clarithromycin under fasted conditions.	An open-label, randomized, two-period, fixed-sequence, DDI study to assess the effect of clarithromycin (a strong CYP3A inhibitor) 500 mg BID on the PK of an oral single 50 mg dose of abemaciclib in 26 patients with advanced/metastatic cancer under fasted conditions. The mean age of the population was 60 years (range: 37 to 78 years). Majority of the patients (73%) were female. PK samples were collected at pre-dose and 1, 2, 4, 6, 8, 10, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours post-dose. • Abemaciclib 50 mg single dose on day 1 followed by a 7-day washout • Abemaciclib 50 mg single dose on day 13 • Clarithromycin 500 mg BID for14 days (days 9 to 22)
Ketoconazole (model prediction)	Simulations were done using 10 trials with 10 subjects per trial (n=100). Healthy Volunteers. Age 40-65 years, 80% females. Abemaciclib 50 mg or 200 mg single doses under fasted conditions. Ketoconazole DDI was simulated by assuming 100% inhibition of CYP3A-mediated metabolism of abemaciclib and reducing the CYP3A-mediated clearance to zero.	Not applicable

Interacting Drugs (purposes)	Simulation Design	Clinical Study Design
Itraconazole (model prediction)	Simulations were done using 10 trials with 10 subjects per trial (n=100). Healthy Volunteers. Age 40-65 years, 80% females. Abemaciclib 50 mg or 200 mg single doses under fasted conditions. Itraconazole DDI was simulated by assuming 90% inhibition of CYP3A-mediated metabolism of abemaciclib and reducing the CYP3A-mediated clearance by 90%.	Not applicable
Diltiazem (model prediction)	Simulations were done using 10 trials with 10 subjects per trial (n=100). Healthy Volunteers. Age 40-65 years, 80% females. Diltiazem oral 120 mg TID for 12 days, abemaciclib 50 mg or 200 mg single doses on day 7 together with diltiazem under fasted conditions.	Not applicable
Verapamil (model prediction)	Simulations were done using 10 trials with 10 subjects per trial (n=100). Healthy Volunteers. Age 40-65 years, 80% females. Verapamil 120 mg TID orally for 12 days, abemaciclib 50 mg or 200 mg single doses on day 7 together with verapamil under fasted conditions.	Not applicable
Rifampicin (model verification)	Simulations were done using 10 trials with 10 subjects per trial (n=100). Healthy Volunteers. Age 40-65 years, 80% females. Rifampin oral 600 mg QD for 24 days, abemaciclib 200 mg single dose on day 7 with rifampin under fasted conditions.	An open-label, randomized, two-period, fixed-sequence, DDI study to assess the effect of rifampin (a strong CYP3A inducer) 600 mg QD on the PK of an oral single 200 mg dose of abemaciclib in 24 healthy subjects under fasted conditions. The mean age of the population was 59 years (range: 44 to 70 years). Majority of the patients (88%) were female. PK samples were collected at pre-dose and 1, 2, 4, 6, 8, 10, 24, 48, 72, 96, 120, 144, 168, and 192 hours post-dose. 1. Abemaciclib 200 mg single dose on day 1 followed by a 9-day washout 2. Abemaciclib 200 mg single dose on day 17 3. Rifampin 600 mg QD for14 days (days 11 to 24)
Carbamazepine (model prediction)	Simulations were done using 10 trials with 10 subjects per trial (n=100). Healthy Volunteers. Age 40-65 years, 80% females.	Not applicable

Interacting Drugs (purposes)	Simulation Design	Clinical Study Design
	Carbamazepine oral 400 mg BID for 24 days, abemaciclib 200 mg single dose on day 7 with carbamazepine under fasted conditions.	

13.4.3.3.1. Model Building

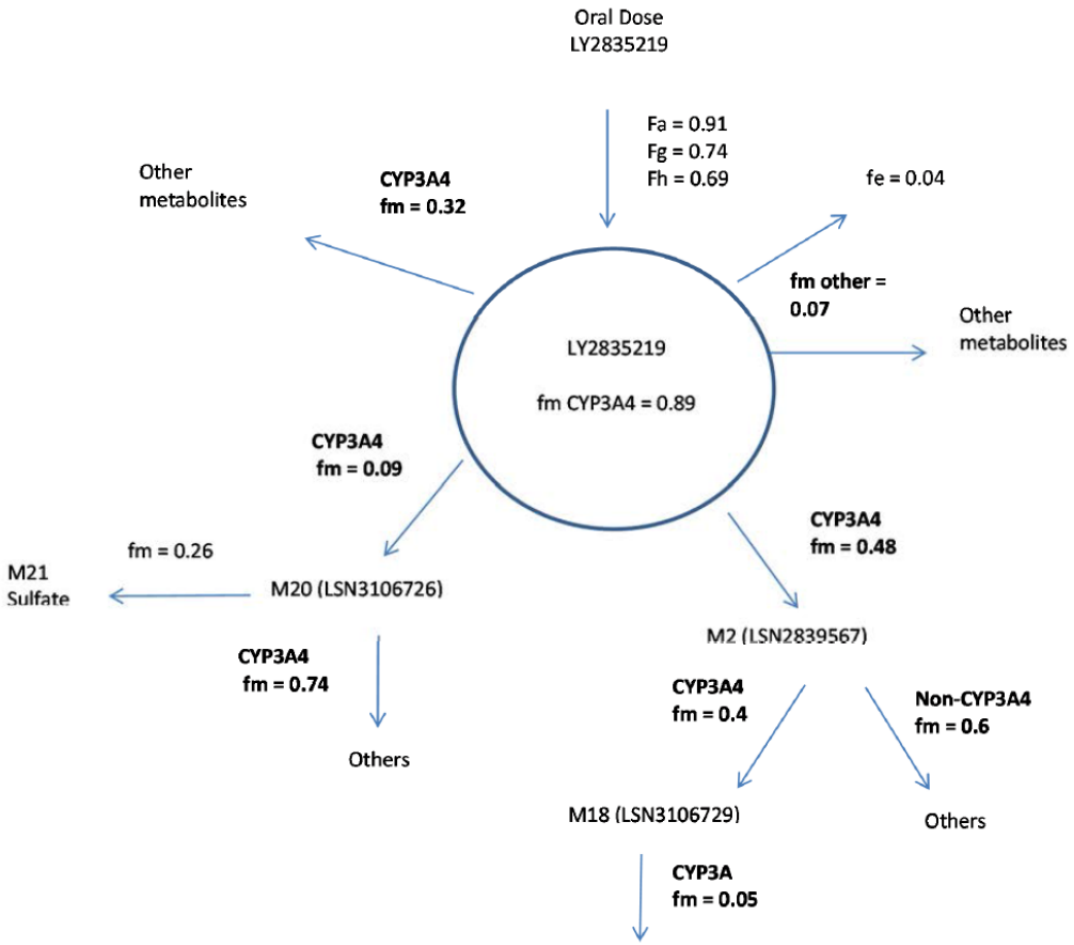
The abemaciclib PBPK models were built using in vitro data and data from clinical studies JPBD, JPBE, and JPBS in healthy subjects and JPBE in patients. A first order absorption model was utilized. The Applicant estimated the fraction escaping gut metabolism (F_G) following abemaciclib 200 mg based on observed data from the human absolute bioavailability study (JPBS) and the human mass balance study (JPBD).

Bioavailability parameter (F) is the product of three absorption parameters: fraction absorbed (Fa), fraction escaping hepatic metabolism (F_H) and F_G according to the equation $F = Fa \times F_g \times F_h$. The value of F was 0.45 according to the results of the absolute bioavailability study following an oral single 200 mg dose of abemaciclib (Study JPBS); Fa was determined as 0.91 based on the mass balance study (Study JPBD). Study JPBD reported less than 10% of abemaciclib was recovered in feces following a single oral dose of 150 mg abemaciclib. Given that abemaciclib is mostly metabolized by CYP3A in liver, the mean systemic plasma clearance (CL_{iv}) of 24 L/h following a single intravenous (IV) dose of abemaciclib was used as a surrogate for hepatic clearance (CL_{liver}). By assuming hepatic blood flow (Qh) as 80 L/h and blood to plasma ratio (B:P) of 0.84 and F_H=0.64, F_G was calculated to be 0.77 for abemaciclib 200 mg; however, the Applicant used an F_G value of 1 when dosing abemaciclib at 50 mg to describe a 2-fold difference in metabolite:parent ratios observed at 200 mg compared with those at 50 mg (Appendix Table 86). On June 27, 2017, FDA issued an information request to provide a mechanistic rationale for differences in Fg based on the dose of 50 mg versus 200 mg.

In the Applicant's IR response [6], the Applicant described that a fit-for-purpose PBPK modeling approach was used to develop the abemaciclib PBPK models, and two Fg were used in order to describe the clinically observed PK of abemaciclib at 50 mg and 200 mg. The Applicant's assumption that Fg varies at these two doses is based on 1) no change in F_H observed due to a lack of change in half-life between 50 mg and 200 mg (Study JPBA); 2) dose-dependent absorption (Fa) is unlikely given high permeability of abemaciclib and fast dissolution in the stomach [4, 6]; and 3) a trend towards a slight increase of gut wall metabolism with increasing dose and no Fa change in the population PK analysis; therefore, the Applicant states that this observed difference is likely due to metabolic differences and not absorption changes [6]. FDA reviewers note that differences in the predicted AUC ratio of total analytes in the presence/absence of CYP3A inhibitors with different F_G values were minimal (less than 20%)

(Appendix Table 87). The observed DDI between abemaciclib (50 mg single dose) and clarithromycin (500 mg BID) from the clinical Study JPBE was used to inform the fraction of abemaciclib metabolized by CYP3A4 ($f_{m,CYP3A4}$) in the PBPK model. Abemaciclib $f_{m,CYP3A4}$ was determined to be 0.89. The $f_{m,CYP3A4}$ for M2, M20, and M18 were 0.40, 0.74, and 0.05, respectively, and were determined by fitting the observed AUC and AUC ratios from the clinical Study JPBF. Figure 26 shows the proposed metabolic pathways for abemaciclib and its active metabolites.

Figure 26. Diagram of the Metabolic Pathways for Abemaciclib and Active Metabolites



Source: 'LY2835219 MM CYP3A4 Inh 200mg' Final Study Report, Figure 1, Page 17.

13.4.3.3.2. Model Verification

The PBPK models for abemaciclib and its three active metabolites were able to reproduce the observed PK parameters following abemaciclib 200 mg from the in vivo DDI study (JPBF) and observed concentration-time profiles of total analyte in healthy subjects (JPBF) and in patients with cancer. Table 80 shows that simulated AUC_{inf} and C_{max} of abemaciclib and its metabolites were within 0.8 and 1.25-fold of the observed values.

Table 80. Comparison of Predicted and Observed PK Parameters of Abemaciclib and Metabolites (M2, M20, M18) Following a Single Oral Dose of Abemaciclib 200 mg

Compound	Parameter	Observed Geo Mean(%CV)	Predicted Geo Mean (%CV)	Observed/ Predicted
LY2835219	AUC_{0-inf} (ng*hr/mL)	4570 (53)	4428 (50)	1.03
	C_{max} (ng/mL)	134 (45)	140 (49)	0.96
LSN2839567	AUC_{0-inf} (ng*hr/mL)	1780 (30)	1927 (37)	0.92
	C_{max} (ng/mL)	35 (47)	39 (39)	0.90
LSN3106726	AUC_{0-inf} (ng*hr/mL)	3760 (33)	3104 (41)	1.21
	C_{max} (ng/mL)	63 (32)	68 (23)	0.93
LSN3106729	AUC_{0-inf} (ng*hr/mL)	660 (38)	640 (55)	1.03
	C_{max} (ng/mL)	12 (69)	14 (58)	0.86

*Observed data from Study JPBF.

Source: 'LY2835219 MM CYP3A4 Inh 200mg' Final Study Report, Table 9, Page 15.

Simulations of repeat doses of abemaciclib 200 mg BID showed a geometric mean AUC of 3844 ng·h/mL, which is comparable to that simulated for a single dose of abemaciclib 200 mg. This is expected since linear PK was observed for abemaciclib.

13.4.3.3.3. Model Applications

The Applicant conducted the following simulations to prospectively predict the PK of abemaciclib and total analytes:

- 200 mg single oral doses of abemaciclib in the presence of moderate CYP3A inhibitors, diltiazem and verapamil.
- 200 mg single oral dose of abemaciclib in the presence of a strong CYP3A inducer, carbamazepine.

For the predicted interaction with ketoconazole, the Applicant assumed that CYP3A-mediated metabolism of abemaciclib was completely inhibited and the CYP3A-mediated clearance was set to zero. The (b) (4) reduction in CYP3A intrinsic clearance by ketoconazole was chosen to reproduce the literature reported AUC ratio COPYRIGHT PROTECTED MATERIAL for midazolam (a sensitive CYP3A substrate), assuming Fg of midazolam is (b) (4) and $f_{m,CYP3A}$ is (b) (4) [1]. For the predicted interaction with itraconazole, the Applicant assumed that 90% CYP3A-mediated metabolism of abemaciclib was inhibited. The (b) (4) reduction in CYP3A intrinsic clearance by itraconazole was chosen to

reproduce the literature reported AUC ratio [COPYRIGHT PROTECTED MATERIAL] for midazolam, assuming Fg of midazolam is [(b) (4)] and fm is [(b) (4)] (Appendix Table 88).

The predictions of the effect of CYP3A inhibition by clarithromycin, diltiazem, verapamil, and CYP3A induction by rifampin and carbamazepine were performed using standard perpetrator models from the Simcyp® v14 drug model library.

13.4.3.4. Results

Q1: Can the abemaciclib PBPK models provide a reasonable description of the observed DDI effects of CYP3A modulators?

Yes. Two major factors critical for a substrate PBPK model are quantitative determination of the contribution of the CYP pathway that is modulated by the co-medication (e.g., assumption of $f_{m,CYP3A}$ for abemaciclib), and ability of the model to predict the PK profile.

The Applicant's abemaciclib PBPK models reasonably described abemaciclib and its three active metabolites, M2, M20, and M18 as shown in Table 81. The fraction of abemaciclib metabolized by CYP3A4 ($f_{m,CYP3A4}$) was determined to be 0.89 based on the observed AUC ratio in the clarithromycin DDI study (JPBE) and was further verified using clinical DDI data with rifampin, a strong CYP3A inducer (Study JPBF). A comparison of simulated abemaciclib and total analyte PK with those observed in Studies JPBE and JPBF is shown in Table 81.

Table 81. Observed and Simulated Exposure Following a Single Dose of Abemaciclib

	Parameter*	Observed Geometric Mean (90% CI)	Predicted	Observed/Predicted Ratio
Abemaciclib 50 mg with Clarithromycin 500 mg BID[a]				
Abemaciclib	AUC ratio	3.37 (2.85, 3.99)	3.89 (3.59, 4.22)	0.87
	C_{max} Ratio	1.30 (1.10, 1.52)	1.64 (2.01, 2.17)	0.79
2839567 (M2)	AUC ratio	1.32 (1.14, 1.53)	0.89	1.48
	C_{max} Ratio	0.326 (0.268, 0.397)	0.33	0.99

	Parameter*	Observed Geometric Mean (90% CI)	Predicted	Observed/Predicted Ratio
3106726 (M20)	AUC ratio	0.944 (0.842, 1.06)	1.33	0.71
	C_{max} Ratio	0.268 (0.214, 0.337)	0.46	0.58
3106729 (M18)	AUC ratio	BLQ	0.30	-
	C_{max} Ratio	BLQ	0.12	-
Total analytes	AUC ratio	2.19 (1.87, 2.56)	2.76	0.79
	C_{max} Ratio	0.927 (0.790, 1.09)	1.27	0.73
Abemaciclib 200 mg with Rifampin 600 mg QD[b]				
Abemaciclib	AUC ratio	0.0467 (0.0376, 0.0581)	0.07 (0.07, 0.09)	0.67
	C_{max} Ratio	0.0771 (0.0671, 0.0886)	0.14 (0.12, 01.5)	0.55
2839567 (M2)	AUC ratio	0.351 (0.322, 0.382)	0.39	0.9
	C_{max} Ratio	0.957 (0.807, 1.13)	0.84	1.14
3106726 (M20)	AUC ratio	0.20 (0.19, 0.22)	0.24	0.85
	C_{max} Ratio	0.642 (0.564, 0.731)	0.61	1.05
3106729 (M18)	AUC ratio	1.31 (1.18, 1.44)	1.72	0.76
	C_{max} Ratio	4.26 (3.42, 5.31)	3.51	1.21
Total analytes	AUC ratio	0.23 (0.21, 0.25)	0.29	0.79
	C_{max} Ratio	0.55 (0.49, 0.61)	0.55	1.0

Sources: [a] JPBE Final Study Report, Tables 7.2, 7.9, Pages 23, 35; [b]JPBF Final Study Report, Tables 7.2, 7.10, Pages 23, 36.

[*]AUC and C_{max} ratios expressed as abemaciclib + perpetrator/abemaciclib alone.

The abemaciclib PBPK models were adequate to predict the DDI effects between abemaciclib and CYP3A modulators including ketoconazole and itraconazole.

Q2: Can the abemaciclib PBPK models be used to support labeling dosing recommendations based on the predicted DDI potential?

Yes, the abemaciclib PBPK models further verified with observed DDI data from the clarithromycin and rifampin clinical studies and observed data from patients in Study JPBA are considered adequate to simulate the DDI effect of other CYP3A modulators under untested clinical DDI scenarios. A summary of the DDI effects of CYP3A modulators on the exposure of abemaciclib and its metabolites is shown in Appendix Table 89.

FDA reviewers recommend the use of potency adjusted unbound exposure (see section 13.4.3.2) to represent total effective exposure of abemaciclib and its metabolites by accounting for the contribution of each active moiety that has a different fu and CDK4/6 IC_{50}. To support the dosing recommendation for abemaciclib with coadministration of CYP3A modulators, DDI-mediated changes in drug exposure should be considered along with exposure-response relationship for safety and efficacy.

Given the magnitude of exposure change in the context of the exposure-response relationships for safety and effectiveness observed with abemaciclib plus its active metabolites, the following recommendations are provided with regard to concomitant use of strong CYP3A inhibitors:

- Avoid concomitant use of ketoconazole given the predicted up to 16-fold increase of abemaciclib and potential concerns for unknown off-target toxicities.
- In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the VERZENIO dose to 100 mg twice daily with concomitant use of other strong CYP3A inhibitors (examples below).
- In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the VERZENIO dose to 50 mg twice daily with concomitant use of other strong CYP3A inhibitors (examples below).
- Examples of other strong CYP3A inhibitors include but are not limited to: boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir

and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, troleandomycin, and voriconazole.

- After discontinuation of a strong CYP3A inhibitor, increase the VERZENIO dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the strong inhibitor.

Regarding CYP3A inducers, the recommendation is avoidance of concurrent use of strong CYP3A inducers. A postmarketing commitment (PMC) will be requested to conduct PBPK analysis (or a PK trial if the results from the PBPK analysis are inconclusive) to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose PK of abemaciclib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations.

13.4.3.5. Conclusion

The Applicant's PBPK models of abemaciclib and its metabolites are considered adequate to predict abemaciclib PK and the effect of various CYP3A modulators on abemaciclib PK**.** Predicted potency adjusted unbound exposure (relative potency [IC_{50}] adjusted unbound exposure of abemaciclib plus its active metabolites, M2, M18, and M20) can be used to support dosing recommendations of abemaciclib when coadministered with CYP3A modulators.

13.4.3.6. Appendices for PBPK Analysis

Abbreviations

BCRP, breast cancer resistance protein; BID, twice daily dosing; B:P, blood to plasma ratio; AUC, area under the concentration-time profile; C_{max}, maximal concentration in plasma; CL, clearance; CL_{int}, intrinsic clearance; CL_{iv}, intravenous plasma clearance; $CL_{B,iv}$, intravenous blood clearance; DDI: drug-drug interaction; E_H, hepatic extraction ratio; F, absolute bioavailability; Fa, fraction of drug absorbed from the intestinal lumen into intestinal wall; Fg, fraction of drug that escapes first pass metabolism in the intestine; F_H, fraction of drug that escapes first pass metabolism in the liver; Fm, fraction of drug metabolized; K_m, Michaelis-Menten Constant; P_{eff}, human effective passive permeability in man; PBPK: physiologically-based pharmacokinetic; P-gp: p-glycoprotein; Q, hepatic blood flow; TID, three times daily dosing; QD, once daily dosing.

Information Requests

A) Your PBPK report states that "The difference between the 50mg and 200mg models is primarily in the fraction of abemaciclib escaping first pass gut metabolism (F_G)." Please provide the mechanistic rationale for differences in Fg based on the dose of 50 mg versus 200 mg.

B) Reference is made to Table 5 of the draft labeling text in module 1.14.1.3 of NDA 208716 submitted on May 5th, 2017:

1. Please provide the rationale for the proposed dosing regimen of (b) (4) .
2. Please provide the rationale for the proposed dosing regimen of (b) (4)

Appendices Tables

Table 82. Abemaciclib PBPK Model Input Parameters for Abemaciclib

Property	Value	Source
Name	LY2835219	
Molecular weight (g/mol)	506.6	Investigator's Brochure
LogP	3.36	Measured, Bhattachar 2009
pKa 1 (basic)	7.95	Measured, Bhattachar 2009
pKa 2 (basic)	4.48	Measured, Bhattachar 2009
B:P	0.84	Measured, Bao and Kulanthaivel 2014
fu	0.027	Measured, Vandana 2009 (average of 0.3 to 3.0 uM)
ka (h^{-1})	0.2	PopPK analysis (JPBA)
Fa	0.91	Estimated from ^{14}-C study (JPBD) Appendix 1
hPeff (10^{-4} cm/s)	2.46	Predicted from HBD and PSA (Simcyp)
fuGut	0.45	Manually fitted to obtain F4574 match observed F = 0.45 (JPBS)
Qgut (L/hr)	10.1	Predicted (Simcyp)
PSA (Å^2)	71.4	Predicted, in-house model
HBD	1	Predicted, in-house model
Vd_{ss} (L/kg)	8.93	ABA study (JPBS)
CL systemic (L/h)	24	ABA study (JPBS)
CL renal (L/h)[a]	1.0	Estimated from ^{14}-C study (JPBD) [a]
CL_{int} CYP3A4 p1 (µL/min/ mg protein)[b]	178.59	Back-calculated from IV CL of ABA Study (JPBS) and fm values from ^{14}-C study (JPBD: Appendix 1)
CL_{int} CYP3A4 p2 (µL/min/ mg protein)[c]	33.01	
CL_{int} CYP3A4 p3 (µL/min/ mg protein)[d]	162.20	
CL_{int} HLM (µL/min/mg protein)	20	

[a] Renal clearance estimated as 4% of systemic clearance based on radioactivity recovery in urine in study JPBD (Appendix 1).
[b] p1 is the CYP3A4-mediated clearance pathway that forms LSN2839567.
[c] p2 is the CYP3A4-medited clearance pathway that forms LSN3106726.
[d] p3 is the CYP3A4-mediated clearance pathway that forms metabolites not included in this model.

Source: 'LY2835219 MM CYP3A4 Inh 200mg' Final Study Report, Table 2, Page 11.

Table 83. Abemaciclib PBPK Model Input Parameters for LSN2839567 (M2)

Property	Value	Source
Compound	LSN2839567	
Molecular weight (g/mol)	478.55	Investigator's Brochure
cLogP	3.66	Predicted (b) (4)
pKa (basic)	9.19	Predicted
fu	0.107	Measured, Sprague and Kulanthaivel 2012
B:P	0.836	Predicted (Simcyp) from physchem properties
Vd_{ss} (L/kg) minimal PBPK model	12.1	Fitted manually to match C_{max} of JPBF
CL_{int} CYP3A4 (µL/min/mg protein) [a]	50	Estimated manually to fit the results of JPBF
CL_{int} HLM (µL/min/mg protein)	75	Estimated manually to fit the results of JPBF

[a] Clearance pathway that forms LSN3106729.

Source: 'LY2835219 MM CYP3A4 Inh 200mg' Final Study Report, Table 3, Page 11.

Table 84. Abemaciclib PBPK Model Input Parameters for LSN3106726 (M20)

Property	Value	Source
Name	LSN3106726	
Molecular weight (g/mol)	522.6	Investigator's Brochure
cLogP	2.78	Predicted (b) (4)
pKa (basic)	8.37	Predicted
B:P	0.67	Predicted (Simcyp) from physchem properties
fu	0.064	Measured, Sprague and Kulanthaivel 2012
Vd_{ss} (L/kg) minimal PBPK model	1.24	Fitted manually to approximate C_{max}
CL_{int} CYP3A4 (µL/min/mg protein)	20	Estimated manually to match results from JPBF as described in Appendix 1
CL_{int} HLM (µL/min/mg protein)	7	Estimated manually to match results from JPBF as described in Appendix 1

Source: 'LY2835219 MM CYP3A4 Inh 200mg' Final Study Report, Table 4, Page 12.

Table 85. Abemaciclib PBPK Model Input Parameters for LSN3106729 (M18)

Property	Value	Source
Name	LSN3106729	
Molecular weight (g/mol)	494.5	Investigator's Brochure
cLogP	2.35	Predicted (b) (4)
pKa (basic)	9.19	Predicted
B:P	0.664	Predicted (Simcyp) from phys-chem properties
f_u	0.088	Measured, Sprague and Kulanthaivel 2012
Vd_{ss} (L/kg) minimal PBPK model	2.5	Fitted manually to approximate C_{max}
CL_{int} CYP3A4 (µL/min/mg protein)	10	Estimated manually to match results from JPBF as described in Appendix 1
CL_{int} HLM (µL/min/mg protein)	160	Estimated manually to match results from JPBF as described in Appendix 1

[a] Renal clearance estimated as 4% of systemic clearance based on radioactivity recovery in urine in study JPBD (Appendix 1).

[b] p1 is the CYP3A4-mediated clearance pathway that forms LSN2839567.

[c] p2 is the CYP3A4-medited clearance pathway that forms LSN3106726.

[d] p3 is the CYP3A4-mediated clearance pathway that forms metabolites not included in this model.

Source: 'LY2835219 MM CYP3A4 Inh 200mg' Final Study Report, Table 5, Page 12.

Table 86. Metabolite: Parent Ratios Following Oral Single Doses of Abemaciclib 50 or 200 mg

Ratio	JPBE (50 mg dose)	JPBF (200 mg dose)	JPBS (200 mg dose)
M2/Parent	0.24	0.41	0.41
M20/Parent	0.47	0.80	0.85
M18/Parent	0.09	0.15	0.17

Source: 'LY2835219 MM CYP3A4 Inh 200mg' Final Study Report, Table A.3, Page 27.

Table 87. Comparison of Predicted AUC Ratios of Total Analytes with Different F_G

	Total Analyte AUC Ratio Following Abemaciclib With/Without CYP3A Inhibitor				
	Clarithromycin	Diltiazem	Verapamil	Itraconazole	Ketoconazole
PBPK model prediction with Fg = 0.77[a]	2.76	2.41	1.63	3.78	6.87
PBPK model prediction with Fg = 1[b]	2.49	1.95	1.48	3.45	6.13

[a]Data obtained from Applicant's "active-species-calculation-inhibition-200mg.xls"
[b]Data obtained from Applicant's "active-species-calculation.xls"

Table 88. Observed and Simulated Midazolam AUC Ratios Following Various CYP3A4 Inhibitors

Inhibitor	Observed Midazolam AUC Ratio	Predicted Midazolam AUC Ratio	Observed/Predicted
Clarithromycin	COPYRIGHT PROTECTED MATERIAL	7.04	0.90
Itraconazole		9.03	0.7
Diltiazem		3.83	1.0
Verapamil		3.08	0.9
Ketoconazole		21.65	0.87

a Observed value reported in Quinney et al. 2007.
b Observed value reported in Olkkola et al. 1994.
c Observed value reported in Zhang et al. 2009.
d Observed value reported in Backman et al. 1994.
e Observed value reported in Halama et al. 2013

Source: 'LY2835219 MM CYP3A4 Inh 200mg' Final Study Report, Table 7, Page 14.

Table 89. Simulated Geometric Mean Abemaciclib, Total Analyte, and potency adjusted unbound Exposure Change (AUC Ratio) Following Various CYP3A Modulators

	Abemaciclib	Total Analyte	CDK4 IC_{50} Adjusted Unbound Exposure	CDK6 IC_{50} Adjusted Unbound Exposure
Ketoconazole[a]	↑ 15.73-fold	↑ 6.87-fold	↑ 2.87-fold	↑ 2.69-fold
Itraconazole[a]	↑ 7.15-fold	↑ 3.78-fold	↑ 2.16-fold	↑ 2.11-fold
Clarithromycin[a]	↑ 4.95-fold	↑ 2.76-fold	↑ 1.71-fold	↑ 1.68-fold
Diltiazem[b]	↑ 3.95-fold	↑ 2.41-fold	↑ 1.66-fold	↑ 1.64-fold
Verapamil[b]	↑ 2.28-fold	↑ 1.63-fold	↑ 1.31-fold	↑ 1.31-fold
Rifampin[c]	↓ 93%	↓ 71%	↓ 67%	↓ 69%
Carbamazepine[c]	↓ 80%	↓ 52%	↓ 38%	↓ 41%

[a] Strong CYP3A4 inhibitors; [b] Moderate CYP3A4 inhibitors;[c] Strong CYP3A4 inducers
Source: 'LY2835219 MM CYP3A4 Inh 200mg' Final Study Report, Table 10, Page 16 and 'LY2835219 PBPK IND CYP3A' Table 9 and 10, Page 21.

13.4.3.7. References for PBPK Analysis

1-Eli Lilly. Posada et al. LY2835219 MM CYP3A4 Inh 200mg. Prediction of the Effect of CYP3A4 Inhibitors on the Systemic Exposure of Abemaciclib (LY2835219) and its Active Metabolites LSN2839567, LSN3106726 and LSN3106729 in Humans After a 200 mg Oral Dose of Abemaciclib (LY2835219) Using Physiologically-Based Pharmacokinetic (PBPK) Modeling. February 2016.

2-Eli Lilly. Posada et al. LY2835219 MM INH PBPK 50mg. Prediction of the Effect of CYP3A4 Inhibitors on the Systemic Exposure of Abemaciclib (LY2835219) and its Active Metabolites LSN2839567, LSN3106726, and LSN3106729 after a 50-mg Oral Dose of LY2835219 in Cancer Patients Using Physiologically-Based Pharmacokinetic (PBPK) Modeling. February 2016.

3-Eli Lilly. Posada et al. LY2835219 PBPK IND CYP3A. Prediction of the Effect of CYP3A Inducers on the Systemic Exposure of Abemaciclib (LY2835219) and its Active Metabolites LSN2839567, LSN3106726 and LSN3106729 in Humans using Physiologically-based Pharmacokinetic (PBPK) Modeling. March 2016.

4-Eli Lilly. Stamatis et al. PRD-02431-TR. Mechanistic Absorption Modeling of Abemaciclib (LY2835219) and particle size sensitivity analysis. January 21, 2016.

5-Eli Lilly. Responses to FDA Information Request received on July 5, 2017.

6-Eli Lilly. Responses to FDA Information Request received on July 10, 2017.

7-Eli Lilly. Pharmacology Written Summary. May 2017.

14 Division Director (DHOT)

X _____

15 Division Director (OCP)

X _____

16 Division Director (OB)

X _____

17 Division Director (Clinical)

X _____

18 Office Director (or designated signatory authority)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit profile was also assessed by Drs. Beaver, Amiri-Kordestani and Howie who recommend approval. I also recommend approval of this application. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

My signature below also represents the approval decision of this application under CDER.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANICE H KIM
09/28/2017

TIFFANY RICKS
09/28/2017

TODD R PALMBY
09/28/2017

JOHN K LEIGHTON
09/28/2017

RUBY LEONG
09/28/2017

YUCHING N YANG
09/28/2017

NAN ZHENG
09/28/2017

NAN ZHENG on behalf of JINGYU YU
09/28/2017

JEANNE FOURIE ZIRKELBACH
09/28/2017
Signed on behalf of the Primary Clinical Pharmacology reviewer (Vadryn Pierre), as well as myself as his Team Leader.

NAM ATIQUR RAHMAN
09/28/2017
I concur.

ERIK W BLOOMQUIST
09/28/2017

SHENGHUI TANG
09/28/2017

RAJESHWARI SRIDHARA
09/28/2017

WILLIAM F PIERCE
09/28/2017

LYNN J HOWIE
09/28/2017

LALEH AMIRI KORDESTANI
09/28/2017

JULIA A BEAVER
09/28/2017

RICHARD PAZDUR
09/28/2017

MEMORANDUM

Date: September 20, 2017
From: Todd Palmby, PhD
Division of Hematology Oncology Toxicology for Division of Oncology Products 1
To: File for NDA 208716 VERZENIO (abemaciclib)

The nonclinical secondary review is complete. My recommendation for this application is approval.

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/s/

TODD R PALMBY
09/21/2017

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 208716 Abemaciclib
Drug Name:	Verzenio (Abemaciclib)
Indication(s):	Metastatic Breast Cancer
Applicant:	Lilly
Date(s):	Submission date: 5/5/2017 PDUFA Goal Date: 1/8/2018
Review Priority:	Priority
Biometrics Division:	5
Statistical Reviewer:	Erik Bloomquist, PhD
Concurring Reviewers:	Shenghui Tang, PhD Rajeshwari Sridhara, PhD
Medical Division:	OHOP/DOP1
Clinical Team:	Lynn Howie, M.D. Laleh Amiri Kordestani, M.D. Julia Beaver, M.D.
Project Manager:	Janice Kim

Keywords: Survival analysis, Breast Cancer

The statistical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. From a statistical standpoint, the NDA is acceptable to support approval.

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/s/

ERIK W BLOOMQUIST
09/20/2017

SHENGHUI TANG
09/20/2017

RAJESHWARI SRIDHARA
09/20/2017

MEMORANDUM

Date: September 15, 2017
From: Tiffany Ricks, PhD
Division of Hematology Oncology Toxicology for Division of Oncology Products 1
To: File for NDA 208716 VERZENIO (abemaciclib)

The nonclinical review is complete and has been added to the NDA 208716 Multidisciplinary Review and Evaluation. My recommendation for this application is approval.

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/s/

TIFFANY RICKS
09/18/2017

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Janice Kim, PharmD, MS
Nonclinical Reviewer	Tiffany Ricks, PhD
Nonclinical Team Leader	Todd Palmby, PhD
Office of Clinical Pharmacology Reviewer(s)	Vadryn Pierre, PharmD; Nan Zheng, PhD, Ruby Leong, PharmD
Office of Clinical Pharmacology Team Leader(s)	Jeanne Fourie-Zirkelbach, PhD; Jingyu Yu, PhD
Clinical Reviewer	Lynn J. Howie, MD
Clinical Team Leader	Laleh Amiri-Kordestani, MD
Statistical Reviewer	Erik Bloomquist, PhD
Statistical Team Leader	Shenghui Tang, PhD
Associate Director for Labeling	William Pierce, PharmD
Cross-Disciplinary Team Leader	Laleh Amiri-Kordestani, MD
Division Director (DHOT)	John Leighton, PhD
Division Director (OCP)	Nam Atiqur Rahman, PhD
Division Director (OB)	Rajeshwari Sridhara, PhD
Division Director (OHOP)	Julia Beaver, MD
Office Director (or designated signatory authority)	Richard Pazdur, MD

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	208,716
Priority or Standard	Priority
Submit Date(s)	5 May 2017
Received Date(s)	5 May 2017
PDUFA Goal Date	5 January 2018
Division/Office	DOP1/OHOP/OND
Review Completion Date	28 September 2017
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 fulvestrant 200 mg orally twice daily as a single agent
Applicant Proposed Indication(s)/Population(s)	(b) (4)

	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	VERZENIO™ is a kinase inhibitor indicated: • 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 • 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 clinical review is complete and has been added to the NDA Multidisciplinary Review and Evaluation. This clinical reviewer recommends the approval of NDA 208716.

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/s/

LYNN J HOWIE
09/15/2017

Regulatory Project Manager	Janice Kim, PharmD, MS
Nonclinical Reviewer	Tiffany Ricks, PhD
Nonclinical Team Leader	Todd Palmby, PhD
Office of Clinical Pharmacology Reviewer(s)	Vadryn Pierre, PharmD; Ruby Leong, PharmD; Nan Zheng, PhD
Office of Clinical Pharmacology Team Leader(s)	Jeanne Fourie-Zirkelbach, PhD; Yuching Yang, PhD; Jingyu Yu, PhD; Yaning Wang, PhD
Clinical Reviewer	Lynn J. Howie, MD
Clinical Team Leader	Laleh Amiri-Kordestani, MD
Statistical Reviewer	Erik Bloomquist, PhD
Statistical Team Leader	Shenghui Tang, PhD
Cross-Disciplinary Team Leader	Laleh Amiri-Kordestani, MD
Division Director (DHOT)	John Leighton, PhD
Division Director (OCP)	Nam Atiqur Rahman, PhD
Division Director (OB)	Rajeshwari Sridhara, PhD
Division Director (OHOP)	Julia Beaver, MD
Office Director (or designated signatory authority)	Richard Pazdur, MD

Reviewers of Multi-Disciplinary Review and Evaluation

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	208,716
Priority or Standard	Priority
Submit Date(s)	5 May 2017
Received Date(s)	5 May 2017
PDUFA Goal Date	5 January 2018
Division/Office	DOP1/OHOP/OND
Review Completion Date	18 September 2017
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	1) 150 mg twice daily in combination with fulvestrant and 2) 200 mg twice daily as monotherapy
Applicant Proposed Indication(s)/Population(s)	The applicant proposed the following indications: 1) VERZENIO 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 2) VERZENIO as monotherapy for the treatment of (b) (4) patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.
Recommendation on Regulatory Action	Approvable
Recommended Indication(s)/Population(s) (if applicable)	1) VERZENIO 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 2) VERZENIO 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 clinical pharmacology review is complete, and has been added to the NDA/BLA Multidisciplinary Review and Evaluation. The Office of Clinical Pharmacology recommends the approval of the NDA 208716 from a clinical pharmacology perspective.

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/s/

VADRYN PIERRE
09/14/2017
The clinical pharmacology review is complete, and has been added to the NDA/BLA Multidisciplinary Review and Evaluation. The Office of Clinical Pharmacology recommends the approval of the NDA 208716 from a clinical pharmacology perspective.

NAN ZHENG
09/14/2017

RUBY LEONG
09/14/2017

JEANNE FOURIE ZIRKELBACH
09/15/2017

JINGYU YU
09/15/2017

YUCHING N YANG
09/15/2017

YANING WANG
09/15/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: NDA 208716 **Applicant: Eli Lilly** **Stamp Date: 05/05/2017**

Drug Name: Abemaciclib **NDA Type: 505(b)(1)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159 htm	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: I3Y-MC-JBPA Study Title: Phase 1 Study of a Dual CDK 4/6 Inhibitor in Patients with Advanced Cancer Sample Size: 225 Treatment Arms: Dose escalation and then dose confirmation in expansion cohorts Location in submission: Section 5	X			

Reference ID: 4108437

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 MONARCH 2 Indication: in combination with fulvestrant for women with disease progression following endocrine therapy Pivotal Study #2 MONARCH 1 Indication: (b) (4) for (b) (4) disease progression following endocrine therapy and (b) (4) prior chemotherapy (b) (4) in the metastatic setting.	X			
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?				
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?	X			
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?				Applicant has submitted narratives for Monarch 1 study and per previous agreement will submit the narratives for Monarch 2 in July, 2017.
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reference ID: 4108437

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			Applicant has submitted the raw data for Monarch 1 study and per previous agreement will submit these for Monarch 2 in July, 2017.
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?				Applicant has submitted these for Monarch 1 study and per previous agreement will submit these for Monarch 2 in July, 2017.
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?				
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___YES____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer Date

Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 4108437

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/s/

LYNN J HOWIE
06/07/2017

LALEH AMIRI KORDESTANI
06/07/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208716	**SDN**	3
Applicant	Eli Lilly	**Submission Date**	05/05/2017
Generic Name	Abemaciclib	**Brand Name**	Verzenio
Drug Class			
Indication	(b) (4)		
Dosage Regimen	150 mg orally, twice daily in combination with fulvestrant 200 mg orally, twice daily as a single agent		
Dosage Form	50, 100, 150, and 200 mg Immediate release tablet	**Route of Administration**	Oral
OCP Division	DCPV	**OND Division**	

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Vadryn Pierre	Jeanne Fourie-Zirkelbach
Pharmacometrics	Zheng Nan	Yu Jingyu
PBPK	Ruby Leong	Yaning Wang
Genomics	Kimberly Maxfield	Rosane Charlab Orbach

Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date	7/7/2017	**74-Day Letter Date**	7/18/2017
Review Due Date	9/18/2017	**PDUFA Goal Date**	9/29/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies ☑ Yes ☐ No Clinical Pharmacology Summary ☑ Yes ☐ No

Reference ID: 4108295

Bioanalytical and Analytical Methods ☑ Yes ☐ No		Labeling ☑ Yes ☐ No
Clinical Pharmacology Studies		
Study Type	**Count**	**Comment(s)**
In Vitro Studies		

☑ Metabolism Characterization	12	• Study 2835219ME
		  ○ In vitro and in vivo identification of abemaciclib metabolite
		• Study 110941
		  ○ Identification of human CYPs responsible for the metabolism of abemaciclib
		• Study 130964
		  ○ Identification of human CYPs responsible for the metabolism of metabolite LSN2839567 (M2)
		• Study 121068
		  ○ Identification of human CYPs responsible for the metabolism of metabolite LSN3106726 (M20)
		• Study 130683
		  ○ Identification of human CYPs responsible for the metabolism of metabolite LSN3106729 (M18)

☑ Transporter Characterization	9	• Study 13ELIP4R3
		  ○ Evaluation of abemaciclib as a P-gp substrate
		• Study 14ELIP3
		  ○ Evaluation of metabolite LSN2839567 (M2) as a P-gp substrate
		• Study 13ELIP5R1
		  ○ Evaluation of abemaciclib as a BCRP substrate
		• Study 15ELIP1
		  ○ Evaluation of metabolite LSN2839567 (M2) as a BCRP substrate
		• Study LY2835219-2016TPSLC-Sub
		  ○ Evaluation of abemaciclib and metabolites LSN2839567 (M2) and LSN3106726 (M20) as substrates of hepatic uptake transporters OCT1, OATP1B1, and OATP1B3
		• Study LY2835219 Pgp Inh
		  ○ Inhibition of P-gp by abemaciclib
		• Study LY2835219-2015TPSLC-Inh
		  ○ Inhibition of hepatic and renal transporters OCT1, OCT2, OAT1, OAT3, OATP1B1, and OATP1B3 by abemaciclib and its metabolites LSN2839567 (M2) and LSN3106726 (M20)
		• Study LY2835219 MATE1 and 2K Inh
		  ○ Inhibition of MATE1 and MATE2-K by abemaciclib and metabolites LSN2839567 (M2) and LSN3106726 (M20)
		• Study LY2835219-2016TPBCRP-Inhib
		  ○ Inhibition of BCRP by abemaciclib

Reference ID: 4108295

☑ Distribution	5	• Study N0574
		  ○ In vitro plasma protein binding of abemaciclib to mouse, rat, dog, and human plasma proteins and human liver microsomes
		
		• Study LY2835219-Metab-prelim-pb
		  ○ In vitro plasma protein binding of metabolites LSN2839567 (M2), LSN3106726 (M20), and LSN3106729 (M18) in mouse, rat, dog, monkey, and human plasma and human liver microsomes
		• Study 150188-EIIDPB-PB-SR
		  ○ Analysis of ex vivo binding of LY2835219 and metabolites LSN2839567 (M2), LSN3106726 (M20), and LSN3106729 (M18) in human plasma for Study I3Y-MC- JPBV (hepatic impairment study)
		• Study N1297
		  ○ In vitro binding of abemaciclib to human albumin and α1-acid-glycoprotein
		• Study LY2835219_in vitro b/p
		  ○ In vitro human blood to plasma ratio of abemaciclib

☑ Drug-Drug Interaction	7	• Study CD-1106
		  ○ Inhibition of CYP3A4, CYP2D6, CYP2C19, CYP2C9, CYP2C8, CYP2B6, and CYP1A2 by abemaciclib
		• Study XT125052
		  ○ Inhibition of CYP3A, CYP2D6, CYP2C9, CYP2C8, CYP2B6, and CYP1A2 by metabolite LSN2839567 (M2)
		• Study 130257/130258
		  ○ Inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A by metabolite LSN2839567 (M20)
		• Study CD-1158
		  ○ Effect of abemaciclib on CYP1A2, CYP2B6, and CYP3A
		• Study XT133052
		  ○ Effect of abemaciclib on cytochrome P450
		• Study XT133051
		  ○ Effect of metabolite LSN2839567 (M2) on cytochrome P450
		• Study XT133108
		  ○ Effect of metabolite LSN3106726 (M20) on cytochrome P450

In Vivo Studies		
Biopharmaceutics		
☑ Absolute Bioavailability	1	JPBS Healthy Subjects

Reference ID: 4108295

			Phase 1, open-label, single-center, single period study to estimate the absolute bioavailability of abemaciclib C3 (Phase 3 capsule formulation 200 mg dose; 50 mg capsules), radio labeled IV formulation ([$^{13}C_8$] 0.14 mg IV dose infused over 15 minutes; 84 µg/mL ([$^{13}C_8$]-abemaciclib) in 10 mM acetate buffer and 0.9% normal saline (pH 4.0) JPBD Single 150-mg dose containing $^{14}C_8$-abemaciclib (approximately 5 µCi) in an oral powder solution
☐ Relative Bioavailability			
☑ Bioequivalence		1	JPCC [Part B] Phase 1, open-label, randomized, multi-period crossover BE and food effect study C3 (Phase 3 formulation; 50 mg x 3 capsules) vs T1 (proposed commercial; 3 x 50 mg; 1x150 mg tablets) formulation Food effect on 150 mg tablet
☑ Food Effect		2	JPBG Phase 1, single center, open-label, randomized, single dose, 3-period, crossover food-effect study C2 Phase 2 formulation; 4 x 50 mg capsules JPBU Phase 1, open-label, randomized, single dose, 2-period, crossover food-effect study C3 Phase 3 formulation 2 x 100 mg capsules JPCC [Part C] Phase 1, open-label, randomized, multi-period crossover BE and food effect study C3 (Phase 3 formulation; 50 mg x 3 capsules) vs T1 (proposed commercial; 3 x 50 mg; 1x150 mg tablets) formulation Food effect on 150 mg tablet
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose		JPCA Ascending dose/QT: single 200, 300, 400, or 600 mg dose or placebo DDI: single 8-mg dose loperamide on Day -3, followed by a single 8-mg dose loperamide with a single 400-mg dose abemaciclib or placebo on Day 1
	☐ Multiple Dose		
Patients	☑ Single Dose	1	JPBA Part A: 50-225 mg Q24H or 75-275 mg Q12H

Reference ID: 4108295

			Parts B-G: no greater than the MTD (200 mg Q12H)
	☑ Multiple Dose	1	JPBA Part A: 50-225 mg Q24H or 75-275 mg Q12H Parts B-G: no greater than the MTD (200 mg Q12H) JPBC
☑ Mass Balance Study		1	JPBD Healthy Subjects Single 150-mg dose containing 14C-abemaciclib (approximately 5 µCi)
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☑ Race		2	JPBC Japanese Patients 100, 150, and 200 mg Q12H Monarch 1/PopPK
☐ Sex			
☑ Geriatrics		1	Monarch 1/PopPK
☐ Pediatrics			
☑ Hepatic Impairment			JPBV Single 200 mg dose Subjects with normal or mild, moderate, or severe hepatic impairment
☑ Renal Impairment		1	Monarch 1/PopPK
☐ Genetics			
Extrinsic Factors			
☑ Effects on Primary Drug			JPBE DDI Period 1: single 50-mg dose DDI Period 2: single 50-mg dose on Day 5 of clarithromycin dosing Safety Extension: 200 mg Q12H JPBF Healthy Subjects DDI Period 1: single 200-mg dose DDI Period 2: single 200-mg dose on Day 7 of rifampin dosing
☑ Effects of Primary Drug			JPCA Ascending dose/QT: single 200, 300, 400, or 600 mg dose or placebo DDI: single 8-mg dose loperamide on Day -3, followed by a single 8-mg dose loperamide with a single 400-mg dose abemaciclib or placebo on Day 1
Pharmacodynamics			
☐ Healthy Subjects			

☑ Patients	1	JPBA pRb and Topo II α expression were assessed as markers of clinical activity
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects	1	
☐ Patients		
☑ QT	1	JPCA Ascending dose/QT: single 200, 300, 400, or 600 mg dose or placebo
PBPK		
	3	LY2835219-MM-CYP3A-INH-200mg • PBPK prediction of CYP3A inhibitors effects on Abemaciclib PK after Abemaciclib 200 mg dose LY2835219-MM-INH-PBPK-50mg • PBPK prediction of CYP3A inhibitors effects on Abemaciclib PK after Abemaciclib 50 mg dose LY2835219-MM-IND-PBPK-CYP3A • PBPK prediction of CYP3A inducers effects on Abemaciclib PK after Abemaciclib 200 mg dose
Pharmacometrics		
☑ Population Pharmacokinetics	1	PopPK report pooling data from all studies was used to develop structural model and conduct ER analyses.
☑ Exposure-Efficacy	1	
☑ Exposure-Safety	1	

Total Number of Studies	**In Vitro**	36	**In Vivo**	8
Total Number of Studies to be Reviewed		36		8

Reference ID: 4108295

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☑Yes ☐No ☐N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☑Yes ☐No ☐N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☑Yes ☐No ☐N/A	

Reference ID: 4108295

Filing Memo
This is optional, discuss with your TL content and format

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VADRYN PIERRE
06/07/2017

JEANNE FOURIE ZIRKELBACH
06/07/2017

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 208716 **Applicant: Eli Lilly and Company** **Stamp Date: May 5, 2017**

Drug Name: abemaciclib **NDA Type: 505 (b)(1); Type 1 – New Molecular Entity**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The Applicant's proposed labeling will be reviewed during the NDA review.
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		The acceptability of the Applicant's proposed specifications will be determined during the NDA review.
11	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___yes____

If the NDA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

None

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this time

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/s/

TIFFANY RICKS
06/01/2017

TODD R PALMBY
06/01/2017